



# 2021 ACTIVITY REPORT

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## IDENTIFICATION OF THE R&D UNIT

### Name of the R&D Unit

IPO Porto Research Center/Centro de Investigação do IPO Porto

### Acronym

CI-IPOP

### Director

Carmen Jerónimo, PhD

### Vice-Directors

Mário Dinis Ribeiro, MD, PhD

Rui Medeiros, PhD

### Host Institution

Instituto Português de Oncologia do Porto Francisco Gentil, EPE (IPO Porto)

### Keywords

Cancer epigenetics

Cancer genetics

Clinical research

Epidemiology and outcomes research

Experimental therapy

Medical physics and radiobiology

Molecular oncology

### Website

<http://ipoporto.pt/centro-de-investigacao/>

### Contacts

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## **R&D UNIT DESCRIPTION**

### **Overall Description**

IPO Porto Research Center (CI-IPOP) is a Department of the Portuguese Oncology Institute of Porto/Instituto Português de Oncologia do Porto Francisco Gentil, EPE (IPO Porto), the largest specialized Portuguese cancer centre (~10.000 new patients/yr) dedicated to patient care, training and research in Oncology (<http://www.ipoport.pt/>). IPO Porto is a member of the Organization of European Cancer Institutes (OECI) and is accredited by OECI as a Comprehensive Cancer Center (Porto Comprehensive Cancer Center Raquel Seruca; Porto.CCC) in collaboration with Instituto de Investigação e Inovação em Saúde (i3S).

CI-IPOP has the mission to coordinate and implement the research activity of IPO Porto. It is a founding member of the Associated Laboratory Health Research Network (RISE) in which it coordinates the Thematic line 2 (TL2)- “CLINICAL AND TRANSLATIONAL RESEARCH IN ONCOLOGY” CI-IPOP is an FCT R&D unit since 2004, rated as Excellent in the last international evaluation (2019). CI-IPOP comprises 5 translational research groups (Cancer Biology & Epigenetics; Cancer Genetics; Experimental Pathology & Therapeutics; Medical Physics, Radiobiology & Radiation Protection; and Molecular Oncology & Viral Pathology), two clinical groups that were created in the end of 2021 (Precancerous Lesions and Early Cancer Management and Clinical Oncology) and two groups devoted to meet the growing needs on epidemiology of cancer, patient outcome and quality of life, as well as value-based healthcare and sustainability (Cancer Epidemiology and Management, Outcomes Research & Economics in Healthcare); along with a Clinical Research Unit, which includes an Early phase clinical trials Unit dedicated to investigator-initiated trials. CI-IPOP activity is supported by IPO Porto’s Biobank.

### **Long-term goal**

CI-IPOP long-term objective is to understand the pathobiologic mechanisms of tumorigenesis and enable Precision Oncology. Patient-centered translational and clinical research is focused on:

- Development of new diagnostic, prognostic and monitoring biomarkers using liquid biopsies;
- Identification of novel therapeutic targets to be tested in early phase clinical trials;
- Improvement of bioimaging, bioinformatics, and outcome assessment tools;
- Support of the Precision Oncology Program at IPO Porto (POP-IPOP).

### External Scientific Advisory Board (ESAB)

CI-IPOP's ESAB, shared with Porto.CCC, is composed by distinguished and internationally renowned researchers in the many facets of Cancer:

- Prof. Ulrik Ringborg (Chairman), Director of Cancer Center Karolinska, Karolinska University Hospital, Solna, Sweden.
- Prof. Alexander Eggermont, Chief Scientific Officer, Princess Maxima Center for Pediatric Oncology, Utrecht, The Netherlands.
- Prof. Alexander Markham, Director of MRC Medical Bioinformatics Centre, Health Data Research UK, London, United Kingdom.
- Prof. Robert C. Bast Jr., Vice President for Translational Research, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA.
- Prof. Stefan Frohling, Managing Director of National Centre for Tumor Diseases, Heidelberg, Germany.

### Facilities

- CI-IPOP facilities are scattered in different buildings, including the clinical research unit which is located at B-Building - 1st floor, and 3 translational research laboratories: Laboratory 1 (RC-LAB1/CI-LAB1) located at E-Building, 6th floor (sharing of equipment and laboratory space with the Service of Laboratorial Genetics); Laboratory 2 (RC-LAB2/CI-LAB2) located at the E-Building, 1st floor and Laboratory 3 (RC-LAB3/CI-LAB3) located at F-building, 1st floor. The Office of the Directorate of the Research Center is located at A-building, 1st floor.

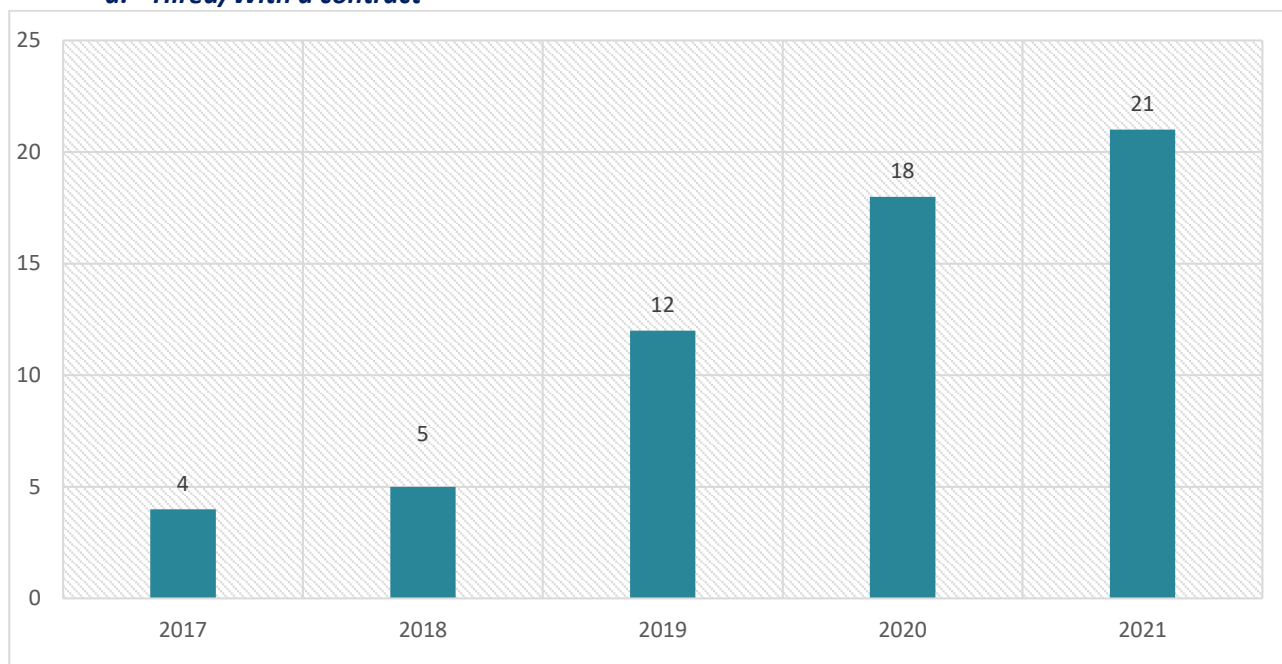
### Research Team

CI-IPOP includes more than 200 members of which 70 hold a PhD and 103 an MSc. In addition to IPO Porto staff, that includes 73 MDs, 39 health technicians, 33 researchers (21 PhDs) and 17 PhD students, 40 members are supported by fellowships (31 PhD students and 8 research assistants) and 24 are MSc students.

### Human Resources (External funding)

In 2021, the number of researchers with a PhD and having a contract with CI-IPOP increased from 18 to 21 (Figure 1), and one PhD student (for the first time) was hired (under a laCaixa grant) along with several Research Assistants (Tables 1A-1D). This was made possible by external funding derived from competitive research projects or individual calls. Moreover, two PhD Researchers (Table 2A) were supported by FCT fellowships, as well as most of the PhD students either supported by fellowships secured in individual or institutional calls (Tables 2B-C).

**a. Hired/With a contract**



**Figure 1** – Number of PhD researchers with a contract funded by external agencies in the last 5 years

**Table 1A** – Assistant Researchers hired by type of funding

Number	Type of Funding
1	FCT funding for up to 6 years (Stimulus of Scientific Employment, Individual Support – 2017 Call)
2	POCI-01-0145-FEDER-028245-FCT funding for up to 6 years (Stimulus of Scientific Employment, Institutional Support – 2018 Call)
1	NORTE-01-0145-FEDER-072678 - TeamUp4Cancer (PCCC) for 2 years-2019 Call

**Table 1B** – Junior Researchers hired by type of funding

Number	Type of Funding
2	FCT funding for up to 6 years (transitional rule, Law nr. 56/2016)
3	FCT research projects, 02/SAICT/2017 Call
3	Base FCT funding for 1-3 years - UIDB/00776/2020
5	Strategic FCT funding for 1-3 years - UIDP/00776/2020
4	NORTE-01-0145-FEDER-072678 - TeamUp4Cancer (PCCC) for up to 2 years-2019 Call

**Table 1C** – PhD Students hired by type of funding

Number	Type of Funding
1	La Caixa Foundation for up to 3 years-2019 Call

**Table 1D** – Research Assistants hired by type of funding

Number	Type of Funding
7	NORTE-01-0145-FEDER-072678 – TeamUp4Cancer (PCCC) for up to 2 years-2019 Call

**b. Fellowships**

**Table 2A** – Post-doctoral researchers holding external fellowships

Number	Type of Funding
1	FCT fellowship for up to 6years-2016 Call
1	FCT fellowship for up to 6years-2015 Call

**Table 2B** – PhD Students by type of external fellowship

Number	Type of Funding
27	FCT Individual grants for up to 4 years
1	FCT R&D Unit fellowship for up to 4 years
2	Unicampania, Naples, Italy
1	LPCC-NRN

**Table 2C** – Research Assistants by type of external fellowship

Number	Type of Funding
3	MindGAP-829040
5	LPCC-Norte

**Ongoing projects supported by competitive funding**

At institutional level, under the framework of Porto.CCC [Porto.CCC: Centro Compreensivo de Cancro do Porto” - NORTE-01-0145-FEDER-072678 (Team UP4Cancer), supported by Norte Portugal Regional Operational Programme (NORTE 2020), under the PORTUGAL 2020 Partnership Agreement, through the European Regional Development Fund (ERDF)], a total of 7.541.887,20€, has been secured to support contracts with researchers and technicians (described above), as well as for acquisition of new equipment that will reinforce the existing CI-IPOP’s facilities, to enlarge/refurbish Laboratories 1, 2 and to build and equip the Early Phase Clinical Trials Unit. Importantly, CI-IPOP research has been supported by several external grants and internal funding obtained according to CI-IPOP’s Regulation. The active projects in 2021 registered at CI-IPOP with

competitive funding by PI/Co-PI primarily affiliated with CI-IPOP are displayed below. Concerning projects supported by internal funding or without specific funding, details are provided in each groups/unit report (Table 3).

**Table 3** – Ongoing projects supported by competitive funding

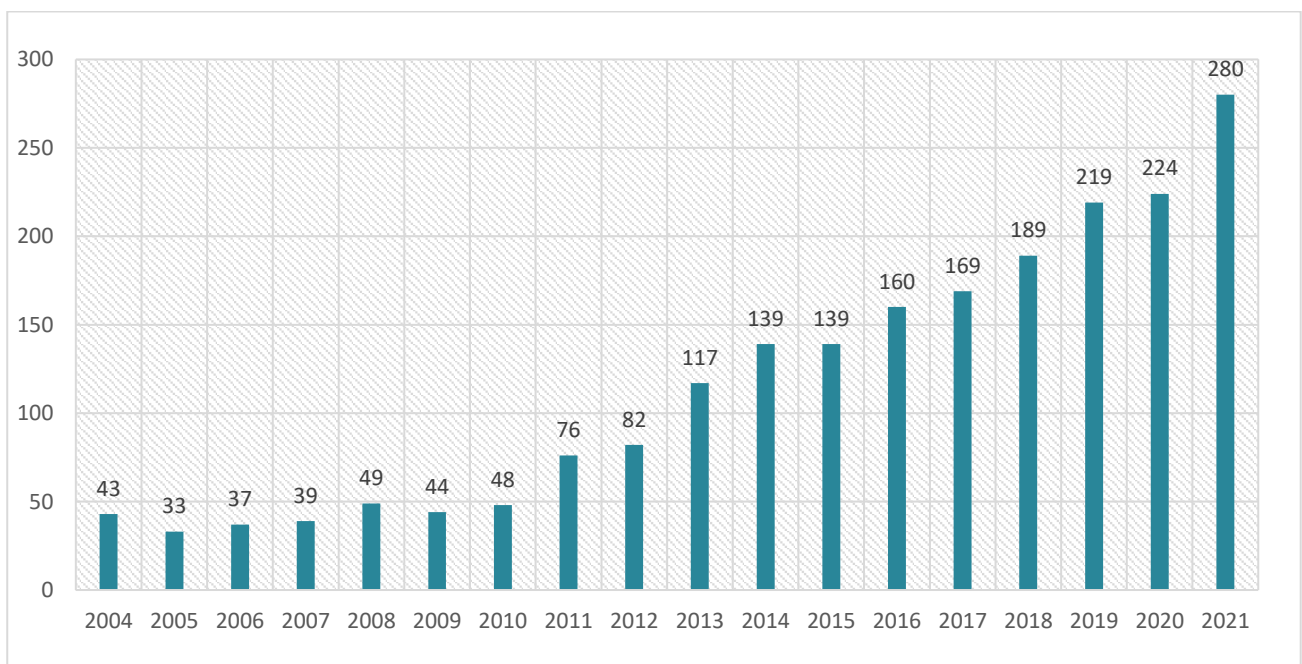
Start	End	Acronym	CODE	Funding Agency	Title	Budget	PI/ Co-PI
01/01/2018	30/06/2021	<b>HyTherCap</b>	PTDC/MEC-ONC/29030/2017 - POCI-01-0145-FEDER-029030	FCT	Hydralazine: a new therapeutic approach in Castration-Resistant Prostate Carcinoma	157 159,09 €	Carmen Jerónimo
01/01/2018	30/06/2021	<b>EpiMarkGermCell</b>	PTDC/MEC-URO/29043/2017-NORTE-01-0145-FEDER-029043	FCT	Development of new prognostic and predictive epigenetic biomarkers for malignant testicular germ cell tumors	191 939,09 €	Rui Henrique/ Carmen Jerónimo
01/07/2018	30/06/2022	<b>TOGETHER</b>	PTDC/PSI-ESP/30980/2017	FCT	Psychosocial adaptation to genetic testing in the context of hereditary cancer risk: A systemic approach	44 771,00 €	Eunice Silva
01/07/2018	31/12/2021	<b>SIRNAC</b>	NORTE-01-0247-FEDER-033399	FCT	Novel siRNA therapy for metastatic colorectal cancer	211 712,60 €	Rui Medeiros
26/07/2018	31/05/2022	<b>TRIMARKCHIP</b>	PTDC/BTM-TEC/30831/2017 - POCI-01-0145-FEDER-030831	FCT	Trifecta assessment of circulating cancer biomarkers: a combined microfluidic platform for detection of CTCs, exosomes and ctDNA	32 940,00 €	Carmen Jerónimo
01/08/2018	31/01/2022	<b>NANOTEC</b>	PTDC/MED-QUI/29800/2017	FCT	Sensitizing nanotechnology of therapy in urological tumors	124 301,54 €	Rui Medeiros
26/07/2018	25/11/2021	<b>SEGMAPP</b>	PTDC/MED-GEN/28245/2017	FCT	Role of chromosome segregation machinery in genetic predisposition to prostate cancer.	176 824,85 €	Paula Paulo/ Manuel Teixeira
17/01/2019	16/07/2022	<b>IPOscore</b>	DSAIPA/DS/0042/2018	FCT	Predict the risk of complications from surgical treatment and define prognosis in cancer patients through the integration of clinical and pathological data.	32 163,00 €	Lúcio Lara Santos
01/04/2019	30/03/2023	<b>MindGap</b>	H2020-FETOPEN-01-2018-2019-2020 – FET-Open Challenging Current Thinking	EU	MINDGAP-BRIDGING THE GAP BETWEEN MIND, BRAIN AND BODY: EXOSOME ROLE AND MONITORING	793 525,00 €	Rui Henrique
01/12/2021	31/12/2024	<b>AFRICA</b>	PTDC/BIA-MOL/3986/2021	FCT	Sub-Saharan panel of tumor lines: from patient-derived cells to specialized population cancer treatment in African ancestry	25 000,00 €	Lúcio Lara Santos

## I. MAJOR SCIENTIFIC OUTCOMES OF CI-IPOP

### A. PUBLICATIONS OVERVIEW

#### Number of Publications

In 2021, CI-IPOP accounted for a total of 280 peer-reviewed scientific articles (Pubmed and/or Scopus, including only those with final publication date in 2021), and 234 of those were published in journals with impact factor. Comparing with 2020, an additional 56 articles were published in 2021, representing an impressive rise of about 20% in this scientific output (Figure 2).



**Figure 2** – Number of publications since 2004, when CI-POP was recognized as R&D FCT Unit (ID 00776)

#### Impact Factor

Of the 280 publications in 2021, 234 were in journals with impact factor. The average impact factor of these published articles was 6.4, which represents an increase of 12.3% compared with 2020. Of note, in the last 5 years, the median impact factor has steadily increased (IF Source Clarivate). Moreover, 114 articles were published in journals with IF above 5 and 31 publications were in journals with IF above 10 (Figure 3).



Figure 3 – Impact factor mean and distribution of published articles by Impact factor (>5 and >10) in the last 10 years

### Publications by Area of Knowledge and Scimago classification categories

The publications by CI-IPOP researchers were mostly in the areas of Medicine and Biochemistry, Genetics and Molecular Biology (data from SCOPUS) (Figure 4).

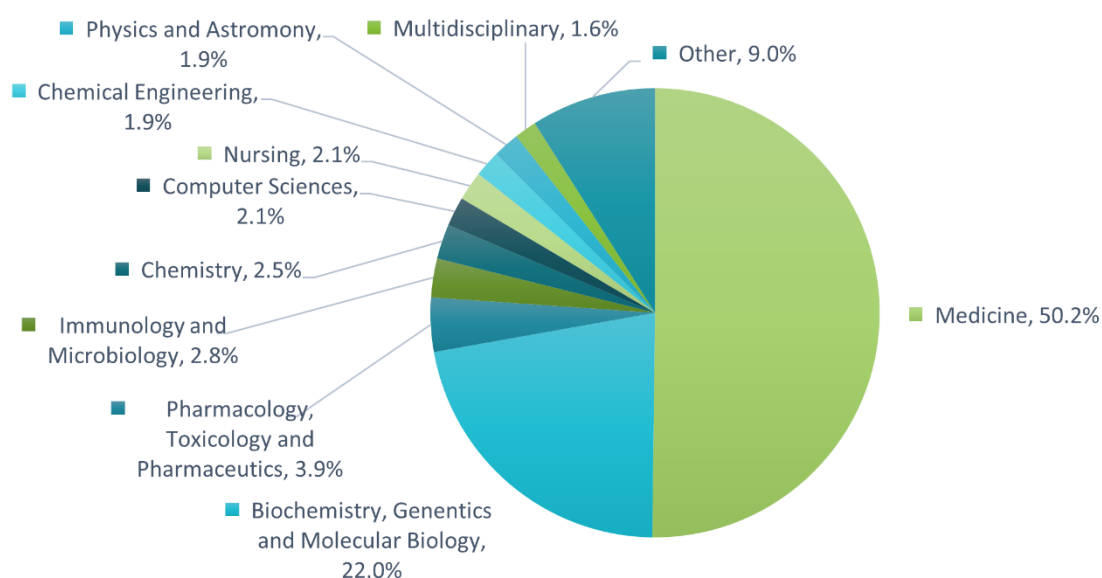


Figure 4 – 2021 Publications in scientific journals according with Scopus categories

From all the indexed publications, 169 (72%) had at least one category in Q1 from Scimago classification. Among these, 51 were in the “Oncology” category, 37 in “Medicine” and 17 were in the “Cancer research” category (Figure 5).

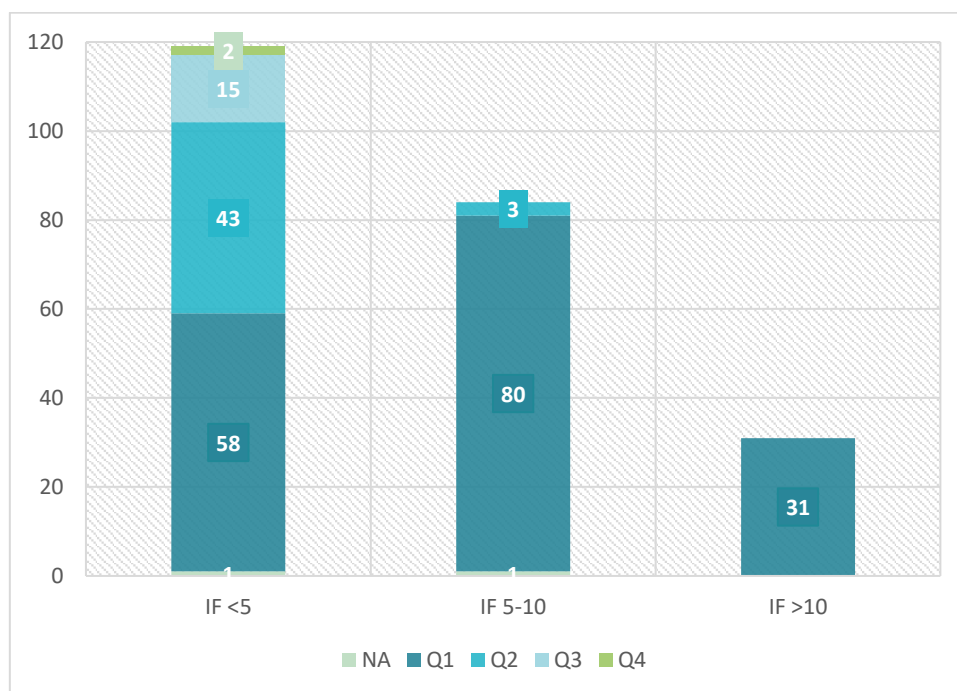
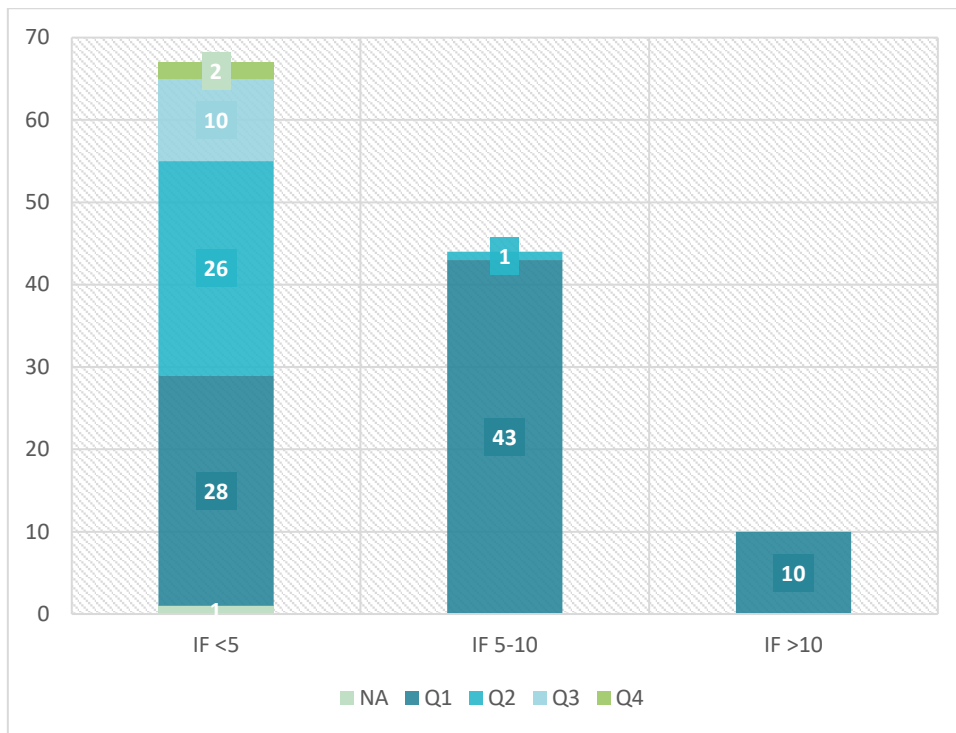


Figure 5 – 2021 Publications according with IF and Scimago classification

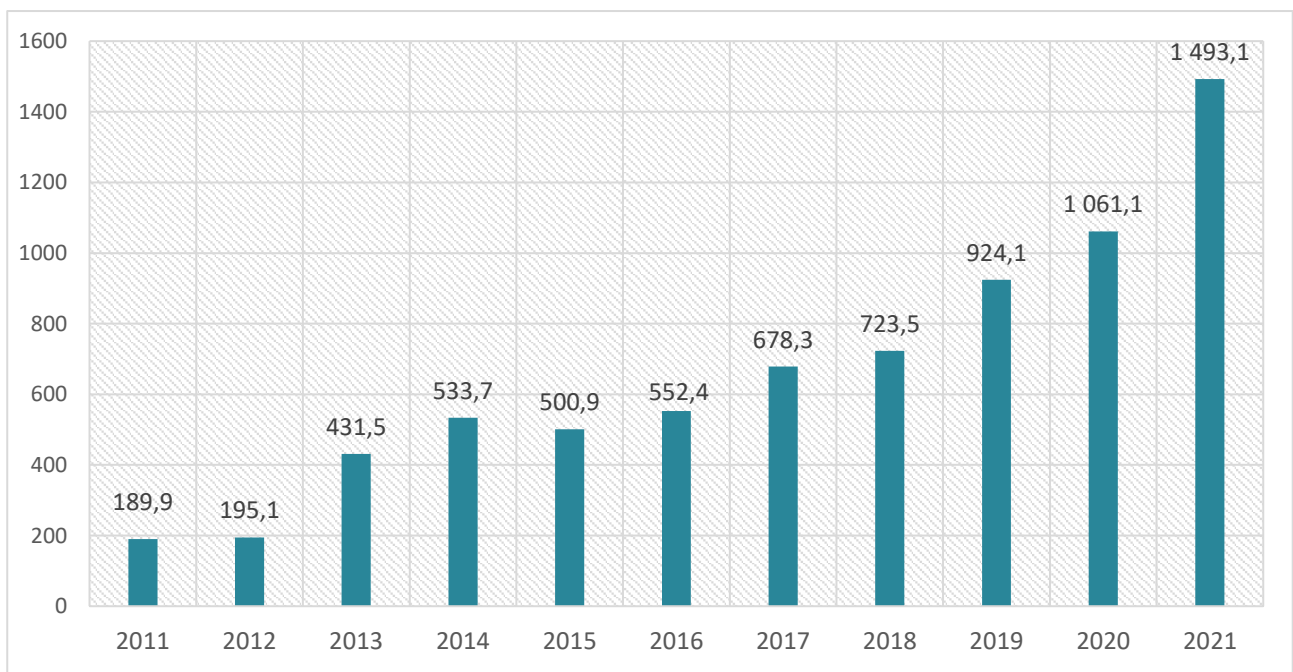
Regarding publications with a 1<sup>st</sup> author or senior author with affiliation to CI-IPOP, 120 were published in scientific journals with Impact Factor. Among these, 10 were published in journals with an Impact factor higher than 10 and 80 have at least one category in Q1 journals (Figure 6).



**Figure 6** – 2021 Publications according with IF and Scimago classification with CI-IPOP researchers as first or senior authors

### Sum of publications' Impact Factors

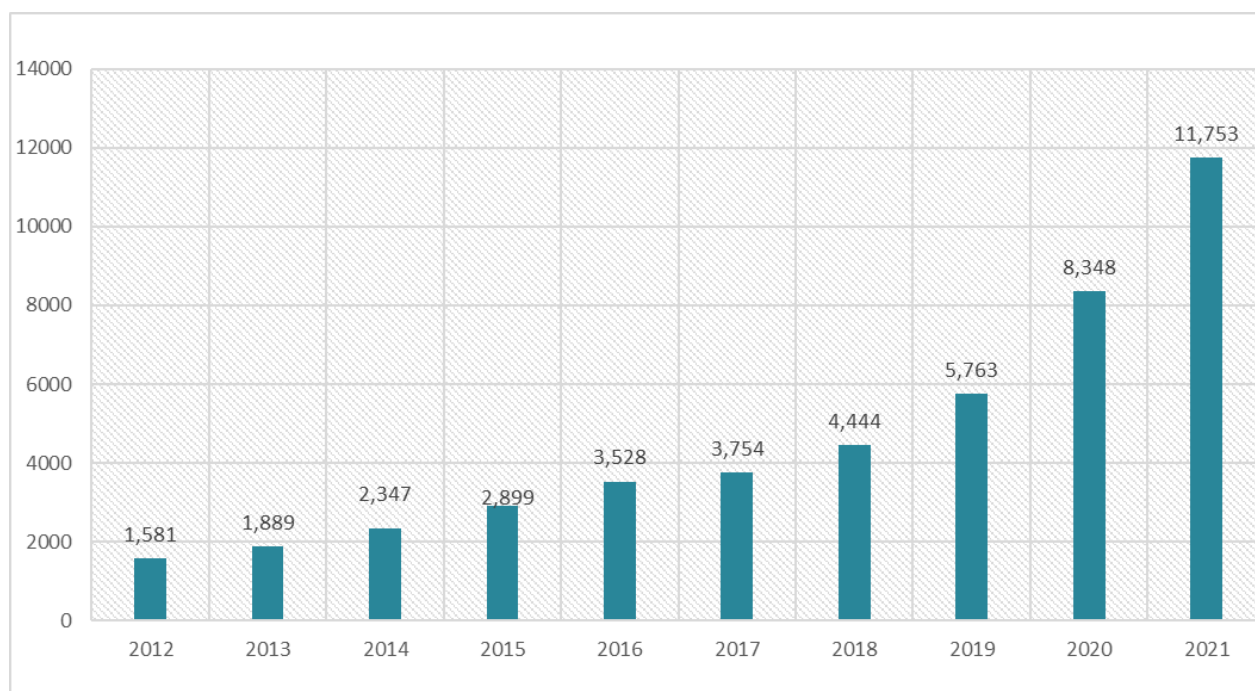
According to the Scopus database, the sum of impact factors of the 234 publications is 2021 was 1 493.1, which represents an increase of 40.7% compared with 2020 (Figure 7).



**Figure 7** – Distribution of the Sum of publications' Impact Factors in the last 10 years

## Number of CI-IPOP publications' Citations

According to the Scopus database, the number of CI-IPOP publications' citations during 2021 was 11753. The evolution over the 10 years of the number of citations per year is shown in Figure 8.



**Figure 8** – The evolution over the 10 years of the number of citations per year

## Publications' Internationalization

The research performed at CI-IPOP has a high degree of internationalization, as evidenced by the fact that 45% of the 280 publications in 2021 resulted from international collaborations, including researchers from foreign institutions as co-authors (Figure 9).

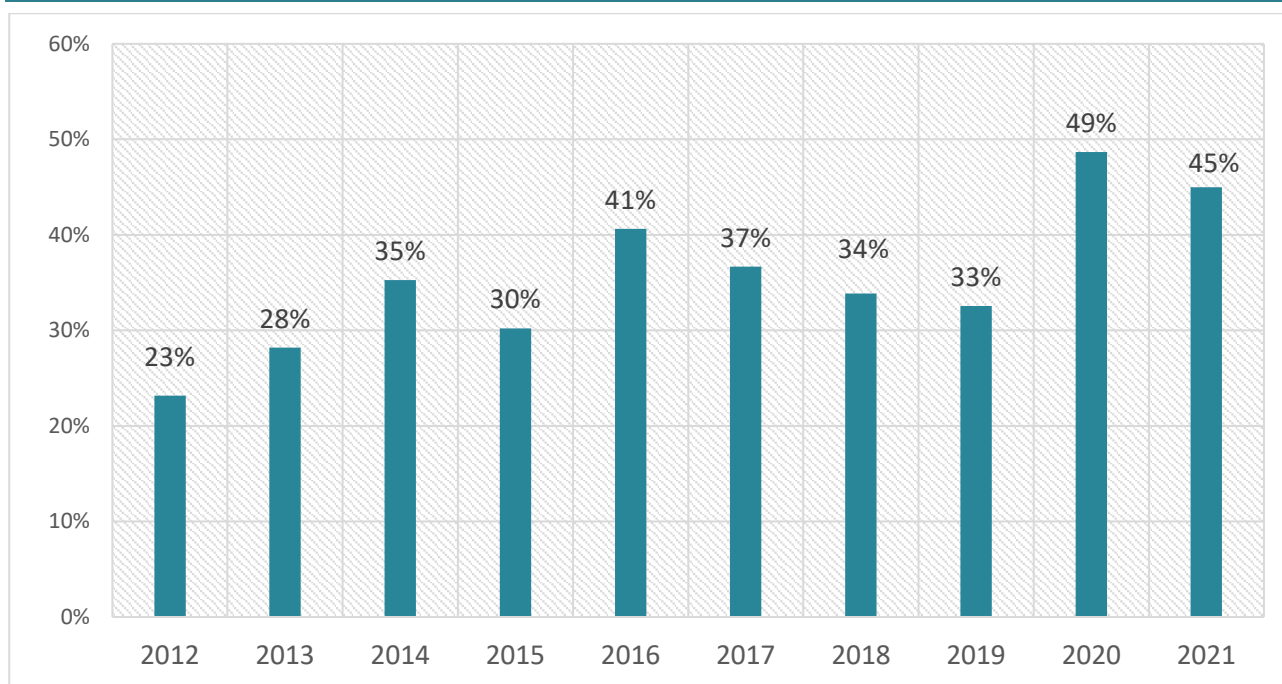


Figure 9 – Proportion of publications with international co-authors over the 10 years

## B. EDUCATION, ADVANCED TRAINING AND SCIENTIFIC MEETINGS

Several Researchers were involved in teaching and/or supervision of pre-graduated and post-graduate students.

### Education

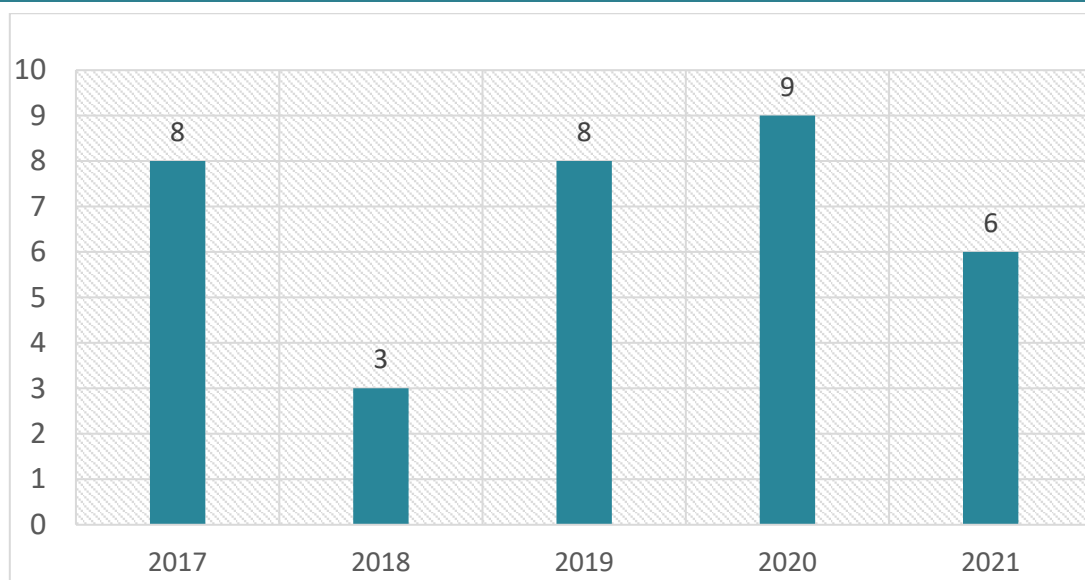
#### PhD Programmes

- Biomedicine (FMUP)
- Molecular and Cellular Biology (ICBAS, IBMC)
- Molecular Oncology and Medicine (FMUP/ICBAS)
- Pathology and Molecular Genetics (ICBAS/FMUP)

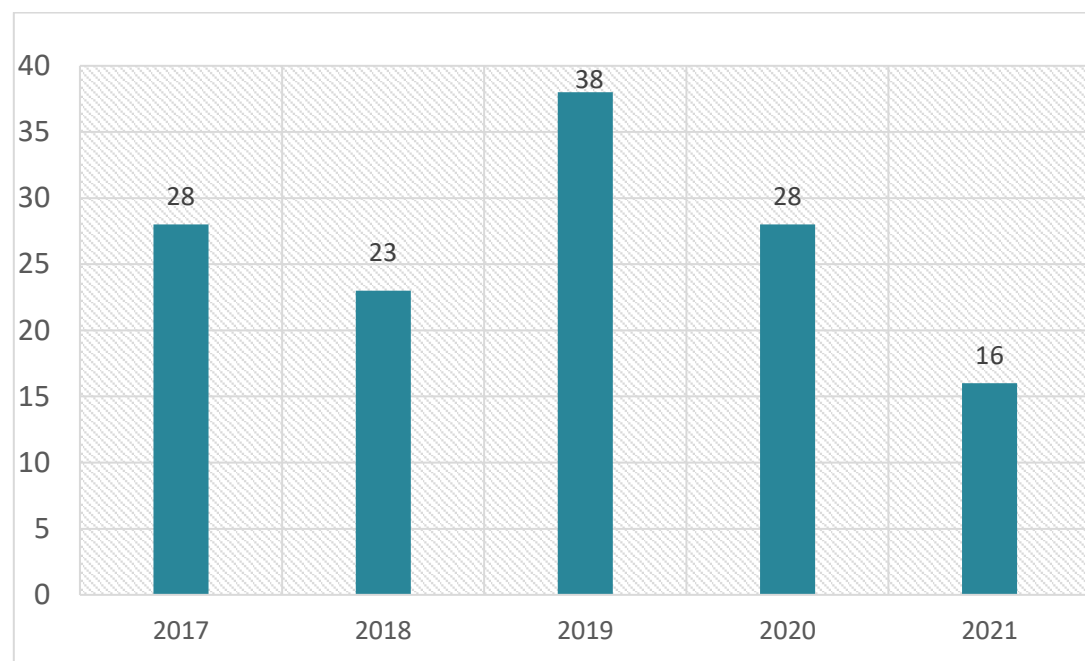
#### MSc Programmes

- Biochemistry (ICBAS/FCUP)
- Integrated MSc in Bioengineering (ICBAS/FEUP)
- Integrated MSc in Medicine (ICBAS)
- Medical Physics (FCUP)
- Molecular Oncology and Medicine (FMUP)
- Oncology (ICBAS)

Regarding young researchers training outputs, during 2021, 6 PhD theses (Figure 10 & Table 4) and 16 MSc dissertations supervised by IPO Porto's researchers were publicly defended (Figure 11 & Table 5).



**Figure 10** – The evolution over the 5 years of the number of PhD Thesis completed Supervised/Co-Supervised by CI-IPOP's Researchers



**Figure 11** – The evolution over the 5 years of the number of MSc Dissertations completed Supervised/Co-Supervised by CI-IPOP's Researchers

### Advanced Courses

- Introduction to the Scientific activity in Oncology (22h)

### Organization/ Host of Scientific Meetings

#### INTERNATIONAL

- **European Cancer Research Summit** (Hybrid), 3 May 2021; <http://ipoporto.pt/en/evento/european-cancer-research-summit-2021/>
- **II ASPIC-ASEICA International Meeting** – Current Trends in Precision Medicine in Cancer (Virtual), 14-15 October 2021; <https://aspicaseicameeting.aspic.pt/>

- **XVII Congress of the Iberian Society of Cytometry** (Virtual), 14-18 June 2021; <https://www.cytognos.com/event/sic-2021/>

**NATIONAL**

- **5th Symposium of the Master in Oncology** (VIRTUAL), 22 & 23 February 2021 (IPOP & ICBAS-UP) <https://www.facebook.com/ipodoporto/photos/a.203085223093164/3739510056117312/?type=3>

- **CI-IPOP Monthly Scientific Meetings**

Date	Format	Speaker	Presentation Theme
2021/01/22	Videoconference (CiscoWEBEX)	<b>Dr. João Lobo,</b> Resident in Pathology & PhD Student at the Cancer Biology & Epigenetics Group, Research Center of Portuguese Oncology Institute of Porto	"Epigenetic biomarkers and epidrugs for improving the clinical care of testicular germ cell tumor patients".
2021/02/26	Videoconference (CiscoWEBEX)	<b>Dr. Giuseppina M. Carbone,</b> Principal Researcher at Prostate Cancer Biology Group, Institute of Oncology Research (IOR), Bellinzona (Switzerland)	"From ETS factors to exosomes: linking epigenetics and tumor microenvironment".
2021/03/19	Videoconference (CiscoWEBEX)	<b>Dr. Samantha Morais,</b> Postdoctoral Researcher at Epidemiology Department; Non-Communicable Diseases Epidemiology Research Group (EPIUnit) at ISPUP	"The impact of the COVID-19 pandemic on the short-term survival of patients with cancer"
2021/05/07	Videoconference (CiscoWEBEX)	<b>Prof. Dr. Manuel Teixeira,</b> Director of Research Center of the IPO Porto	Annual Report 2020 (CI-IPOP)
2021/05/21	Videoconference (CiscoWEBEX)	<b>Dr. Francisca Dias,</b> Junior Researcher at the Molecular Oncology and Viral Pathology Group	"Synergic effect of microRNAs and metalloproteinases derived from extracellular vesicles in the establishment of the metastatic niche in renal cell carcinoma"
2021/06/18	Videoconference (CiscoWEBEX)	<b>Dr. Ana Luísa Teixeira Ferreira,</b> Junior Researcher at the Cancer Genetics Group	"Cancer - From fundamental biology to translational research"
2021/07/16	Videoconference (CiscoWEBEX)	<b>Dr. Andreia Peixoto,</b> Junior Researcher at the Experimental Pathology and Therapeutics Group	"Exploring glyco-biomarkers for advanced stage bladder cancer: adding the influence of hypoxia to the equation"
2021/09/17	Videoconference (CiscoWEBEX)	<b>Dr. Leyla Ebrahimpour,</b> Research Fellowship at Medical Physics, Radiobiology and Radiation Protection Group	"Increasing VMAT Planning Accuracy Using Modulation Indices (MI)"
		<b>Laura Providência,</b> MSc Student at Medical Physics, Radiobiology and Radiation Protection Group	"An automatic algorithm for the assessment of bone lesions in bone scintigraphy images"
2021/10/22	Videoconference (CiscoWEBEX)	<b>Dr. Sara Monteiro-Reis,</b> Invited Researcher, Cancer Biology & Epigenetics Group & Postdoctoral Researcher, Health & Biomechanical Unit, Institute of Science and Innovation in Mechanical and Industrial Engineering (INEGI),	"Uncovering the role of epigenetic mechanisms in bladder cancer aggressiveness: from biology to clinical setting".
2021/11/19	Videoconference (CiscoWEBEX)	<b>Dr. Mariana Brandão,</b> Medical Oncology Service of Institut Jules Bordet (Brussels, Belgium) and Researcher in EPIUnit - Institute of Public Health of the University of Porto	"Breast cancer heterogeneity: etiology, clinical management, use of health resources and survival".

**Table 4 – PhD Theses completed in 2021 supervised by CI-IPOP’s researchers**

Name	Fellowship	Title	Program	Faculty/University	Supervising team	Date Public defense
Joaquim de Castro Silva	NA	Quality of life and biochemical markers in the assessment of cachexia in patients with head and neck cancer	Medicine	School of Medicine & Biomedical Sciences; University of Porto	S: Eurico Monteiro; Co-S: Lúcio Lara Santos	16/12/2021
João Lobo	SFRH/BD/132751/2017	Uncovering novel prognostic and predictive epigenetic biomarkers in malignant testicular germ cell tumors	Pathology & Molecular Genetics	School of Medicine & Biomedical Sciences; University of Porto	S: Rui Henrique; Co-S: Carmen Jerónimo & Leendert HJ Looijenga	06/10/2021
Fernando Miguel	NA	Organization of oncology units in Angola: epidemiological profile of oncological diseases and necessary resources for early diagnosis and adequate treatment	Medicine	School of Medicine & Biomedical Sciences; University of Porto	S: Lúcio Lara Santos; Co-S: Carlos Lopes	15/04/2021
Atílio Monteiro de Morais	NA	Research to improve Surgical Oncological care on the Surgical Department, Maputo Central Hospital	International Health	Institute of Hygiene & Tropical Nova Medical School	S: Lúcio Lara Santos; Co-S: Moshin Sidate & Maria Rosário Martins	07/05/2021
Jotamo Come	NA	Esophageal cancer in Mozambique. Disease characterization for the definition of a proficient action program	Medicine	School of Medicine & Biomedical Sciences; University of Porto	S: Carla Carrilho; Co-S: Lúcio Lara Santos	02/03/2021
Sara Monteiro-Reis	SFRH/BD/112673/2015	Uncovering the role of epigenetic mechanisms in bladder cancer aggressiveness: from biology to clinical setting	Pathology & Molecular Genetics	School of Medicine & Biomedical Sciences; University of Porto	S: Carmen Jerónimo Co-S: Rui Henrique	08/02/2021

**Table 5 – MSc Dissertations completed in 2021 supervised by CI-IPOP’s researchers**

Name	Fellowship	Title	Program	Faculty/University	Supervising team	Date Public defense
Ana Catarina Pinto Azevedo	NA	Clarifying the role of GRPR and ETV1 overexpression in EGFR-mediated JAK/STAT signalling-putative therapeutic targets for prostate carcinomas with ETV1 rearrangements	Oncology	School of Medicine & Biomedical Sciences; University of Porto	S: Paula Paulo; Co-S: Manuel Teixeira	14/12/2021
Eugénio Tobias	NA	Validation of commercial treatment planning algorithm for multiple photon beams and preparation for clinical implementation	Medical Physics	Faculty of Sciences of the University of Porto	S: João Santos	10/12/2021
Patrícia Oliveira Maia	NA	Flow cytometry immunological monitoring of patients with NSCLC undergoing immunotherapy	Biochemistry	University of Aveiro	S: Carlos Palmeira; Co-S: Bruno Neves	09/12/2021
Ana Sofia Oliveira Couto	NA	CT segmentation in the context of Prostate Cancer	Mathematical Engineering	Faculty of Sciences - University of Porto; University of Porto	S: João Santos; Co-S: Inês Domingues	07/12/2021
Joseane Müller	NA	Performance of the clinical pharmacist and reduction of medication-related errors during the treatment of cancer patients at IPOPorto	Oncology	School of Medicine & Biomedical Sciences; University of Porto	S: Maria José Bento;	07/12/2021
Laura Providência	NA	Bone scan lesions uptake quantification for therapy response in metastatic prostate cancer	Medical Physics	Faculty of Sciences of the University of Porto	S: Inês Domigues; Co-S: João Santos	07/12/2021
Andreia Reis Leite	NA	Respiratory Virus Transmission and Prevention Mechanisms	Pharmaceutical Sciences	Faculty of Health Sciences, University Fernando Pessoa	S: Fátima Cerqueira	02/12/2021
José Pedro Sequeira	NA	LiKidMiRs: unveiling the diagnostic potential of liquid biopsy-based circulating microRNAs in renal cell tumors	Oncology	School of Medicine & Biomedical Sciences; University of Porto	S: Carmen Jerónimo; Co-S: Rui Henrique	3/12/2021
Alexandra de Castro e Costa	NA	The role of microRNAs and mast cells infiltration in HPV-induced carcinogenesis: studies in K14-HPV16 transgenic mice	Molecular Medicine and Oncology	Faculty of Medicine; University of Porto	S: Rui Medeiros; Co-S: Rui Gil da Costa	24/11/2021
Tânia Rolo Dias	NA	Identification of dysregulated long non-coding RNAs in HPV-induced carcinogenesis and cancer cachexia	Molecular Medicine and Oncology	Faculty of Medicine; University of Porto	S: Rui Medeiros; Co-S: Rui Gil da Costa	24/11/2021

Nicole Viveiros	NA	Immunoprofiling of Bladder Cancer: Setting the Basis for Novel Immunotherapeutic Strategies	Biochemistry	Faculty of Sciences/School of Medicine & Biomedical Sciences; University of Porto	S: Carmen Jerónimo; Co-S: Bianca Troncarelli Flores	16/11/2021
Manuel Luis da Costa Marques	NA	Artificial Generation of Clothes with Generative Adversarial Networks: Analysis of Hyper-Parameter Performance	Mathematical Engineering	Faculty of Sciences of the University of Porto	J. Costa/I. Domingues	12/11/2021
Tatiana Nunes Varandas	NA	Characterization of CYP2R1 rs2060793 and CYP2R1 rs12794714 Genetic Polymorphisms: Potential Biomarkers in Endometriosis Predisposition	Clinical Analysis and Public Health	Higher School of Health of the Polytechnic of Porto	S: Francisca Dias	20/10/2021
Tiago Peralta Cordeiro	NA	Laboratory Diagnosis of Infection and Determination of Immune Status for SARS-CoV-2	Pharmaceutical Sciences	Faculty of Health Sciences, University Fernando Pessoa	S: Fatima Cerqueira	17/09/2021
Oriana Ribeiro	NA	Prostate Cancer Radiotherapy Resistance: role of epigenetic enzymes	Molecular Biomedicine	University of Aveiro	S: Carmen Jerónimo Co-S: Luisa Helguero	21/7/2021

## II. CLINICAL RESEARCH

### A. PRECISION ONCOLOGY PROGRAM (POP)

As the knowledge about cancer biology evolves and the accessibility to sequencing technologies increases, genome-driven cancer treatment emerges as a valuable strategy. Over the last years, molecular biomarker determination has become standard for specific tumor types, though the widespread and systematic use of genetic profiling remains limited in the routine clinical practice. To effectively translate the molecular profiles into clinical benefit for the patients, the establishment of a multidisciplinary molecular tumor board (MTB) is of outmost importance as the success of a molecular screening program relies on a continuous institutional commitment.

IPO Porto MTB is coordinated by Júlio Oliveira, Medical Oncologist and Clinical Pharmacologist, coordinator of Early Phase Clinical Trials Unit and is composed by José Dinis [Medical Oncology, Coordinator of the Clinical Research Unit (CRU)]; Deolinda Pereira (Medical Oncology, Director of the Medical Oncology Service); José Mário Mariz (Clinical Hematology, Director of the Onco-Hematology Service), Ana Maia Ferreira (Pediatric Oncology, Director of the Pediatric Oncology Service); Lúcio Santos (Surgical Oncology, Coordinator of the Pathology and Experimental Therapy); Manuel Teixeira (Oncogenetics, Coordinator of the Oncogenetics Group); Rui Henrique (Pathology, Senior Researcher of the Epigenetics and Biology of Cancer) and Joana Assis (Junior Researcher, CRU).

The IPO Porto Precision Oncology Program is a tumor type-agnostic prospective observational study to evaluate the feasibility of using molecular profile-based evidence to propose individualized cancer therapy for patients with advanced/refractory rare or hard-to-treat cancers. All eligible and consented patients have their tumor tissue or blood samples profiled by next generation sequencing (NGS). The sequencing results are systematically reviewed and discussed within a multidisciplinary MTB. The MTB provides clinical recommendations and prioritize for the subsequent clinical management. Ultimately, this program identifies patients who may benefit from further targeted therapies when standard-of-care regimens have failed, in addition, to allowing for prompt enrolment into biomarker-driven clinical trials. Indeed, this program complies with the most recent ESMO guidelines that strongly recommend the clinical research centers to perform multigene sequencing as part of their missions to accelerate cancer research and drug development, providing access to innovation to patients and to prospectively collect data that could further inform how to optimize the use of NGS among clinical practice. During 2021, 156 cancer patients were discussed

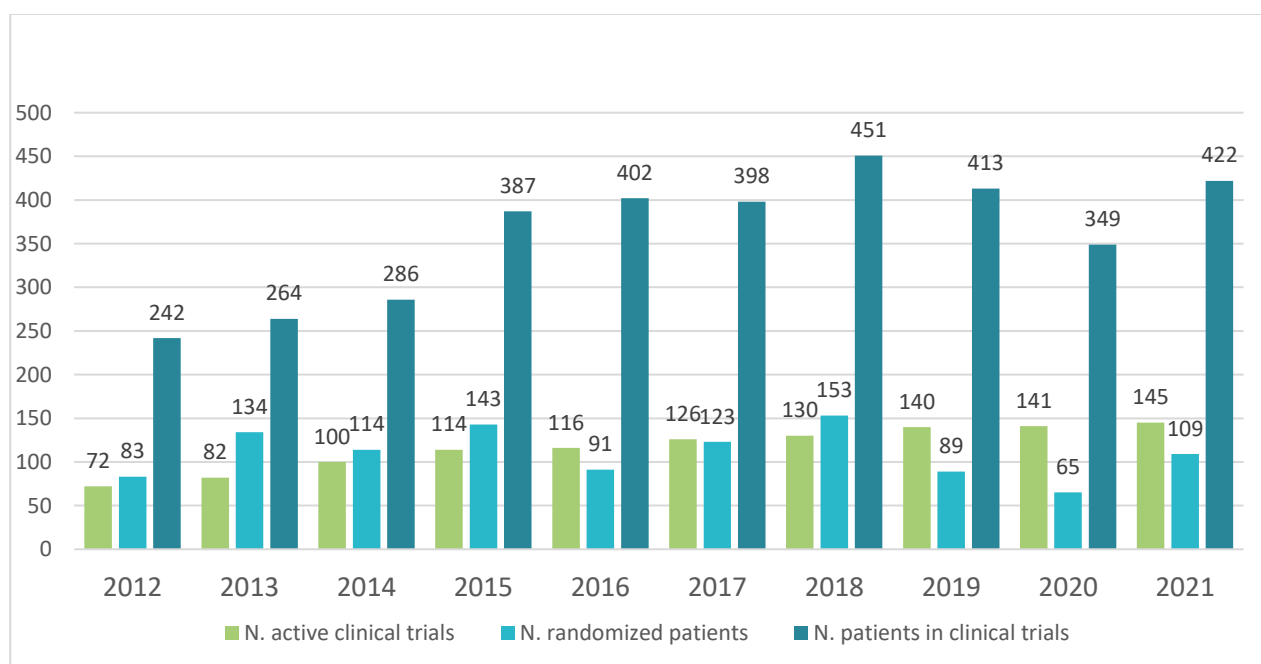
at the MTB, from which those harboring digestive pathology were highest number discussed in the TMB (Table 6).

**Table 6** – Number of patients per tumor type discussed at the Molecular Tumor Board in 2021

Tumor	Number of patients
Breast	12
Central Nervous System	3
Digestive Pathology	27
Endocrine Tumors	22
Gynecology	19
Head and Neck	19
Lung	13
Occult primary	9
Skin, Soft Tissues and Bone	26
Urology	6

### B. CLINICAL TRIALS OVERVIEW

In 2021, 145 clinical trials were active in the Clinical Trials Unit, including a total of 422 patients enrolled and 109 new patients randomized. Although COVID-19 pandemics impacted on Clinical Trials activity, the number of active clinical trials increased (from 141 to 145 comparing with 2020), as well as the number of patients enrolled or randomized (Figure 12).



**Figure 12** – Clinical trials features (number of active clinical trial; number of randomized patients in each year and number of patients on ongoing clinical trials) over the 10 years

Breast cancer patients were the most frequently recruited and for the largest number of active clinical trials, followed by hematological malignancies (Table 3).

In 2021, although most of the clinical trials were late phase, 8 Phase I trials were actively recruiting patients (Table 4). Moreover, an investigator-initiated trial was active in the same year: Neoadjuvant immunotherapy with durvalumab (MEDI4736) in non-surgical early stage or locally advanced non-small cell lung cancer (NSCLC) followed by radical radiotherapy or chemoradiotherapy (CI-IPOP 74/2017 IDEAR, PI: Dr. Júlio Oliveira).

**Table 3** – Number of clinical trials and randomized patients by tumor location

Tumor/Area	N. active clinical trials	N. randomized patients	N. Patients in clinical trials
Digestive	12	6	14
Gynecology	2	1	4
Lung	20	15	40
Oncohematology	30	3	73
Head & Neck	9	17	29
Breast	33	34	173
Urology	12	11	33
Pediatric	5	0	4
Skin, soft tissue & bone	9	8	22
Unknown primary	1	5	6
Intensive Care	0	0	0
Endocrine Tumors	1	0	1
Bone Marrow Transplantation	3	0	2
Interventional Radiology	0	0	0
Immunohemotherapy	0	0	0
Gastroenterology	1	1	1
Multiple Patology/Early Trials	7	8	20
Total	145	109	422

**Table 4** – Number of trials actively recruiting patients and number of patients recruited in 2021

Trial	CTs Recruiting	Recruited patients
Phase I	8	27
Phase II	12	152
Phase ≥III	47	154
Total	67	333

### III. COMPETITIVE FUNDING GRANTED IN 2021

During 2021, IPO Porto's Researchers as PI or CO-PI were able to attain 5 projects funded by FCT and participated in the research team of 3 projects also funded by FCT and one by other funding agency.

#### A. RESEARCH PROJECTS

##### FCT-Call for R&D Projects in All Scientific Domains

##### CI-IPOP's PI/Co-PI

Code	Title	PI	Co-PI	Budget
EXPL/SAU-EPI/1606/2021	The impact of the COVID-19 pandemic on the diagnosis, treatment, and survival of patients with cancer	Samantha Morais Institute of Public Health of the University of Porto (ISPUP/UP)	Luisa Conceição (IPO Porto)	49 538,10 €
PTDC/MED-OUT/2512/2021	RESOLVE: Rational Design of Multivalent Glycocode-Inspired Nanovaccines for Gastric Cancer Immunotherapy	José Alexandre Ferreira (IPO Porto)	Juan José Lasarte University of Aveiro (UA)	249 645,00€
PTDC/BIA-MOL/3986/2021	Sub-Saharan cancer cell line panel: from primary patient-derived cells to population tailored cancer treatment for the African ancestry	Luisa Pereira Institute of Research and Innovation in Health of the University of Porto - (i3S)	Lúcio Lara Santos (IPO Porto)	249 997,50 €
EXPL/BIA-CEL/1225/2021	READOUT-Bridging iRon metabolism and immunE cells at the irrAdiated tumOUR microenvironment to identify novel therapeutic targets in rectal cancer	Tania Cruz Institute of Research and Innovation in Health of the University of Porto (i3S)	Olga Sousa (IPO Porto)	49 977,50€
EXPL/SAU-PUB/1073/2021	New mRNA signatures as risk markers in cancers triggered by tobacco smoking	Isabel Pereira Castro Institute of Research and Innovation in Health of the University of Porto (i3S)	Maria José Bento (IPO Porto)	50 000,00 €

##### CI-IPOP's team members

Code	Title	PI	Co-PI	Budget
PTDC/MEC-ONC/0491/2021	A new frontier in extracellular vesicle-mediated cancer immunomodulation	Celso Reis Institute of Research and Innovation in Health of the University of Porto (i3S)	Joana Neto Gomes Institute of Research and Innovation in Health of the University of Porto (i3S)	248 403,75€
EXPL/MED-ONC/0522/2021	The role of endothelial Nrf2 in the vascular niche remodelling induced by acute myeloid leukemia	Delfim Duarte Institute of Research and Innovation in Health of the University of Porto (i3S)	Laura Mosteo Lopez Institute of Research and Innovation in Health of the University of Porto (i3S)	49 955,00 €
PTDC/BIA-CEL/0456/2021	diffNET- "Restoring differentiation in cancer cells by manipulating RNA-binding protein NETWORKS",	Bruno Pereira Institute of Research and Innovation in Health of the University of Porto (i3S)	Vanessa Mendes Machado Institute of Research and Innovation in Health of the University of Porto (i3S)	249 935,00 €

### Other Funding Agencies

Code/ Agreement	Title	PIs	Funding Agency	Budget
No. 777500	IMI Pain - Prompt - Providing Standardized Consented PROMs (Patient Reported Outcome Measures) for Improving Pain Treatment.	Germano Cardoso (IPO Porto PI) Winfried Meissner (Project Coordinator: Jena University Hospital)	Funding for IMI-PainCare is granted by the Innovative Medicines Initiative 2 Joint Undertaking, Grant Agreement No. 777500	26 750 €

Regarding funding attained for human resources, one Researcher was funded by 4<sup>th</sup> Edition of Scientific Employment Stimulus and a posgraduation student was awarded with a PhD Fellowship.

### FCT-Individual Call to Scientific Employment Stimulus – 4<sup>th</sup> Edition

Code	Title	Researcher	Category
2021.03835.CEECIND	Leveraging multi-omics approaches under a polygenic disease model to identify potential new target biological pathways in early-onset/familial prostate cancer	Andreia Brandão	Junior Researcher

### FCT-PhD Fellowships-Individual Call

Code	Title	Student	Supervisor	Co-Supervisor
2021.06731.BD	EMBRACIVE – A microfluidic assisted technology for non-invasive identification and characterization of plasma extracellular vesicles in bladder cancer patients	Catarina Lourenço	Carmen Jerónimo; (IPO Porto)	Ângela Carvalho; Institute for Research and Innovation in Health (i3S)

#### **IV. RESEARCH GROUPS/UNITS**

CI-IPOP comprises 5 translational research groups (Cancer Biology & Epigenetics; Cancer Genetics; Experimental Pathology & Therapeutics; Medical Physics, Radiobiology & Radiation Protection; and Molecular Oncology & Viral Pathology), two clinical groups (Precancerous Lesions and Early Cancer Management and Clinical Oncology) and two groups devoted to meet the growing needs on epidemiology of cancer, patient outcome and quality of life, as well as value-based healthcare and sustainability (Cancer Epidemiology and Management, Outcomes Research & Economics in Healthcare); along with a Clinical Research Unit, which includes an Early phase clinical trials Unit dedicated to investigator-initiated trials. The activity report of each group, excepting of Precancerous Lesions and Early Cancer Management and Clinical Oncology that were only created in the end of 2021, is presented in the following pages (in alphabetical order), followed by that of the Clinical Research Unit.

## Cancer Biology and Epigenetics Group

### 1. Coordinator

Carmen Jerónimo, PhD

### 2. Research team (as of December 31st 2021)

Name	Academic degree	Professional situation	Category/position	Time %
Ana Beatriz Ferreira Costa	BSc	Student	MSc Student	100
Ana Catarina Macedo Silva	MSc	Fellowship	PhD student 2019-UNA2CLE-0170010	100
Ana Isabel Atanásio Varelas	MD, MSc	Contract	MD Resident in Pathology	5
Ana Fernandes Rodrigues	MD, MSc	Contract	Medical Oncologist; PhD Student	20
Ana Luísa Peixoto da Costa e Cunha	MD, MSc	Contract	MD Junior pathologist	5
Ana Paula Marques Silva Lopes	BSc	Contract	Lab technician	20
Ana Rita Teixeira Marques	BSc	Student	MSc Student	100
Ana Teresa Pinto Teixeira Martins	MSc	Contract	Lab technician	5
Ângelo de Jesus Rodrigues	MD, MSc	Contract	Pathologist	10
António Rui Azevedo Freitas	MD, MSc	Contract	Urologist	10
Bárbara Costa Matos	MSc	Fellowship	PhD Student FCT IBIMED-UA/IPOP-FCT SFRH/BD/146032/2019	20
Bianca Troncarelli-Flores	PhD	Contract	Junior Researcher-PCCC	100
Carina Raquel Carvalho Maia	MSc	Fellowship	Research assistant MindGaP- H2020-FETOPEN	100
Carla Maria Magno Bartosch	PhD	Contract	Pathologist & Junior researcher	20
Carmen De Lurdes Fonseca Jerónimo	Aggregation	Contract	Assistant Researcher; Group coordinator	100
Catarina Sofia Guimarães Teixeira	MSc	Fellowship	PhD Student FCT DFA/BD/6038/2020	100
Catarina Lourenço	MSc	Fellowship	Research assistant MindGaP- H2020-FETOPEN	100
Cláudia Martins Lima	MSc	Fellowship	PhD student 2020-UNA2CLE-0203198	100
Daniela Cristina Barros Silva	MSc	Fellowship	PhD student FCT SFRH/BD/136007/2018	100
Davide Gigliano	MD, MSc	Contract	Resident in Pathology	10
Diana Montezuma Felizardo	MD, MSc	Hired (External)	PhD student	20
Diana Fernandes	MSc	Fellowship	Research Assistant LPCC	100
Fernanda Maria Ferreira da Silva	BSc	Contract	Lab technician	5
Filipa Domingues dos Reis	BSc	Student	MSc Student	100
Filipa Moreira Silva	MSc	Contract	Research Assistant P.C.C.C. NORTE-01-0145-FEDER-072678 - TeamUp4Cancer	100
Gonçalo Outeiro Pinho	MSc	Contract	Research Assistant P.C.C.C. NORTE-01-0145-FEDER-072678 - TeamUp4Cancer	100
Guilherme Machado da Silva	BSc	Student	MSc student	100
Helena Estevão Pereira	MSc	Student	MSc Student	70
Isa Cristiana Silva Carneiro	MSc	Contract	Lab technician	10
Isaac Braga	MD, MSc	Contract	Urologist; PhD Student	20
João Lima Vaz Silva	MD, PhD	Contract	Resident in Pathology	10
João Pedro da Silva Machado Lobo	MD, PhD	Contract	Resident in Pathology; Junior Researcher	100

João Pedro Oliveira Costa	MD, MSc	Contract	Resident in Pathology	10
José Pedro Sequeira	BSc	Student	MSc student	100
Jorge Silvério Torres Ferreira	MSc	Contract	Lab technician	10
Lígia Pires Gonçalves	MD	Contract	Radiologist; PhD Student	20
Margareta Isabel Pereira Correia	PhD	Contract	Assistant researcher CEECINST/00091/2018	100
Maria Miguel Castro	MSc	Fellowship	PhD Student FCT i3S/IPOP-FCT-2020.07439.BD	30
Mariana Cantante Ferreira	BSc	Contract	Lab technician	20
Marta Peixoto	MD, MSc	Hired (External)	Resident in Medical Oncology; PhD Student	20
Miguel Oliveira Morim	BSc	Student	MSc Student	70
Mónica Pires	MD	Contract	Gynecologist; PhD Student	20
Nair Susana C. Florim Ribeiro Lopes	PhD	Contract	Junior researcher UIDP/00776/2020-2	100
Nuno David Monteiro Coimbra	MD, MSc	Contract	Pathologist; PhD student	20
Nuno Tiago Tavares	MSc	Contract	Research Assistant P.C.C.C. NORTE-01-0145-FEDER- 072678 - TeamUp4Cancer	100
Paula Cristina Monteiro	MD	Contract	Pathologist	20
Paula Cristina Monteiro Dias	BSc	Contract	Lab technician	5
Renata Lage Vieira	BSc	Contract	Lab technician	5
Rita Manuela Guimarães	MSc	Contract	Lab technician	10
Rita Patrícia Faria Dias Canário	MSc	Fellowship	PhD student FCT PD/BD/128001/2016	30
Rui Manuel Ferreira Henrique	Aggregation	Contract	MD Senior pathologist; Senior researcher	30
Rui Miguel Silva Santos	MSc	Contract	Lab technician	50
Sandra Isabel Pinto Nunes	MSc	Fellowship	PhD student FCT: SFRH/BD/144241/2019	100
Sara Lopes Petronilho	MD, MSc	Contract	Resident in Pathology	5
Sara Raquel Monteiro dos Reis	PhD	Fellowship INEGI	Invited Researcher	20
Saulê Gumauskaitė	BSc	Student	MSc Student	100
Sérgio Miguel Pereira Chacim	MD, MSc	Contract	Clinical Hematologist; PhD Student	20
Sofia Paupério e Silva Paulino	MSc	Contract	Lab technician	10
Sofia Raquel Fernandes Salta	MSc	Fellowship	PhD student FCT SFRH/BD/143717/2019	100
Tânia Marisa da Costa Lima	MSc	Fellowship	PhD Student FCT IBIMED-UA/IPOP-FCT- SFRH/BD/136904/2018	10
Tiago Brito da Rocha	BSc	Student	MSc Student	100
Vera Inês Salvado Constâncio	MSc	Contract	PhD Student IPOP/FChampalimaud- LCF/BQ/DR20/11790013	100
Vera Miranda-Gonçalves	PhD	Contract	Junior Researcher-PCCC	100
Verónica Martins Ferreira	BSc	Contract	Lab technician	5

### 3. Group description and objectives

The long-term core goal of the Cancer Biology and Epigenetics Group (CBE) is to portray the epigenetic mechanisms involved in the genesis of cancer, with an emphasis on urological tumors, and translate these into clinically useful tools for patient management. More recently, we started tackling the contribution of deregulated non-coding RNAs expression and its interaction with other epigenetic mechanisms that may induce/promote malignant transformation.

Specifically, within the framework of Precision Medicine, we have four major lines of investigation ongoing: (1) Using body fluids - liquid biopsies (plasma or serum) and urine – to detect cell-free tumor-specific epigenetic biomarkers (methylated DNA or noncoding RNA) we aim at developing new cancer biomarkers for screening/ detection and to assist in patient's clinical management. We have identified several putative markers in tissues of the four major human malignancies [those of breast (BrCa) (Salta, doi: 10.3390/jcm7110420; Amorim, doi: 10.3389/fgene.2019.00815), prostate (PCa) (Moreira-Barbosa, doi: 10.1186/s13148-018-0564-2), colorectal (CRC) (Freitas, doi: 10.1186/s12967-018-1415-9) and lung (LCa) Nunes, doi: 10.3390/jcm8091500)] as well in other urological cancers [bladder (BICa) (Padrão, doi: 10.1038/bjc.2016.454, kidney (KCa) ( Pires-Luis, doi: 10.1186/s12967-017-1248-y and testicular germ-cell tumors (TGCT) (Vilela-Salgueiro, doi: 10.1098/rstb.2017.0338; Costa, doi: 10.2217/epi-2018-0034, Lobo doi: 10.3390/cancers11091385)] that are already being tested in body fluids (Estevão-Pereira doi: 10.1186/s12967-019-02193-y.; Nunes, doi: 10.3390/cancers10100357 &, Bidarra & Constâncio, doi: 10.3389/fonc.2019.00900; Constâncio doi: 10.1186/s13148-019-0779-x).

(2) Due to the heterogeneous biology of PCa, only a limited proportion of tumors are deemed to be clinically significant. Because non-coding protein genes / non-coding RNA aberrations, particularly, long non-coding RNAs have been recently implicated in PCa carcinogenesis (Ramalho-Carvalho, doi: 10.1007/s10555-016-9628-y; Barros-Silva, 10.1038/s41419-017-0241-y, Barros-Silva, doi: 10.3390/cancers12040771) we plan to focus our research to better understand their role in molecular pathways associated with PCa aggressiveness, AR and PTEN signaling pathways. Moreover, since long noncoding RNA (lncRNA) are also targeted by internal chemical modifications, such as N6-methyladenosine (m6A), that may impact in various cellular processes, through post-transcriptional regulation of gene expression (Barros-Silva, doi: 10.1080/15476286.2021.1991167) we are attempting to discover their role in PCa onset. The same holds true for other urological tumors, being implicated not only in aggressive features, but also in treatment resistance.

(3) Despite nephrectomy being performed with curative intent, approximately 30% of patients with localized clear cell Renal Cell Carcinoma (ccRCC), develop metastases and die. Thus, we aim to discover Non-coding RNAs (ncRNAs) that might regulate Von Hippel-Lindau Pathway and its implication in metastization. In parallel, we plan to explore the interplay between epigenetics and metabolism in this tumor subtype to unveil new therapeutic targets that may be more effective against advanced stages of this disease (Miranda-Gonçalves, doi: 10.3390/cells9041053).

(4) The potential of epigenetic modulators (e.g., DNA methyltransferase and histone deacetylase inhibitors) for cancer therapy is under investigation, through manipulation of cell lines, characterizing their biological effects and antineoplastic capabilities (Lobo, doi: 10.3390/cancers12102903; Marques-Magalhães, doi: 10.1016/j.biopha.2021.111681). Owing to the relevance that Immuno-oncology has demonstrated in recent years (Lobo doi: 10.3390/cancers11101535), we are also investigating the epigenetic modulation of expression of biomolecules involved in immune checkpoint regulation, aiming at the improvement of immunotherapeutic strategies by combination with epi-drugs.

### 4. Active projects and funding

- ExomiRsBICaMarkers- “Identification of Exosomal-derived miRNAs as non-invasive high-risk BICa biomarkers” (PI-160-CI-IPOP-153-2021), Budget: 10K€ (2021) (PI: Carmen Jerónimo).
- EpiRNAderegInPCa - “Epigenetic regulation of non-coding RNAs in Prostate Cancer” (PI-157-CI-IPOP-121-2019), Budget: 10K€ (2021) (PI: Carmen Jerónimo).
- PCaEXOBone - “Prostate Cancer pre-metastatic niche formation: Exosomal osteotropism” (PI 158-CI-IPOP-151-2021), Budget: 20K€ (2021) (PI: Carmen Jerónimo).

- EpiPaRTy - "Advances in Epigenetic targeting for PCa: Dissecting the interplay between ncRNAs and chromatin remodelers and their role as biomarkers of RadioTherapy resistance" (PI-159-CI-IPOP-152-2021), Budget: 10K€ (2021) (PI: Carmen Jerónimo).
- DNAmCERVIX-"DNA methylation biomarkers for triage of hrHPV positive cases in the Northern Portugal population-based cervical cancer screening program" funded by the Research Centre of Portuguese Oncology Institute (PI 142-CI-IPOP-130-2020), Budget: 15K€ (2020-2021) (PI: Carmen Jerónimo; Co-PI Rui Henrique).
- "Immunoprofiling characterisation of clinical samples by IHC and gene expression analysis and correlation with clinical outcomes in support of translational medicine strategies for ICOS and PD-L1-IC antibody therapeutics. Evaluation of expression of macrophage and dendritic targets across multi-tumour tissue arrays for assessment of clinical relevance.", Kymab Ltd. (Cambridge, UK); Funding: 159K€ (2019-2022) (PI: Prof. Rui Henrique; Co-PI: Carmen Jerónimo)
- "EpiImmunoPCa-"Epigenetic regulation of Immune Response in prostate Cancer" funded by the Research Centre of Portuguese Oncology Institute (PI 143-CI-IPOP-131-2020), Budget: 30K€ (2020-2021) (PI: Carmen Jerónimo; Co-PI Margareta Correia).
- MindGaP-"Bridging the gap between Mind, Brain and Body: Exosome role and monitoring"-H2020-FETOPEN-2018-2020, Budget: 799K€ (2019-2023) (PI: Goreti Sales; Co-PI: Rui Henrique; WP leader: Carmen Jerónimo).
- MCTKidCancer-"Monocarboxylate Transporters (MCTs) in Kidney Cancer: The Role of Epigenetic Mechanisms" (CI-IPOP-98-2018), Budget: 75K€ (2018-2021) (PI: Carmen Jerónimo; Co-PI Vera Miranda-Gonçalves).
- HyTherCaP-"Hydralazine: Testing an off-label effect in Castration-Resistant Prostate Cancer", Funding agency: Fundação para a Ciência e Tecnologia (Technology and Science Foundation)-POCI-01-0145-FEDER-29030, Budget: 196K€ (2018-2021) (PI: Carmen Jerónimo; Co-PI: João F. Mano).
- EpiMarkGermCell-"DEVELOPMENT OF NOVEL PROGNOSTIC AND PREDICTIVE EPIGENETIC BIOMARKERS FOR MALIGNANT TESTICULAR GERM CELL TUMORS", Funding agency: Fundação para a Ciência e Tecnologia (Technology and Science Foundation)-POCI-01-0145-FEDER-29043, Budget: 240K€ (2018-2021) (PI: Rui Henrique; Co-PI: Carmen Jerónimo).
- TRIMARKCHIP-"Assessing the trifecta of cancer circulating biomarkers: a combined microfluidics platform for detection of CTCs, exosomes and ctDNA" IN COLLABORATION with INEB/3S", Funding agency: Fundação para a Ciência e Tecnologia (Technology and Science Foundation) - POCI-01-0145-FEDER-030831, Budget: 41K€ (2018-2021) (PI: Fernando J. Monteiro; Co-PI: Carmen Jerónimo).
- ACCuseD-"ACCuseD renAl Cell Carcinoma Detection Renal Cancer detection: a translational metabolomics research based on Volatile Organic Compounds fingerprinting ", Funding agency: Fundação para a Ciência e Tecnologia (Technology and Science Foundation) - POCI-01-0145-FEDER-030388, Budget 14K€ (2018-2021) (PI: Paula Guedes)
- MehylBiom4Can-"Assessment and validation of a panel of methylation-based Biomarkers in cell free DNA for Detection of recurrent first primary cancer (RFPC) and second primary cancers (SPC)" funded by the Research Centre of Portuguese Oncology Institute (CI-IPOP-74-2016), Budget: 183K€ (2016-2021) PI: Carmen Jerónimo).

##### 5. Major achievements in 2021 (based on the 2 most relevant publication for the group)

- ***Salta, S, Maia-Moco, L, Estevao-Pereira, H, Sequeira, JP, Vieira, R, Bartosch, C, Petronilho, S, Monteiro, P, Sousa, A, Baldaque, I, Rodrigues, J, Sousa, H, Tavares, F, Henrique, R and Jeronimo, C. Performance of DNA methylation-based biomarkers in the cervical cancer screening program of northern Portugal: A feasibility study. Int J Cancer. 2021;149(11):1916-25.; <https://www.ncbi.nlm.nih.gov/pubmed/34460099> (IF: 7.396)***

Cervical cancer remains a health concern. Effective screening programs are critical to reduce the incidence and mortality. High-risk HPV (hr-HPV) testing as primary screening tool discloses high sensitivity but suboptimal specificity. Adequate triage tests to reduce unnecessary colposcopy referrals and overdiagnosis/overtreatment are crucial. Hence, we aimed to validate a panel of DNA methylation-based

markers as triage test for women hr-HPV+ in the population-based Regional Cervical Cancer Screening Program of Northern Portugal. Higher MALme, FAM19A4me and hsa-miR124-2me methylation levels were disclosed in histological HSIL or worse (HSIL+) in testing set. In combination, these markers reached 74% specificity and 61% sensitivity for identification of histological HSIL+. We concluded that host gene methylation might constitute a useful referral triage tool of hr-HPV+ women enrolled in the Cervical Cancer Screening Program of Northern Portugal (doi: 10.1002/ijc.33778).

- **Miranda-Goncalves, V., Lobo, J., Guimaraes-Teixeira, C., Barros-Silva, D., Guimaraes, R., Cantante, M., Braga, I., Mauricio, J., Oing, C., Honecker, F., Nettersheim, D., Looijenga, L.H.J., Henrique, R., and Jeronimo, C.,** *The component of the m(6)A writer complex VIRMA is implicated in aggressive tumor phenotype, DNA damage response and cisplatin resistance in germ cell tumors. J Exp Clin Cancer Res, 2021. 40(1): p. 268.. <https://www.ncbi.nlm.nih.gov/pubmed/34446080> (IF: 11.161)*

Herein, we demonstrated the differential expression of the various m6A writers, readers and erasers in seminomas and non-seminomas representative GCT cell lines, as well as among cells sensitive and resistant to cisplatin treatment. Knockdown of VIRMA led to disruption of the remaining methyltransferase complex and decrease in m6A abundance, as well as overall reduced tumor aggressiveness (with decreased cell viability, tumor cell proliferation, migration, and invasion) and increased sensitivity to cisplatin treatment, both in vitro and confirmed in vivo. Enhanced response to cisplatin after VIRMA knockdown was related to significant increase in DNA damage with higher  $\gamma$ H2AX and lower XLF and MRE11 protein levels, respectively. Hence, we have shown that VIRMA has an oncogenic role in GCTs confirming our previous tissue-based study and is further involved in response to cisplatin by interfering with DNA repair. These data contribute to our better understanding of the emergence of cisplatin resistance in GCTs and support recent attempts to therapeutically target elements of the m6A writer complex (DOI: 10.1186/s13046-021-02072-9).

## 6. Scientific output in 2021

### c. Peer-reviewed indexed publications (final publication date in 2021)

- Adam-Artigues, A., Garrido-Cano, I., Carbonell-Asins, J.A., Lameirinhas, A., Simon, S., Ortega-Morillo, B., Martinez, M.T., Hernando, C., **Constancio, V.**, Burgues, O., Bermejo, B., **Henrique, R.**, Lluch, A., **Jeronimo, C.**, Eroles, P., and Cejalvo, J.M., Identification of a Two-MicroRNA Signature in Plasma as a Novel Biomarker for Very Early Diagnosis of Breast Cancer. *Cancers (Basel)* 13(11) 3112, 2021. [IF: 6.639]
- Adam-Artigues, A., Garrido-Cano, I., Simon, S., Ortega, B., Moragon, S., Lameirinhas, A., **Constancio, V.**, **Salta, S.**, Burgues, O., Bermejo, B., **Henrique, R.**, Lluch, A., **Jeronimo, C.**, Eroles, P., and Cejalvo, J.M., Circulating miR-30b-5p levels in plasma as a novel potential biomarker for early detection of breast cancer. *ESMO Open* 6(1):100039, 2021. [IF: 6.540]
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- **Barros-Silva, D.**, Klavert, J., Jenster, G., **Jeronimo, C.**, Lafontaine, D.L.J., and Martens-Uzunova, E.S., The role of OncoSnoRNAs and Ribosomal RNA 2'-O-methylation in Cancer. *RNA Biol* 18(sup1): 61-74, 2021. [IF: 4.652]
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  - **Carneiro, I.**, **Carvalho, S.**, **Henrique, R.**, Selifonov, A., Oliveira, L., and Tuchin, V.V., Enhanced Ultraviolet Spectroscopy by Optical Clearing for Biomedical Applications. *IEEE Journal of Selected Topics in Quantum Electronics* 27(4):1-8, 2021 [IF: 4.544]
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- **Tavares, M., Chacim, S., and Mariz, J.M.,** Compassionate use of glasdegib in combination with low-dose cytarabine for relapsed, refractory acute myeloid leukemia or high-risk myelodysplastic syndrome. *Ann Hematol.* 100(3):837-839, 2021. [IF: 3.673]

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#### **d. Other outputs**

##### **Book Chapters**

1. Daniela Barros-Silva, Carmen Jerónimo, Elena S. Martens-Uzunova. Deciphering RNA Methylation in Cancer. In book: Epitranscriptomics (2021). DOI: 10.1007/978-3-030-71612-7\_9
2. Vera Miranda-Gonçalves, Catarina Guimarães-Teixeira, Rui Henrique and Carmen Jerónimo. Metabolic regulation in urological tumors: interplay with epigenetics and epitranscriptomics. In book: Epigenetics and Metabolomics (2021). DOI: 10.1016/B978-0-323-85652-2.00019-1
3. Lobo, J., Gillis, A.J.M., and Looijenga, L.H.J., Targeted Methylation Analyses: From Bisulfite Treatment to Quantification. In book: Methods Mol Biol (2021). DOI: 10.1007/978-1-0716-0860-9\_12.

##### **Oral Communications by Invitation**

- Henrique R. Workshop 5: The Role of Pathological Anatomy in Aiding a Therapeutic Strategy in Lung Cancer. Lung Cancer: the patient at the center of immunotherapy (MSD), Lisbon, October 16, 2021. Title: “Immunotherapy Resistance”.
- Henrique R. 18th Congress of the Portuguese Society of Pathological Anatomy and 21st Congress of the Portuguese Society of Cytology, Lisbon, 17-20 November, 2021. Title: “IHC pan-TRK Protocol Implementation: Challenges and Solutions”.
- Henrique R. 18th National Congress of Oncology, 18- 20 November, 2021, Title: “European Plan for the Fight Against Cancer: Strategy for research in health institutions in Portugal” (Clinical Research).
- Jerónimo C. e-EpiMeeting 2021-5th EpiCongress organized by Canceropole Grand-Ouest, (Videoconference) 10-11 May, 2021; Title: “Epigenomics and epitranscriptomics: unravelling urological cancer biology and novel clinical biomarkers”.
- Jerónimo C. II ASPIC-ASEICA International Meeting – Current Trends in Precision Medicine in Cancer, 14-15 October, (Virtual), 2021 Title: “DNA promoter methylation of homologous recombination genes: a predictive biomarker for the responsiveness to PARP inhibitor treatment in testicular germ cell tumors”.
- Monteiro-Reis S. Oncobiology Conferences, FF-UP, 17th December, 2021; Title: “Bladder Cancer: from biology to tumor mechanics.

##### **Oral Communications in International Scientific Meetings**

- Salta S, Maia-Moço L, Estevão-Pereira H, Sequeira JP, Vieira R, Bartosch C, Petronilho S, Monteiro P, Sousa A, Baldaque I, Rodrigues J, Sousa S, Tavares F, Henrique R and Jerónimo C. (2021) Triage of hr-HPV positive women enrolled in cervical cancer screening program: DNA methylation markers as potential tool. The Epigenome in Human Health and Diseases Conference – Autumn school. (18-20th October); Virtual Event
- Miranda-Gonçalves, V.; Lobo, J.; Guimarães-Teixeira, C.; Barros-Silva, D.; Guimarães, R.; Cantante, M.; Braga, I.; Maurício, J.; Oing, C.; Honecker, F.; Nettersheim, D.; Looijenga, L.; Henrique, R.; Jerónimo, C. Unraveling the role of m6A writer complex VIRMA in Germ Cell Tumors progression. EPITRAN Final Conference- COST action (20-21th September) - Virtual Edition

- Margareta P Correia. XVII Congress of the Iberian Society of Cytometry. Speaker in the Session “Flow cytometry in solid tumors” with the lecture “Characterization of intratumoral innate lymphocyte populations” - (14-18th June, 2021); Virtual Edition.

#### **Oral Communications in National Scientific Meetings**

- Lobo J. (2021) Testicular Cancer and Reference Centers – New Biomarkers, What's the future? National Congress of the Portuguese Association of Urology (26-28th November).
- Monteiro-Reis S. (2021) Uncovering the role of epigenetic mechanisms in bladder cancer aggressiveness: from biology to clinical setting. Scientific Meeting of the Research Center/EPOP IPO-Porto (22nd October).
- Sequeira JP, Lobo J, Constâncio V, Carvalho-Maia C, Braga I, Maurício J, Henrique R, Jerónimo C. (2021) DigiMir: pipeline for the quantification of miR-371a in patients with testicular germ cell tumors through PCR digital droplet. 3rd National Meeting of Young Researchers in Oncology (24th September).
- Teixeira-Marques A, Monteiro-Reis S, Constâncio V, Sequeira JP, Felizardo D, Carvalho-Maia C, Freitas R, Vasconcelos MH, Henrique R, Jerónimo C. (2021) Urinary Extracellular Vesicles: A comparison between isolation methods. First Meeting of the Portuguese Network on Extracellular Vesicles (PNEV) (13-14th September).
- Monteiro-Reis S. (2021) Uncovering the role of epigenetic mechanisms in bladder cancer aggressiveness: from biology to clinical setting. 20th “Tele-Meeting in Biomechanics” (INEGI) (18th June).
- Sequeira JP, Lobo J, Constâncio V, Carvalho-Maia C, Braga I, Maurício J, Henrique R, Jerónimo C. (2021) ddPCR pipeline optimization for liquid biopsy based miRNA detection in a clinical context. IJUP-14th Youth Research Meeting of the University of Porto (5-7th May).
- Sequeira JP, Constâncio V, Lobo J, Henrique R, Jerónimo C. (2021) KidLBmiRs: Kidney Tumors' subtyping characterization using microRNAs based Liquid biopsies. 5th Symposium of the MSc in Oncology, ICBAS-IPO (22-23rd February).
- Lobo J. (2021) The heterogeneity of Prostate Cancer: morphology, genetics and epigenetics. Clinical Sessions: Genetic Considerations in Urologic Tumors – Prostate Cancer (23rd February).

#### **Posters in international conferences**

- Sequeira JP, Lobo J, Constâncio V, Carvalho-Maia C, Braga I, Maurício J, Henrique R, Jerónimo C. (2021), ddPCR: liquid biopsy-based miRNA detection concept in a clinical context. 16th YES Meeting (16-19th September).
- Macedo-Silva C, Ribeiro O, Correia MP, Lencarte J, Silva S, Santos J, Benedetti R, Altucci L, Jerónimo C. (2021) Tackling the interplay between epigenetic and DNA damage repair in radioresistant PCa. II ASPIC-ASEICA International Meeting - Current Trends of Precision Medicine in Cancer (14-15th October).
- Moreira-Silva F, Outeiro-Pinho G, Lobo J, Guimarães R, Gaspar VM, Mano JF, Agirre X, Prosper F, Paramio JM, Henrique R, Correia MP, Jerónimo C. (2021) G9a inhibition by CM-272: a novel epigenetic target-based strategy for Castration-resistant Prostate Cancer. II ASPIC-ASEICA International Meeting - Current Trends of Precision Medicine in Cancer (14-15th October).
- Outeiro-Pinho G, Moreira-Silva G, Barros-Silva D, Lobo J, Carneiro I, Morais A, Gonçalves CS, Costa BM, Correia MP, Henrique R, Jerónimo C. (2021). MiR-30 family-TWF1 axis in ccRCC progression. II ASPIC-ASEICA International Meeting - Current Trends of Precision Medicine in Cancer (14-15th October).
- Macedo-Silva C, Ribeiro O, Lencarte J, Silva S, Santos J, Benedetti R, Altucci L, Jerónimo C. (2021) Prostate cancer radioresistance mediated by chromatin openness: the critical role of histone post-translational modifications. 27th Porto Cancer Meeting, Stemness & Metastasis: Advances in Research and Clinical Translation (20-21st May).

- Moreira-Silva F, Agirre X, Morais A, Henrique R, Correia MP, Jerónimo C. (2021) 2D versus 3D Models: effect of CM-272 on Prostate Cancer Cell Lines. 27th Porto Cancer Meeting, Stemness & Metastasis: Advances in Research and Clinical Translation (20-21st May).
- Garrido-Cano I, Adam-Artigues A, Lameirinhas A, Pattanayak B, Tormo E, Miranda-Gonçalves V, Macedo-Silva C, Rojo F, Zazo S, Madoz-Gúrpide J, Burgués O, Hernando C, Martínez MT, Moragón S, Bermejo B, Llich A, Jerónimo C, Eroles P, Cejalvo JM. (2021) MiR-503-5p induces doxorubicin resistance in Triple-Negative Breast Cancer. ASCO Annual Meeting (4-8th June).
- Sequeira JP, Constâncio V, Salta S, Brito-Rocha T, Carvalho-Maia C, Braga I, Henrique R, Jerónimo C. (2021), KidLBMiRs: unveiling the diagnosis world of circulating microRNAs in renal cell tumors based liquid biopsies by ddPCR. II ASPIC-ASEICA International Meeting - Current Trends of Precision Medicine in Cancer (14-15th October).
- Salta S, Maia-Moço L, Estevão-Pereira H, Sequeira JP, Vieira R, Bartosch C, Petronilho S, Monteiro P, Sousa A, Baldaque I, Rodrigues J, Sousa S, Tavares F, Henrique R and Jerónimo C. (2021) "DNA methylation markers as potential tool for colposcopy referral in hr-HPV positive women enrolled in cervical cancer screening program". II ASPIC-ASEICA International Meeting - Current Trends in Precision Medicine in Cancer, Virtual event (14-15th October).
- Miranda-Gonçalves V, Lobo J, Guimarães-Teixeira C, Barros-Silva D, Guimarães R, Cantante M, Braga I, Maurício J, Oing C, Honecker F, Nettersheim D, Looijenga L, Henrique R, Jerónimo C. (2021) The role of m6A methyltransferase VIRMA in the aggressiveness and cisplatin response of testicular germ cell tumors II ASPIC-ASEICA International Meeting – Current Trends in Precision Medicine in Cancer (14-15th October).

**Editorial Board Positions**

Journal	Publishing Company	Position	Researcher
Epigenomes	MDPI	Associate Editor	Carmen Jerónimo
International Journal of Molecular Sciences	MDPI	Associate Editor	Carmen Jerónimo
International journal of Molecular Sciences	MDPI	Section of Molecular Genetics and Genomics	Rui Henrique
Clinical Epigenetics	BMC-Springer Nature	Section Editor: Cancer epigenetics & diagnostics	Carmen Jerónimo
Tumori Journal	Public Library of Science	International Editorial Board Member	Carmen Jerónimo; Rui Henrique
Frontiers in Genetics	Frontiers	Associate Editor of Section of Epigenomics and Epigenetics	Rui Henrique
Frontiers in Cell and Developmental Biology	Frontiers	Associate Editor of Section of Epigenomics and Epigenetics	Rui Henrique
Plos ONE	Public Library of Science	Associate Editor	Rui Henrique
CANCERS	MDPI	GUEST EDITOR: "Germ Cell Tumors" <a href="http://www.mdpi.com/journal/cancers/special_issues/germ_testicular">www.mdpi.com/journal/cancers/special_issues/germ_testicular</a>	Carmen Jerónimo; Rui Henrique

**Peer Review**

British Journal of Cancer; Cancer Letters; Cancers; Cancer Communications; Cells; Clinical Chemistry; Clinical Epigenetics; EBiomedicine; Epigenetics; Epigenomics; European Urology; FEBS Open Bio; Frontiers in Genetics; Frontiers in Oncology; Histology & Histopathology; International Journal of Cancer; International Journal of Molecular Sciences; Journal of Experimental & Clinical Cancer Research; Journal of Urology; Human Pathology; Mol Cancer; Mol Oncology; Nature Reviews in Urology; Neoplasia; PLOS One; Prostate; Therapeutic Advances in Medical Oncology; Theranostics; Virchows Archiv, etc.,

**Grant Reviewer**

Agency	Call	Country	Date	Researcher
Call 8 DIM ELICIT	Technologies for Life Sciences	France	2021	Carmen Jerónimo
Dutch Cancer Society (KWF)	Research Project Evaluation for Funding	The Netherlands	2021	Rui Henrique
Fund for Scientific Research-FNRS	Bourses et Mandats/Grants and Fellowships	Belgium	2021	Carmen Jerónimo
Fund of the Mayor of the City of Vienna/Viennese Fund for Cancer Research	Research Project Evaluation	Austria	2021	Rui Henrique
Prostate Cancer Research of United Kingdom	Posdoctoral Fellowship	United Kingdom	2021	Carmen Jerónimo
Swiss National Science Foundation (SNSF) & Swiss Innovation Agency (Innosuisse)	Research Project Evaluation- BRIDGE Discovery	Switzerland	2021	Rui Henrique
The Wellcome trust/DBT India Alliance Fellowship	The Wellcome Trust DBT India Alliance Fellowship	India	2021	Carmen Jerónimo

**Participation as Opponent in MSc Evaluation Committees**

Student	Title	Program	Researcher
João Munhoz Ferreira	Impact of ERβ in crosstalk between immune cells and colorectal cancer cells	MSc in Oncology; ICBAS-UP	Margareta Correia
Patricia Fontão	Embryonic T-box transcription factor Brachyury as a predictive biomarker and therapeutic target in prostate and lung cancer	Master's in applied Biochemistry School of Sciences-University of Minho	Vera Miranda Gonçalves

**Participation as Opponent in PhD/ Aggregation Evaluation Committees**

Student	Title	Program	Researcher
Antonella Riccardi	Undifferentiated Connective Tissue Disease at risk for Systemic Sclerosis: development of a predictive score and a risk stratification tool	PhD in Translational Medicine; European Degree, School in Life Sciences, Università degli studi della Campania "Luigi Vanvitelli", Italy	Carmen Jerónimo
Bernadette Lauensteine	Multiples Roles of AXL Receptor Tyrosine Kinase in Colorectal Cancer Development	PhD in Translational Medicine; European Degree, School in Life Sciences, Università degli studi della Campania "Luigi Vanvitelli", Italy	Carmen Jerónimo
Giulia Martini	RAS mutant allele fraction in plasma predicts response to anti-angiogenic based first line treatment in metastatic colorectal cancer	PhD in Translational Medicine; European Degree, School in Life Sciences, Università degli studi della Campania "Luigi Vanvitelli", Italy	Carmen Jerónimo
Nunzia Matrone	Mechanism of Resistance to EGFR-targeted therapies	PhD in Translational Medicine; European Degree, School in Life Sciences, Università degli studi della Campania "Luigi Vanvitelli", Italy	Carmen Jerónimo
Ricardo José David Costa Vieira	Lesson: Surgical Treatment of Melanoma	Aggregation Health Sciences, Medicine; Faculty of Medicine, University of Coimbra	Rui Henrique

**Participation in academic recruitment Committees**

Call/Jury	Researcher
School of Medicine, University of Minho 2021 Call for the recruitment of Assistant Researcher, in the scientific area of Health Sciences of the Institute for Research in Life and Health Sciences (1 job) Appointment: Public Notice No. 239/2021, published in Diário da República, 2nd series, No. 39, of February 25, 2021	Rui Henrique

**Teaching Activity: Coordination of Curricular Units/Courses**

Member	Curricular Units	Programme	Position	Faculty/University
Carmen Jerónimo	Laboratory Oncology, Project – Research Seminars, Epigenetics	MSc in Oncology	Director, Coordination and teaching	ICBAS; UP
Rui Henrique	Pathology I, Pathology II, Anatomic Pathology	Integrated MSc in Medicine	Coordination and teaching	ICBAS; UP
Carmen Jerónimo	Research Methodologies in Biopathology	Integrated MSc in Medicine	Coordination and teaching	ICBAS; UP
Rui Henrique	Biopathology I, Biopathology II	Integrated MSc in Dental Medicine	Coordination and teaching	FMD; UP

Rui Henrique	Oncobiology	MSc in Biochemistry	Coordination and teaching	FC/ICBAS; UP
Carmen Jerónimo	Oncobiology	MSc in Bioengineering	Coordination and teaching	FEUP/ICBAS
Rui Henrique	Pathological Oncology	MSc in Oncology	Coordination and teaching	ICBAS; UP
Carmen Jerónimo	Epigenetics and Cancer I,	MSc in Molecular Medicine and Oncology	Coordination and teaching	ICBAS/FMUP
Carmen Jerónimo	Epigenetics and Cancer II	PhD Programme in Molecular Medicine and Oncology	Coordination and teaching	FMUP
Carmen Jerónimo	Techniques in Molecular Biology, Epigenetic Mechanisms in Oncology	PhD Programme in Pathology and Molecular Genetics	Coordination and teaching	ICBAS/FMUP
Carmen Jerónimo	Pathology I Pathology II	Integrated MSc in Medicine	Teaching	ICBAS; UP
Carmen Jerónimo	Biopathology I, Biopathology II	Integrated MSc in Dental Medicine	Teaching	FMD; UP
Carmen Jerónimo	Oncobiology	MSc in Biochemistry	Teaching	FC/ICBAS; UP
Carmen Jerónimo	Oncobiology	MSc in Bioengineering	Teaching	FEUP/ICBAS

#### International Internships

Period	Researcher/student	Position/Programme	Country
August-September	Romina Silva	PhD student in Translational Medicine Conway Institute of Biomolecular and Biomedical Research	Dublin, Ireland

#### Prizes, Honors and Awards

Researcher	Prize designation	Foundation/ Company	Date	Amount
Diana Fernandes	LPPC-NRN fellowship	Portuguese League Against Cancer- North region	January 2021	12000€
João Lobo	Rui Osório de Castro/Millennium bcp	Rui Osório de Castro Foundation	January 2021	15.000€
João Lobo	Life 2021 Young Investigator Award	Life	December 2021	1000 CHF

#### Scientific Appointments

Organization	Researcher
Board member of EAU Section of Urological Research (ESUR)	Carmen Jerónimo
European Network Individualized Treatment Endometrial Cancer (ENITEC)	Carla Bartosch
European Organization of Cancer Institutes (OECI): Member of Biobanks and Pathobiology Working Group	Rui Henrique
European Society of Pathology (ESP): Member of the Molecular Pathology and Uropathology Working Groups	Rui Henrique
Member of the European Network of Urologic Pathology - ENUP	Rui Henrique
National Academy of Medicine of Portugal, Full Academic	Rui Henrique

**National collaborations**

Title	Researchers	Collaborators	Funding	Period
Stemness and metabolic plasticity in hereditary-breast cancer PhD Project; Rita Canário	Carla Bartosch, Carmen Jerónimo	Joana Paredes (Epithelial Interactions in Cancer) IPATIMUP/i3S	FCT: PD/BD/128001 /2016	2017-2022
Development of a diagnosis device for the management of Prostate Cancer through urine analysis” PhD Project; Tânia Marisa da Costa Lima	Rui Henrique, Carmen Jerónimo	Margarida Fardilha; Biochemistry, Univ. of Aveiro	FCT: SFRH/BD/1369 04/2018	2019-2022
Epitranscriptomics in gastric cancer: characterization of YTHDF3 Function; PhD Project; Catarina de Oliveira	Carmen Jerónimo, Daniela Barros-Silva	Raquel Almeida (Differentiation & Cancer) IPATIMUP/i3S	SFRH/BD/1457 12/2019	2020-2024
Reprogram-Reconstructing the Program of Cancer Stem Cells	Carmen Jerónimo, Rui Henrique	Raquel Almeida (Differentiation & Cancer) IPATIMUP/i3S	POCI-01-0145-FEDER-029017	2018-2021
TRIMARKCHIP-Assessing the trifecta of cancer circulating biomarkers: a combined microfluidics platform for detection of CTCs, exosomes and ctDNA.	Carmen Jerónimo, Catarina Guimarães Teixeira	Fernando J. Monteiro (Biocomposites ) INEB/i3S	POCI-01-0145-FEDER-030831	2018-2021
HyTherCaP-Hydralazine: Testing an off-label effect in Castration-Resistant Prostate Cancer	Carmen Jerónimo	João F. Mano University of Aveiro	POCI-01-0145-FEDER-29030	2018-2021
ACCuseD- renal Cell Carcinoma Detection Renal Cancer detection: a translational metabolomics research based on Volatile Organic Compounds fingerprinting	Carmen Jerónimo, Rui Henrique, Carina Carvalho-Maia,	Paula Guedes REQUIMTE, FF-UP	POCI-01-0145-FEDER-030388	2018-2021
MindGaP-Bridging the gap between Mind, Brain and Body: Exosome role and monitoring	Rui Henrique, Carmen Jerónimo; Carina Carvalho-Maia, Sara Monteiro-Reis Catarina Lourenço	Goreti Sales; University of Coimbra	H2020-FETOPEN-2018-2020	2019-2023
Developing a new approach for PCa treatment: modulation of phosphoprotein phosphatase 1 complexes using bioportides; PhD Project; Bárbara Costa Matos	Carmen Jerónimo, Catarina Macedo-Silva	Margarida Fardilha; Biochemistry, Univ. of Aveiro	FCT: SFRH/BD/1460 32/2019	2020-2024
The role of cell-cell adhesion in the survival of inflammatory breast cancer tumor emboli; PhD Project; Maria Miguel Menezes de Castro	Carmen Jerónimo, Nuno Coimbra, Carina Carvalho-Maia,	Joana Paredes, (Epithelial Interactions in Cancer) IPATIMUP/i3S	FCT: 2020.07439.BD	2021-2024
Identification of EVs-derived miRNAs as non-invasive high-risk BICa biomarkers EXOmIRsBICaMark	Carmen Jerónimo, Rui Henrique, Ana Rita Teixeira-Marques, Diana Montezuma, Rui Freitas	Helena Vasconcelos, Ricardo Ribeiro	Porto.CCC Beacons	2021-2022

**International collaborations**

Title	Researchers	International Team	Institute	Country	Funding
EpiMarkGermCell- Development of novel prognostic and predictive epigenetic biomarkers for malignant testicular germ cell tumors; PhD Project; João Lobo	Rui Henrique, Carmen Jerónimo	Leendert H. J. Looijenga,	Princess Máxima Center for Pediatric Oncology,	The Netherlands	FCT: SFRH/BD/132 751/2017
Epigenetic regulation of non-coding RNAs in Prostate Cancer; PhD Project; Daniela Barros-Silva	Carmen Jerónimo, Rui Henrique	Elena S Martens-Uzunova	ERASMUS MC	The Netherlands	FCT: SFRH/BD/136 007/2018
Advances in epigenetic targeting to prostate cancer tumors: Chromatin remodelers profiling as prognostic tools and radioresistance biomarkers PhD Project; Ana Catarina Macedo-Silva	Carmen Jerónimo, Rui Henrique, Margareta P. Correia,	Lucia Altucci, Rosaria Benedetti	Università Luigi Vanvitelli	Italy	2019-UNA2CLE-0170010
MindGaP-Bridging the gap between Mind, Brain and Body: Exosome role and monitoring	Rui Henrique, Carmen Jerónimo; Carina Carvalho-Maia, Sara Monteiro-Reis Catarina Lourenço	Seppo Vainio, Ian Nicholls, Jussi Hiltunen,	Univ.OULU, Linaeus Univ. Technical Research Center	Sweden, Finland	H2020-FETOPEN-2018-2020
Bladder Cancer: Tackling Epigenetic Players and Imuno-Oncology; PhD Project; Sandra P. Nunes	Carmen Jerónimo, Rui Henrique, Margareta P. Correia,	Jesús M. Paramio	CIEMAT Hospital 12 Octubre	Spain	FCT: SFRH/BD/144 241/2019
The tumor microenvironment impact in epithelial-mesenchymal transition: understanding the non-muscle to muscle-invasive bladder cancer progression; PhD Project; Cláudia Martins de Lima	Margareta P. Correia, Carmen Jerónimo	Rosaria Benedetti Lucia Altucci,	Università Luigi Vanvitelli	Italy	2020-UNA2CLE-0203198

**International Consortia**

Organization	Researcher
MC Substitute-COST ACTION INTERNATIONAL NUCLEOME CONSORTIUM-CA18127-INC	Carmen Jerónimo
International Bladder Cancer Network	Carmen Jerónimo

## Cancer Epidemiology Group

### 1. Coordinator

Maria José Bento, MD, PhD

### 2. Research team (as of December 31<sup>st</sup> 2021)

Name	Academic degree	Professional situation	Category/Position	Time %
Ana Filipa dos Santos Gonçalves	PhD	Contract	Higher technician	30
Catarina Sofia Aluai Cunha	MSc	Fellowship	Research assistant	100
Jéssica Rocha Rodrigues	MSc	Fellowship	Research fellowship FCT-PhD	100
Juliana dos Santos Engel	MSc	Fellowship	Research assistant	100
Maria José Afonso Teodósio Bento	PhD	Contract	MD Senior P. Health Physician	30
Maria Teresa Pegado Barroso Abilheira Monjardino	PhD	Contract	Junior researcher	100
Marta Daniela Marques Magalhães	MSc	Fellowship	Research assistant	100
Pedro Nuno Leite Silva	MSc	Contract	Higher technician	30
Rita Isabel da Silva Calisto	MSc	Contract	Higher technician	30

### 3. Group description and objectives

The aims of this group are epidemiological research related to cancer etiology in priority areas, such as tobacco consumption and socio-economical level, as well as clinical epidemiological research related with predictive and prognostic factors of survival in cancer patients.

The research activity encompasses two main levels: population level (Northern Region of Portugal) and hospital level (IPO Porto). The use of advanced statistical methods is allowing to deepen our knowledge about the epidemiology of cancer, namely the geographical distribution of incidence, the influence of the socio-economical level, the projection of the evolution of incidence, and the evaluation of the impact of the disease in the population through quantification of disease burden. Another aim is the evaluation of costs by disease staging.

### 4. Active projects and funding

- Clinical characteristics, treatment patterns, and outcomes of Lenalidomide-refractory Multiple Myeloma patients in real-world settings: a multi-center retrospective cohort study.
- Cost-effectiveness study of neoadjuvant pertuzumab therapy for breast cancer treatment.
  - EU Breast Cancer Evidence Platform.
- European Oncology Evidence Network (E-OEN):
- Evaluation of the cost of treatment and its aggressiveness among oncology patients at end-of-life.
- German Cancer Research Center - Comparative analysis of the distribution and time trends of colorectal cancer incidence, mode of detection, stage at diagnosis, and survival rates: an international population-based study.
  - I-O Optimise initiative (Lung Cancer).
- IPOscore – predicting the risk of surgical treatment complications and defining prognosis in cancer patients by integrating clinical and biopathological data.
- Mieloma Múltiplo – Integração precoce dos Cuidados Paliativos na melhoria da qualidade de vida dos doentes.
- ODISSEIA (Oncology Disease Information System); Fundo Social Europeu (FSE); 2.291.315,67€
- Participant in the project “Impacto da pandemia COVID-19 nos cuidados prestados a doentes oncológicos”. Research 4 Covid-19 – FCT; 22 020,00€
  - Real world evidence in Epithelial Ovarian Cancer. A retrospective multi-centre cohort study.

- Real-world response/survival and treatment patterns among patients with relapsed/refractory indolent Non-Hodgkin Lymphoma in USA, UK, France, Spain and Portugal oncology practices;
- Risco e sobrevivência de segundos tumores primários relacionados com câncros da mama, endométrio, ovário e colo do útero.
- RISK - New mRNA signatures as risk markers in cancers triggered by tobacco smoking, Budget: 50.000€ (2021-2022) (co-PI: Maria José Bento)
- Risk, survival rates and healthcare resources use on second primary tumors related to female breast cancer, prostate cancer, colorectal cancer, lung cancer and thyroid cancer.

#### 5. Major achievements in 2021 (based on the 2 most relevant publication for the group)

Cardoso R, Guo F, Heisse T, Hackl M, Ihle P, De Schutter H, Van Damme N, Valerianova Z, Atanasov T, Májek O, Mužík J, Christina Nilbert M, Tybjerg AJ, Innos K, Mägi M, Malila N, Bouvier AM, Bouvier V, Launoy G, Woronoff AS, Cariou M, Robaszkiewicz M, Delafosse P, Poncet F, Katalinic A, Walsh PM, Senore C, Rosso S, Vincerževskienė I, Lemmens VEPP, Elferink MAG, Johannesen TB, Kørner H, Pfeffer F, Bento MJ, Rodrigues J, Costa FA, Miranda A, Zadnik V, Žagar T, Marques ALM, Marcos-Gragera R, Puigdemont M, Galceran J, Carulla M, Chirlaque MD, Ballesta M, Sundquist K, Sundquist J, Weber M, Jordan A, Herrmann C, Mousavi M, Ryzhov A, Hoffmeister M, Brenner H: **Divergent trends in colorectal cancer incidence, mortality, and stage distribution in European countries in the colorectal cancer screening era: an international population-based study.** *The Lancet Oncology.* 2021; 22(7): 1002-1013. (Impact factor: 33.752) <https://pubmed.ncbi.nlm.nih.gov/34048685/>

Libânio D, Rodrigues J, Bento MJ, Ebigbo A, Messmann H, Verhoeven RHA, Van Damme N, Bisschops R, Spaander M, Dinis-Ribeiro M. **Gastric cancer incidence and mortality trends between 2007-2016 in three European countries.** *Endoscopy;* 2021. Online ahead of print. (Impact factor: 10.093) <https://pubmed.ncbi.nlm.nih.gov/34666399/>

#### 6. Scientific output in 2021

##### a. Peer-reviewed indexed publications (final publication date in 2021)

- **Antunes, L., Mendonca, D., Bento, M.J., Njagi, E.N., Belot, A., and Rachet, B., Dealing with missing information on covariates for excess mortality hazard regression models - Making the imputation model compatible with the substantive model. *Stat Methods Med Res.* 30(10):2256-2268, 2021. [IF: 3.021]**
- Barreira, D.F., Lourenco, R.A., **Calisto, R.,** Moreira-Goncalves, D., **Santos, L.L.,** and Videira, P.A., Assessment of the Safety and Therapeutic Benefits of Convalescent Plasma in COVID-19 Treatment: A Systematic Review and Meta-Analysis. *Front Med (Lausanne),* 8:660688, 2021. [IF: 5.091]
- **Borges, A., Pereira, F., Redondo, P., Antunes, L., Vieira, C., Antunes, P., Bento, M.J., Sousa, S., Lopes, J.M., Rocha-Goncalves, F., de Sousa, J.A., Pereira, D.S., and Borges, M., The addition of neoadjuvant pertuzumab for the treatment of HER2+ breast cancer: a cost estimate with real-world data. *Health Econ Rev* 11(1):33, 2021 [IF: 2.306]**
- Bouvier, A.M., Jooste, V., Sanchez-Perez, M.J., **Bento, M.J., Rocha Rodrigues, J.,** Marcos-Gragera, R., Carmona-Garcia, M.C., Luque-Fernandez, M.A., Minicozzi, P., Bouvier, V., Innos, K., Sant, M., and Working Group on, C., Differences in the management and survival of metastatic colorectal cancer in Europe. A population-based study. *Dig Liver Dis.* 53(5):639-645, 2021. [IF: 4.088]
- Cardoso, R., Guo, F., Heisser, T., Hackl, M., Ihle, P., De Schutter, H., Van Damme, N., Valerianova, Z., Atanasov, T., Majek, O., Muzik, J., Nilbert, M.C., Tybjerg, A.J., Innos, K., Magi, M., Malila, N., Bouvier, A.M., Bouvier, V., Launoy, G., Woronoff, A.S., Cariou, M., Robaszkiewicz, M., Delafosse, P., Poncet, F., Katalinic, A., Walsh, P.M., Senore, C., Rosso, S., Vincerzevskiene, I., Lemmens, V., Elferink, M.A.G., Johannesen, T.B., Korner, H., Pfeffer, F., **Bento, M.J., Rodrigues, J.,** Alves da Costa, F., Miranda, A., Zadnik, V., Zagar, T., Lopez de Munain Marques, A., Marcos-Gragera, R., Puigdemont, M., Galceran, J., Carulla, M., Chirlaque, M.D., Ballesta, M., Sundquist, K., Sundquist, J., Weber, M., Jordan, A., Herrmann, C., Mousavi, M., Ryzhov, A., Hoffmeister, M., and Brenner, H., Colorectal cancer incidence, mortality, and stage distribution in European countries in the colorectal cancer screening era: an international population-based study. *Lancet Oncol* 22(7): 1002-1013, 2021. [IF: 41.316]

- Girardi, F., Rous, B., Stiller, C.A., Gatta, G., Fersht, N., Storm, H.H., **Rodrigues, J.R.**, Herrmann, C., Marcos-Gragera, R., Peris-Bonet, R., Valkov, M., Weir, H.K., Woods, R.R., You, H., Cueva, P.A., De, P., Di Carlo, V., Johannesen, T.B., Lima, C.A., Lynch, C.F., Coleman, M.P., Allemani, C., and Group, C.W., The histology of brain tumors for 67 331 children and 671 085 adults diagnosed in 60 countries during 2000-2014: a global, population-based study (CONCORD-3). *Neuro Oncol* 23(10): 1765-1776, 2021. [IF: 12.300]
- **Guimaraes-Teixeira, C., Barros-Silva, D., Lobo, J., Soares-Fernandes, D., Constancio, V., Leite-Silva, P., Silva-Santos, R., Braga, I., Henrique, R., Miranda-Goncalves, V., and Jeronimo, C.**, Deregulation of N6-Methyladenosine RNA Modification and Its Erasers FTO/ALKBH5 among the Main Renal Cell Tumor Subtypes. *J Pers Med*, 2021. 11(10) [IF: 4.945]
- Morais, A., Simao, M., Cossa, M., Come, J., Selemene, C., Tivane, A., Tulsidas, S., Lorenzoni, C., **Rodrigues, J., Antunes, L., Brito, D.**, Costa, M.J., Sidat, M., Martins, M., and **Santos, L.L.**, Designing a National Curriculum to Advance Surgical Oncology in Mozambique: A Delphi Consensus Study. *J Surg Educ*. 78(1):140-147, 2021. [IF: 2.891]
- Morais, S., **Antunes, L., Rodrigues, J., Fontes, F., Bento, M.J.**, and Lunet, N., The impact of the COVID-19 pandemic on the short-term survival of patients with cancer in Northern Portugal. *Int J Cancer* 149(2) 287-296, 2021. [IF: 7.396]
- **Ribeiro, T., Marques, A., Ferreira, G., Castro, C., Tavares, M., Espírito-Santo, A., Moreira, C., and Mariz, J.**, El análisis semicuantitativo de la PET con [18F]FDG interim es superior para predecir la evolución en los pacientes con linfoma de Hodgkin en comparación con el análisis visual. *Revista Española de Medicina Nuclear e Imagen Molecular* 40(5):281-286, 2021 [IF: 1.359]
- **Salta, S., Maia-Moco, L., Estevo-Pereira, H., Sequeira, J.P., Vieira, R., Bartosch, C., Petronilho, S., Monteiro, P., Sousa, A., Baldaque, I., Rodrigues, J., Sousa, H., Tavares, F., Henrique, R., and Jeronimo, C.**, Performance of DNA methylation-based biomarkers in the cervical cancer screening program of northern Portugal: A feasibility study. *Int J Cancer*149(11)1916-1925, 2021 [IF: 7.396]
- Selemene, C., Jamisse, L., Arroz, J., Tulsidas, S., Morais, A.G., Carrilho, C., Modcoicar, P., Sidat, M., **Rodrigues, J., Moreira-Goncalves, D.**, Ismail, M., and **Santos, L.L.**, Demographic, clinical and pathological characterisation of patients with colorectal and anal cancer followed between 2013 and 2016 at Maputo Central Hospital, Mozambique. *Ecancermedicalscience*. 15:1205, 2021. [IF: NA]
- **Soares, M., Antunes, L., Redondo, P., Borges, M.**, Grimson, F., Hermans, R., Chaib, C., Lacoïn, L., Juarez-Garcia, A., Daumont, M.J., Penrod, J.R., **Bento, M.J.**, and Goncalves, F.R., Small cell lung cancer treatment and survival in Portugal: A retrospective analysis from the I-O Optimise initiative. *Eur J Cancer Care (Engl)*, 30(6):e13496, 2021 [IF: 2.520]
- **Soares, M., Antunes, L., Redondo, P., Borges, M.**, Hermans, R., Patel, D., Grimson, F., Munro, R., Chaib, C., Lacoïn, L., Daumont, M., Penrod, J.R., O'Donnell, J.C., **Bento, M.J.**, and Goncalves, F.R., Treatment and outcomes for early non-small-cell lung cancer: a retrospective analysis of a Portuguese hospital database. *Lung Cancer Manag*. 10(2):LMT46, 2021. [IF: NA]
- Sousa Menezes, A., Fernandes, A., **Rocha Rodrigues, J., Salome, C.**, Machado, F., **Antunes, L., Castro Silva, J., Monteiro, E.**, and **Lara Santos, L.**, Optimizing classical risk scores to predict complications in head and neck surgery: a new approach. *Eur Arch Otorhinolaryngol* 278(1):191-202, 2021. [IF: 2.503]

**b. Other outputs**

**Teaching activity & coordination positions by group members**

Member	Curricular Unit	Programme	Position	Faculty/University
M <sup>a</sup> José Bento Rita Calisto Jéssica Rodrigues	Research Methodologies and Statistics I	MSc in Oncology	Coordination and teaching	ICBAS; UP
M <sup>a</sup> José Bento	Cancer Screening & Prevention	MSc in Oncology	Coordination and teaching	ICBAS; UP
M <sup>a</sup> José Bento	Research Methodologies and Statistics II	MSc in Oncology	Teacher	ICBAS; UP

M <sup>a</sup> José Bento	Epidemiology	MSc in Oncology	Coordination and teaching	ICBAS; UP
M <sup>a</sup> José Bento	Project - Research Seminars	MSc in Oncology	Teacher	ICBAS; UP
M <sup>a</sup> José Bento	Epidemiology & Public Health	Integrated MSc in Medicine	Teacher	ICBAS; UP
M <sup>a</sup> José Bento	Medical Epidemiology	Integrated MSc in Medicine	Teacher	ICBAS; UP
M <sup>a</sup> José Bento	Patologia II	Integrated MSc in Medicine	Teacher	ICBAS; UP
M <sup>a</sup> José Bento	Epidemiologia do Cancro e Registo Oncológico	MSc in Biochemistry	Teacher	FC/ICBAS; UP

**National collaborations**

Title	Institute
Atlas of Cancer Mortality in Portugal and Spain 2003–2012	UCL Great Ormond Street Institute of Child Health, University College London
IPOscore - predicting the risk of surgical treatment complications and defining prognosis in cancer patients by integrating clinical and biopathological data (DSAIPA/DS/0042/2018)	Institute of Mechanical Engineering
The impact of the COVID-19 pandemic on the diagnosis, treatment, and survival of cancer patients” (EXPL/SAU-EPI/1606/2021)	Institute of Public Health of the University of Porto
Impact of the COVID-19 pandemic on the care provided to cancer patients (RESEARCH 4 COVID-19 174_596850546)	Institute of Public Health of the University of Porto

**International collaborations**

Title	Member	International Team	Institute	Country	Funding
BENCHISTA: International benchmarking of population-based childhood cancer survival by stage at diagnosis	Maria José Bento, Teresa Monjardino	Kathy Pritchard-Jones	UCL Great Ormond Street Institute of Child Health, University College London	England	NA
IPAAC WP7 PILOT 2	Maria José Bento, Ana Filipa Gonçalves, and Rita Calisto	Roberta De Angelis	Italian National Institute of Health	Italy	NA
CONCORD	Maria José Bento, Jéssica Rodrigues, and Rita Calisto	Claudia Alemani	London School of Hygiene & Tropical Medicine	England	NA

## Cancer Genetics Group

### 1. Coordinator

Manuel Teixeira, MD, PhD

### 2. Research team (as of December 31<sup>st</sup> 2021)

Name	Academic degree	Professional situation	Category/position	Time %
Adriana Cardoso Resende	MSc	Contract	Research Assistant	100
Ana de Fátima Fernandes Barbosa	BSc	Contract	Lab Technician	20
Ana Luísa Pinto da Silva Lobo Peixoto de Moura	PhD	Contract	Lab Technician	20
Ana Luísa Teixeira Ferreira	PhD	Contract	Junior Researcher	100
Andreia Filipa Moreira Aguiar Brandão	PhD	Contract	Junior Researcher	100
Carla Alexandra Cavaco Pinto	MSc	Contract	Lab Technician	20
Carla Patrícia Brandão Gomes Paulo Escudeiro	MSc	Contract	Lab Technician	20
Catarina Gomes Rodrigues Santos	MSc	Contract	Lab Technician	20
Cecília Maria Gaspar Guedes Figueiredo e Correia	MSc	Contract	Lab Technician	20
Eunice Donzília Rocha da Silva	PhD	Contract	Psychologist	20
Isabel Maria da Silva Veiga dos Santos	MSc	Contract	Lab Technician	20
Joana Sofia Gonçalves Guerra	MSc	Fellowship	PhD student	100
Joana Virgínia Pinto Valejo de Magalhães Vieira	MSc	Contract	Lab Technician	20
João Fernando Pinho Silva	BSc	Contract	Clinician	20
Manuel António Rodrigues Teixeira	Aggregation	Contract	Group Leader; Coordinating Researcher	70
Manuela Cristina Dias Pinheiro	PhD	Contract	Assistant Researcher	100
Maria de Lurdes Eiras Torres	MSc	Contract	Lab Technician	20
Maria Pedro Pessoa de Barros Pereira da Silva	MSc	Fellowship	PhD student	100
Marta Filipa Gomes Loureiro	BSc	Student	MSc student	100
Marta Ribeiro José Cardoso	MSc	Fellowship	PhD student	100
Miguel Ângelo Sota Porto da Silva	MSc	Contract	Research Assistant	100
Nuno Manuel Botelho G. Sampaio Cerveira	PhD	Contract	Lab Technician	20
Patrícia Margarida Ferreira Saraiva Baptista Arinto	MSc	Contract	Research Assistant	100
Patrícia Maria Carvalho Rocha	MSc	Contract	Lab Technician	20
Paula Cristina Martins dos Santos Paulo	PhD	Contract	Assistant Researcher	100
Pedro Emanuel Martins Silva Gomes	MSc	Fellowship	PhD student	20
Raquel Margarida Gomes Martins	PhD	Contract, IPOC	Clinician	20
Sara Maria Baptista Machado Moreira Ribeiro	MSc	Contract	Clinician	20
Sofia de Melo Feiteira Maia	PhD	Contract, CHUC	Clinician	20

### 3. Group description and objectives

The general objectives of the Cancer Genetics Group are to characterize the pattern of acquired genetic alterations that presumably give rise to cancer, as well as to understand the mechanisms of tumor progression and therapy response. In addition, we want to characterize the inherited mutations associated with cancer predisposition, as well as the pattern of somatic genetic changes that occur in hereditary cancer syndromes. Several biologically and clinically relevant tumor models are studied, as they can provide transversal input. To make possible tailor-made therapy specifically directed towards the altered metabolism of tumor cells, exact knowledge about the inherited and acquired genomic abnormalities of individual patients, not just about diagnostic categories, is becoming a decisive factor in the selection of the optimal therapy.

One major line of research for the next years aims to identify and characterize genetic causes predisposing to inherited prostate cancer (PCa). This project is likely to result in the identification of at least part of the missing heritability associated with highly penetrant mutations that is expected to exist in up to 10% of the PCa cases, especially those with early onset and heavy family history of the disease. Besides providing the possibility for a molecular diagnosis of inherited predisposition for these families, finding the genes will allow pre-symptomatic testing of relatives at risk. This will enable offering targeted screening to high-risk carriers, since it is likely that this will result in increased positive predictive value for biopsy as compared to population-based studies. Pre-symptomatic testing for high-risk genes will also avoid unspecific PCa screening in non-carriers of a known high-risk family mutation, thereby avoiding the risk of overdiagnosis and overtreatment in men that have the population risk despite belonging to a high-risk family.

The second major line of research for the next years involves using circulating cell-free tumor DNA (ctDNA) to perform molecular diagnosis, predictive testing for targeted therapy, and cancer screening. In theory, somatic genetic changes present in cancer cells can be used as markers for early cancer detection, as well as during follow up to evaluate therapy response. The detection of mutations in ctDNA has emerged as a noninvasive strategy to assess primary tumors as well as eventual secondary lesions. This strategy has already been implemented in our group for monitoring the response and the mechanisms of resistance to targeted therapy and will be tested also in high-risk carriers in the context of families with hereditary breast/ovarian cancer, Lynch syndrome, Hereditary diffuse gastric cancer, and metastatic prostate cancer.

### 4. Active projects and funding

- SEGMAPP (POCI-01-0145-FEDER-028245): The role of chromosome segregation machinery defects in genetic predisposition to prostate cancer; (26/07/2018-25/11/2021); Paula Paulo & Manuel Teixeira; Budget: 176 824,85 €.
- TOGETHER (PTDC/PSI-ESP/30980/2017): Connecting people and systems to support an effective psychosocial adjustment to genetic testing in the context of inherited cancer risk (01/07/2018-30/06/2022); Eunice Silva; Budget: 44 771,00 €.
- LUNG-ctDNA (CI-IPOP-126-2019): Characterization of targeted therapy resistance mechanisms in EGFR/ALK/ROS1/BRAF-positive NSCLC by gene panel NGS in circulating cell-free DNA (01/09/2021-31/12/2023); Manuel Teixeira; Budget: 15 000,00 €.
- HPC (CI-IPOP-24-2015): Inherited predisposition to prostate cancer (01/10/2011-31/12/2024); Manuel Teixeira; Budget: 65 356,93 €.
- ctDNA-BRCA (CI-IPOP-35-2016): Identification of somatic and germline mutations in circulating tumor DNA in ovarian cancer patients and in germline BRCA1/BRCA2 mutation carriers undergoing cancer screening (01/05/2016-31/12/2024); Ana Barbosa & Manuel Teixeira; Budget: 90 000,00 €.
- ctDNA-Lynch (CI-IPOP-36-2016): Detection of cancer specific genetic alterations in circulating free tumor DNA as a tool for early cancer diagnosis and follow up in Lynch syndrome patients (01/09/2016-31/12/2024); Manuela Pinheiro & Manuel Teixeira; Budget: 20 000,00 €.

- ctDNA-Cancer (CI-IPOP-54-2017): Validation of liquid biopsies for predictive biomarker testing, therapy response monitoring, and resistance mechanism identification in cancer patients (01/09/2017-31/12/2024); Manuel Teixeira; Budget: 35 000,00 €.
- CaGaGen (CI-IPOP-56-2017): Identification of germline mutations by gene-panel next generation sequencing in familial tubular and mixed tubular-diffuse gastric cancer (01/09/2018-31/12/2023); Joana Guerra & Manuel Teixeira; Budget: 90 000,00 €.
- STOP-TKI (CI-IPOP-120-2019): The role of immune system for treatment-free remission in CML patients who stopped TKI therapy (01/09/2019-31/12/2023); Manuel Teixeira; Budget: 12 000,00 €.
- VATER (CI-IPOP-128-2020): Landscape of somatic and germline genetic alterations in ampullary carcinomas (01/09/2019-31/12/2023); Inês Ribas & Manuel Teixeira; Budget: 15 000,00 €.
- MetPC (CI-IPOP-129-2020): Simultaneous detection of germline and somatic mutations in DNA repair genes by next generation sequencing of tumor samples and cell-free DNA from metastatic prostate cancer patients (01/04/2021-31/12/2024); Manuel Teixeira; Budget: 55 000,00 €.

#### 5. Major achievements in 2021 (based on the 2 most relevant publication for the group)

##### ***The role of TP53 pathogenic variants in early-onset HER2-positive breast cancer.***

*In this study, we assessed the prevalence of germline TP53 variants by Sanger sequencing or next-generation sequencing in 149 women with HER2-positive breast cancer diagnosed until age 40. The pattern of HER2 amplification was evaluated with dual-probe FISH in a subset of breast carcinomas from patients with germline TP53 variants as compared with those of noncarriers. Among 149 women tested, three presented a deleterious TP53 germline variant (2%), with one patient diagnosed at age 31 and the other two with bilateral breast cancer at ages 29/33 and 28/32, respectively. Three of the 36 patients (8.3%) with the first breast cancer diagnosed at age 31 or younger presented a pathogenic TP53 variant. Additionally, all TP53 deleterious variant carriers had a first degree relative diagnosed with different early-onset cancers (frequently not belonging to the Li-Fraumeni syndrome tumor spectrum) diagnosed at age 45 or younger. Higher levels of HER2 amplification were found in breast carcinomas of TP53 pathogenic variant carriers than in those of noncarriers. Deleterious germline TP53 variants account for a small proportion of early-onset HER2-positive breast cancers, but these seem to have higher HER2 amplification ratios. All TP53 pathogenic variant carriers found in this study had the first breast carcinoma diagnosed at age 31 or younger and a first-degree relative with early-onset cancer. Further studies are needed to clarify if HER2 status in early-onset breast cancer patients, in combination with other personal and/or familial cancer history, is useful to update the TP53 testing criteria. (Fam Cancer 2021, 20(3):173-180. Impact factor: 2.375).*

##### ***Next generation sequencing of tumor and matched plasma samples: Identification of somatic variants in ctDNA from ovarian cancer patients.***

*In this study, using a custom panel of 27 genes, next-generation sequencing (NGS) was performed on tumor and matched plasma samples from 96 OC patients, which were combined in two groups (treatment naive and post-treatment). Overall, at least one somatic variant present in the tumor sample was also detected in the matched plasma sample in 35.6% of the patients, a percentage that increased to 69.6% of the treatment naive patients and 83.3% of those with stage IV disease, showing the potential of ctDNA analysis as an alternative to identify somatic variants in these patients, namely those that have predictive value for targeted therapy. In fact, of the two treatment-naive patients with somatic BRCA1 variants identified in tumor samples, in one of them we detected in ctDNA a BRCA1 somatic variant that was present in the tumor with a VAF of 53%, but not in the one that had a VAF of 5.4%. We also showed that ctDNA analysis has a complementary role to molecular unraveling of inter- and intra-tumor heterogeneity, as exemplified by one patient diagnosed with bilateral OC in which different somatic variants from both tumors were detected in ctDNA. Interestingly, as these bilateral tumors shared a rare combination of two of the three variants identified in ctDNA, we could conclude that these morphologically different tumors were clonally related and not synchronous independent neoplasias. Moreover, in the post-treatment group of patients with plasma samples collected after surgery, those with detectable somatic variants had poor prognosis when compared with patients with no detectable somatic variants, highlighting the potential of ctDNA analysis to identify patients at higher risk of recurrence. Concluding, this study demonstrated that somatic variants can be detected in plasma samples of a significant*

proportion of OC patients, supporting the use of NGS-based ctDNA testing for noninvasive tumor molecular profiling and to stratify patients according to prognosis. (*Front Oncol* 2021, 11:754094. Impact factor: 6.244).

## 6. Scientific output in 2021

### a. Peer-reviewed indexed publications (final publication date in 2021)

- Bancroft, E.K., Page, E.C., Brook, M.N., Thomas, S., Taylor, N., Pope, J., McHugh, J., Jones, A.B., Karlsson, Q., Merson, S., Ong, K.R., Hoffman, J., Huber, C., Maehle, L., Grindedal, E.M., Stormorken, A., Evans, D.G., Rothwell, J., Lalloo, F., Brady, A.F., Bartlett, M., Snape, K., Hanson, H., James, P., McKinley, J., Mascarenhas, L., Syngal, S., Ukaegbu, C., Side, L., Thomas, T., Barwell, J., **Teixeira, M.R.**, Izatt, L., Suri, M., Macrae, F.A., Poplawski, N., Chen-Shtoyerman, R., Ahmed, M., Musgrave, H., Nicolai, N., Greenhalgh, L., Brewer, C., Pachter, N., Spigelman, A.D., Azzabi, A., Helfand, B.T., Halliday, D., Buys, S., Ramon, Y.C.T., Donaldson, A., Cooney, K.A., Harris, M., McGrath, J., Davidson, R., Taylor, A., Cooke, P., Myhill, K., Hogben, M., Aaronson, N.K., Ardern-Jones, A., Bangma, C.H., Castro, E., Dearnaley, D., Dias, A., Dudderidge, T., Eccles, D.M., Green, K., Eyfjord, J., Falconer, A., Foster, C.S., Gronberg, H., Hamdy, F.C., Johannsson, O., Khoo, V., Lilja, H., Lindeman, G.J., Lubinski, J., Axcrone, K., Mikropoulos, C., Mitra, A.V., Moynihan, C., Ni Raghallaigh, H., Rennert, G., Collier, R., Collaborators, I.S., Offman, J., Kote-Jarai, Z., and Eeles, R.A., A prospective prostate cancer screening programme for men with pathogenic variants in mismatch repair genes (IMPACT): initial results from an international prospective study. *Lancet Oncol* 22(11): 1618-1631, 2021. [IF: 41.316]
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**b. Other outputs**

**Editorial board Positions**

Journal	Publishing Company	Position	Researcher
Genes Chromosomes and Cancer	Wiley	Associate Editor	Manuel Teixeira
Cancers	MDPI	Editorial Board Member	Manuel Teixeira
Cells	MDPI	Editorial Board Member	Manuel Teixeira

**Peer Reviewer**

European Journal of Human Genetics; Cancers; Familial Cancer; The Journal of Pathology

**Teaching activity & coordination positions by group members**

Member	Curricular Unit	Programme	Position	Faculty/University
Manuel Teixeira	Medical Genetics	Integrated MSc in Medicine	Coordination and teaching	ICBAS; UP
Manuel Teixeira	Oncobiology	MSc in Oncology	Coordination and teaching	ICBAS; UP
Manuel Teixeira	Genes and Cancer	PhD in Pathology and Molecular Genetics	Coordination and teaching	ICBAS; UP
Manuel Teixeira	Molecular Cytogenetics I	MSc in Molecular Medicine and Oncology	Coordination and teaching	FMUP; UP
Manuel Teixeira	Molecular Cytogenetics II	PhD in Molecular Medicine and Oncology	Coordination and teaching	FMUP
Manuel Teixeira	Pathology II	Integrated MSc in Medicine	Teaching	ICBAS; UP
Manuel Teixeira	Molecular Biology Techniques	PhD in Pathology and Molecular Genetics	Teaching	ICBAS; UP
Manuel Teixeira	Oncobiology	MSc in Biochemistry	Teaching	ICBAS; UP
Manuel Teixeira	Oncobiology	MSc in Bioengineering	Teaching	FEUP/ICBAS
Manuel Teixeira	Genomic Instability Associated Diseases	Integrated MSc in Medicine	Teaching	FMUP

**National collaborations**

Title	Researchers	Collaborators	Funding Agency	Period
Recurrent germline mutations in patients with early-onset and/or familial prostate cancer; PhD project; Marta Cardoso,	Manuel Teixeira, Paula Paulo,	José Bessa	FCT: SFRH/BD/116557/2016	2017-2022
BRCA-STEM: Exploring stemness in high grade serous carcinoma of the ovary using hereditary breast-ovarian cancer syndrome as a model system; PhD project; Rita Canário	Manuel Teixeira	Joana Paredes	FCT: PD/BD/128001/2016	2017-2022
Germline mutations in genes involved in the chromosome segregation machinery associated with inherited prostate cancer predisposition; PhD project; Maria Pedro Silva	Manuel Teixeira, Paula Paulo	Hélder Maiato	FCT: SFRH/BD/132441/2017	2018-2022
Inherited predisposition to gastric cancer: novel susceptibility genes and a minimally invasive screening strategy in germline mutation carriers; PhD Project; Joana Guerra	Manuel Teixeira	Carla Oliveira	FCT: SFRH/BD/138670/2018	2019-2022
The role of chromosome segregation machinery defects in genetic predisposition to prostate cancer	Paula Paulo, Manuel Teixeira, Luísa Ferreira, Andreia Brandão, Maria Pedro Silva	Hélder Maiato	FCT/FEDER: POCI-01-0145-FEDER-028245; CEECINST/0091/2018; UIDP/00776/2020; SFRH/BD/132441/2017;	2019-2021

**International collaborations**

Title	Researchers	International Team	Institute	Country	Funding
Rare Germline Variants in ATM Predispose to Prostate Cancer: A PRACTICAL Consortium Study	Manuel Teixeira, Paula Paulo, Marta Cardoso	Rosalind Eeles, Zsofia Kote-Jarai	Institute of Cancer Research	UK	PRACTICAL; CEECINST/0091/2018; SFRH/BD/116557/2016
Inherited predisposition to gastric cancer: novel susceptibility genes and a minimally invasive screening strategy in germline mutation carriers	Joana Guerra, Manuel Teixeira	Luis G Carvajal-Carmona	UC Davis Genome Center	USA	UC Davis; CI-IPOP; SFRH/BD/138670/2018
Identification of Men with a genetic predisposition to Prostate Cancer: Targeted screening in men at higher genetic risk and controls	Manuel Teixeira, Marta Cardoso	Rosalind Eeles	Institute of Cancer Research	UK	Institute of Cancer Research; SFRH/BD/116557/2016

**International Consortia**

Organization	Researcher
CIMBA-The Consortium of Investigators of Modifiers of BRCA1/2	Manuel Teixeira
IMPACT-Identification of Men with a genetic predisposition to Prostate Cancer: Targeted screening in men at higher genetic risk and controls)	Manuel Teixeira
PRACTICAL- Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome	Manuel Teixeira
BCAC-The Breast Cancer Association Consortium	Manuel Teixeira
COGENT (COlorectal cancer GENeTics)	Manuel Teixeira
Genturis: European Reference Network (ERN) for GENetic TUmour Risk Syndromes	Manuel Teixeira
EU funded COST Action CA17118: Identifying biomarkers through translational research for prevention and stratification of colorectal cancer (National Delegate)	Manuel Teixeira

## Experimental Pathology and Therapeutics Group

### 1. Coordinator

Lúcio Santos, MD, PhD

### 2. Research team (as of December 31<sup>st</sup> 2021)

Name	Academic degree	Professional situation	Category/ Position	Time %
Adriana Carneiro	Msc	Fellowship	Research Assistant	20
Ana Carolina Fernandes Vieira de Castro	Msc	Fellowship	PhD student	100
Ana Catarina Oliveira Trigo	BSc	Student	MSc student	100
Andreia Filipa Ferreira Peixoto	MSc	Contract, IPOP	Junior researcher	100
Andreia Rafaela Linhares Miranda	BSc	Student	MSc student	100
Beatriz Faria Alves Oliveira	BSc	Student	MSc student	100
Carina Caneppele	MSc	Student	MSc student	100
Carlos Alberto Palmeira de Sousa	PhD	Contract	Higher health technician	30
Carolina Ferraz Neto Pinhal	Bsc	Student	MSc Student	100
Carolina Gomes Ferreira	BSc	Student	MSc student	100
Catarina Alexandra da Rocha Rodrigues	Msc	Fellowship	PhD student	50
Clara Alice Gentil Daher Mota	Msc	Fellowship	PhD student	20
Cristiana Milhazes Gaiterio	MSc	Contract	Lab technician/PhD student	100
Cristina Patrícia Mendes Santos	PhD	Contract, Fraunhofer Portugal	Researcher	100
Dora Maria Barrocas Bernardo	MSc	Contract	Higher health technician/PhD student	30
Dylan Gomes Ferreira	MSc	Fellowship	PhD student	100
Eduardo da Silva Ferreira	BSc	Student	MSc Student	100
Eliana Janine de Paiva Soares	MSc	Fellowship	PhD student	100
Elisabete Cristina Nunes Fernandes	PhD	Fellowship	Postdoc	30
Fabício Filgueira Fernandes	BSc	Student	MSc student	100
João Miguel Monteiro Antunes	Msc	Fellowship	PhD student	45
José Alexandre Ribeiro de Castro Ferreira	PhD	Contract	Assistant researcher	100
Lícia Beatriz Alves Araújo	BSc	Student	MSc student	100
Lúcio José de Lara Santos	Aggregation	Contract	Group Leader	30
Luís Carlos Oliveira Lima	PhD	Contract	Junior researcher	100
Luís Pedro Fernandes Afonso	BSc	Contract	Pathologist	20
Mafalda Barbosa Pedrosa	BSc	Student	MSc Student	50
Maria de Fátima Sousa e Santos	BSc	Contract	PhD student /clinician	20
Maria do Rosário Lima Viseu de Carvalho Pinto Leite	PhD	Contract, CHTMAD	Collaborator	30
Marta Filipa Relvas dos Santos	MSc	Fellowship	PhD student	60
Patrícia Pilar Gomes Oliveira Maia	Msc	Fellowship	Research Assistant	100
Rui Filipe Neves Freitas	MSc	Student	PhD student	100
Samuel da Silva Barbosa	BSc	Student	MSc Student	50
Sofia Ribeiro Cotton	MSc	Fellowship	PhD student	100

### 3. Group description and objectives

The Experimental Pathology and Therapeutics Group, established in 2008 as one of the research groups of the IPO PORTO FG EPE, is coordinated by Professor Lúcio Santos (MD PhD). The group currently includes 7 senior researchers (Phd level), 12 Phd students and 11 Msc student and 4 collaborators. The group also provides a solid platform for training and higher education in cancer research. Reflecting this commitment, over the past four years the group has welcomed several post-graduate students from the University of Aveiro, Porto, Coimbra, Minho and UTAD as well as international students from Angola. The group is also involved in GlyCoCan, a Marie Curie European Training Network composed of 15 leading European partners in the fields of glycobiology, glyco-immunology and biomarker research. It provides a multidisciplinary training for a new generation of researchers in the young field of glyco-oncology, bridging academic and industrial sectors.

The Experimental Pathology and Therapeutics group will devote the efforts of the next years to both basic and translational cancer research with the purpose of identifying glycobiomarkers for early detection of the disease, prognosis, drug response and to guide therapeutic decision. Ultimately it will also focus on translating this knowledge into novel therapeutics. One of the main goals for 2022-2024 is to determine the clinical relevance of circulating tumor cells (CTC) expressing the short chain O-glycan, STn, in gastrointestinal tumors using an innovative microfluidics device and development of CTC ex vivo models for individualized testing drug susceptibility. Regarding target therapeutics, the goal is to identify specific proteoglycoforms and develop specific ligands for CAR-T therapeutics and antibody development for glycan-based nanotherapeutics for cancer for this study. Other study line will be the implementation of an immunological profile of patients who are candidates for therapeutic approaches in the field of immunology and the development of strategies for dendritic cell stimulation.

### 4. Active projects and funding

- IPOscore (DSAIPA/DS/0042/2018): Predicting the risk of complications of surgical treatment and define prognosis of cancer patients through the integration of clinical and biopathological data. PI: Rafael Costa. Main Institution: IST. Participating Institutions: IPO. Budget: IPO-24,7056.00€; Total-247,056.00€
- PROTECT(PTDC/SAU-DES/7945/2020): Prehabilitation to enhance cancer treatment in patients with adenocarcinoma of the gastroesophageal junction and the stomach. PI: Lúcio Lara Santos. Main Institution: IPO. Participating Institutions: Instituto de Investigação e Inovação em Saúde da Universidade do Porto - Associação (i3S), Faculdade de Desporto da Universidade do Porto (FADE/UP). Budget: IPO-135,695.00€, Total-250,000.00€
- Laserthermia (PI 130-CI-IPOP-125-2019): Synergistic antitumor effect of combined laser thermotherapy and immunomodulators in malignant melanoma. (PI130-CI-IPOP-125-2019) PI: Carlos Palmeira. Main Institution: IPO. Participating Institutions: Instituto de Investigação e Inovação em Saúde da Universidade do Porto - Associação (i3S), Faculdade de Desporto da Universidade do Porto (FADE/UP). Budget: 79,347.00€. Sponsor: Laserthermia (Sweden)
- Immunomimetic (PI-133-CI-IPOP 109-2018): Development of a biomimetic multifunctional pre-clinical model to assist immunotherapy optimization. Main Institution: I3S. Participating Institution: IPO. Budget: IPO-4000€; Total-32,880.00€
- OptimizingLiverMet -Immunological and circulating tumour cells evaluation in colorectal cancer liver metastasis. PI: Lúcio Lara Santos. Main Institution: IPO. Budget: 38,000.00€. Sponsor: Roche
- GlycoBodies -Development of monoclonal antibodies for chemoresistant bladder cancer based on glycobiomarkers (CI-IPOP-58-2020) – PI: Lúcio Lara Santos/co-PI: José Alexandre Ferreira. Budget: 28,111.00€
- DCMatters- Combination of dendritic cell vaccine with immune checkpoint inhibitors as first-line therapy in patients with solid malignancies. PI: Lúcio Lara Santos. Main Institution: IPO. Budget: 822,007.92€.
- AFRICA(PTDC/BIA-MOL/3986/2021): - Sub-Saharan panel of tumor lines: from patient-derived cells to specialized population-based cancer treatment in African ancestry. PI: Lúcio Lara Santos. Budget: 25,000.00€.

### 5. Major achievements in 2021 (based on the 2 most relevant publication for the group)

- **Peixoto A, Ferreira D, Azevedo R, Freitas R, Fernandes E, Relvas-Santos M, Gaitero C, Soares J, Cotton S, Teixeira B, Paulo P, Lima L, Palmeira C, Martins G, Oliveira MJ, Silva AMN, Santos LL, Ferreira JA. Glycoproteomics identifies HOMER3 as a potentially targetable biomarker triggered by hypoxia and glucose deprivation in bladder cancer. J Exp Clin Cancer Res. 2021 Jun 9;40(1):191. <https://pubmed.ncbi.nlm.nih.gov/34108014/> (IF: 11.161)**

The group has been exploiting HOMER3-glycoforms that allow the identification of patients' subsets facing worst prognosis, holding potential to address more aggressive hypoxic cells with limited off-target effects. The molecular rationale for identifying novel bladder cancer molecular targets has been established (doi:10.1186/s13046-021-01988-6).

- **Santos, L.L., Santos, J., Gouveia, M.J., Bernardo, C., Lopes, C., Rinaldi, G., Brindley, P.J., and Costa, J., Urogenital Schistosomiasis-History, Pathogenesis, and Bladder Cancer. J Clin Med 10(2), 2021. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7826813/> (IF: 4.241)**

Another relevant dimension of the group is to provide sustainable frameworks for infections related carcinogenesis. Therefore, Schistosomiasis is the most important helminthiasis worldwide in terms of morbidity and mortality. Most of the infections occurs in Africa, which about two thirds are caused by *Schistosoma haematobium*. The infection with *S. haematobium* is considered carcinogenic leading to squamous cell carcinoma (SCC) and urothelial carcinoma of the urinary bladder. Additionally, it is responsible for female genital schistosomiasis leading to infertility and higher risk of human immunodeficiency virus (HIV) transmission. We present a historical perspective of schistosomiasis, and review the infection-associated pathologies and studies on host–parasite interactions that unveil tentative mechanisms underlying schistosomiasis-associated carcinogenesis (doi: 10.3390/jcm10020205).

### 6. Scientific output in 2021

#### a. Peer-reviewed indexed publications (final publication date in 2021)

- Alexandre, L., Costa, R.S., **Santos, L.L.**, and Henriques, R., Mining Pre-Surgical Patterns Able to Discriminate Post-Surgical Outcomes in the Oncological Domain. IEEE J Biomed Health Inform 25(7):2421-2434, 201. [IF: 5.772]
- Baraças, C., **Farinha, M., Afonso, L.P.**, and **Bacelar, M.T.**, The Extremely Rare Hypopharyngeal Fetal Rhabdomyoma in an Adult. Cureus. 13(9):e18096. 2021. [IF: NA]
- Barbosa, J., Faria, J., Garcez, F., Leal, S., **Afonso, L.P.**, Nascimento, A.V., Moreira, R., Pereira, F.C., Queiros, O., Carvalho, F., and Dinis-Oliveira, R.J., Repeated Administration of Clinically Relevant Doses of the Prescription Opioids Tramadol and Tapentadol Causes Lung, Cardiac, and Brain Toxicity in Wistar Rats. Pharmaceuticals (Basel) 14(2) , 2021. [IF: 5.863]
- Barreira, D.F., Lourenco, R.A., **Calisto, R.**, Moreira-Goncalves, D., **Santos, L.L.**, and Videira, P.A., Assessment of the Safety and Therapeutic Benefits of Convalescent Plasma in COVID-19 Treatment: A Systematic Review and Meta-Analysis. Front Med (Lausanne), 8:660688, 2021. [IF: 5.091]
- **Bernardo, C.**, Monteiro, F.L., Direito, I., Amado, F., Afreixo, V., **Santos, L.L.**, and Helguero, L.A., Association Between Estrogen Receptors and GATA3 in Bladder Cancer: A Systematic Review and Meta-Analysis of Their Clinicopathological Significance. Front Endocrinol (Lausanne) 12:684140, 2021. [IF: 5.555]
- Come, J., Pereira, J.B., Pinto, R., Carrilho, C., Pereira, L., and **Lara Santos, L.**, The Upper Digestive Tract Microbiome and Oesophageal Squamous Cell Carcinoma: Epidemiology, Pathogenesis, and Clinical Implications in Africa. Pathobiology 88(2):141-155, 2021. [IF:4.342]
- **Cotton, S., Ferreira, D., Soares, J., Peixoto, A., Relvas-Santos, M., Azevedo, R., Piai, P., Dieguez, L., Palmeira, C., Lima, L., Silva, A.M.N., Lara Santos, L., and Ferreira, J.A.**, Target Score-A Proteomics Data Selection Tool Applied to Esophageal Cancer Identifies GLUT1-Sialyl Tn Glycoforms as Biomarkers of Cancer Aggressiveness. Int J Mol Sci 22(4), 2021. [IF: 5.923]

- da Costa, J.M.C., Gouveia, M.J., Rinaldi, G., Brindley, P.J., Santos, J., and **Santos, L.L.**, Control Strategies for Carcinogenic-Associated Helminthiasis: An Integrated Overview. *Front Cell Infect Microbiol* 11: 626672, 2021. [IF:5.293]
- Duarte H.O., Rodrigues J.G., Gomes C., Hensbergen P.J., Ederveen A.L.H., de Ru A.H., Mereiter S., Polónia A., **Fernandes E., Ferreira J.A.**, van Veelen P.A., **Santos L.L.**, Wuhrer M., **Gomes J., Reis C.A.** ST6Gal1 targets the ectodomain of ErbB2 in a site-specific manner and regulates gastric cancer cell sensitivity to trastuzumab *Oncogene* 40(21): 3719-3733, 2021. [IF: 9.933]
- **Ferreira, J.A., Relvas-Santos, M., Peixoto, A.**, A, M.N.S., and **Lara Santos, L.**, Glycoproteogenomics: Setting the Course for Next-generation Cancer Neoantigen Discovery for Cancer Vaccines. *Genomics Proteomics Bioinformatics* 19(1): 25-43, 2021. [IF: 7.691]
- **Freitas, R., Relvas-Santos, M., Azevedo, R., Soares, J., Fernandes, E., Teixeira, B., Santos, L.L.**, Silva, A.M.N., and **Ferreira, J.A.**, Single-pot enzymatic synthesis of cancer-associated MUC16 O-glycopeptide libraries and multivalent protein glycoconjugates: a step towards cancer glycovaccines. *New Journal of Chemistry*. 45(20):9197-9211. 2021 [IF: 3.591]
- Goncalves, D., Henriques, R., **Santos, L.L.**, and Costa, R.S., On the predictability of postoperative complications for cancer patients: a Portuguese cohort study. *BMC Med Inform Decis Mak*, 2021. 21(1):200 [IF: 2.796]
- Martins, M., Arantes, R., Botelho, P., Souto, M., Moutinho, O., and **Pinto Leite, R.**, Familial del3p syndrome: The uncertainty of the prognosis. A case report. *Clin Case Rep*. 9(4):2365-2368, 2021. [IF: NA]
- Morais, A., Simao, M., Cossa, M., Come, J., Selemene, C., Tivane, A., Tulsidas, S., Lorenzoni, C., **Rodrigues, J., Antunes, L., Brito, D.**, Costa, M.J., Sidat, M., Martins, M., and **Santos, L.L.**, Designing a National Curriculum to Advance Surgical Oncology in Mozambique: A Delphi Consensus Study. *J Surg Educ*. 78(1):140-147, 2021. [IF: 2.891]
- **Morais, M., Machado, V., Dias, F., Palmeira, C., Martins, G.**, Fonseca, M., Martins, C.S.M., **Teixeira, A.L.**, Prior, J.A.V., and **Medeiros, R.**, Starch-Capped AgNPs' as Potential Cytotoxic Agents against Prostate Cancer Cells. *Nanomaterials (Basel)* 11(2), 2021. [IF: 5.076]
- **Peixoto, A., Cotton, S., Santos, L.L.**, and **Ferreira, J.A.**, The Tumour Microenvironment and Circulating Tumour Cells: A Partnership Driving Metastasis and Glycan-Based Opportunities for Cancer Control. *Adv Exp Med Biol*1329:1-33, 2021 [IF: 2.722]
- **Peixoto A., Ferreira D., Azevedo R., Freitas R., Fernandes E., Relvas-Santos M., Gaiteiro C., Soares J., Cotton S., Teixeira B., Paulo P., Lima L., Palmeira C., Martins G., Oliveira M.J., Silva A.M.N., Santos L.L., Ferreira J.A.** Glycoproteomics identifies HOMER3 as a potentially targetable biomarker triggered by hypoxia and glucose deprivation in bladder cancer *Journal of Experimental & Clinical Cancer Research* 40(1), 2021. [IF: 11.161]
- Rebelo R., Polónia B., **Santos L.L.**, Vasconcelos M.H., Xavier C.P.R. Drug repurposing opportunities in pancreatic ductal adenocarcinoma *Pharmaceuticals* 14(3), 2021. [IF: 5.863]
- **Santos, L.L.**, Santos, J., Gouveia, M.J., Bernardo, C., **Lopes, C.**, Rinaldi, G., Brindley, P.J., and Costa, J., Urogenital Schistosomiasis-History, Pathogenesis, and Bladder Cancer. *J Clin Med* 10(2), 2021. [IF: 4.241]
- Selemene, C., Jamisse, L., Arroz, J., Tulsidas, S., Morais, A.G., Carrilho, C., Modcoicar, P., Sidat, M., **Rodrigues, J., Moreira-Goncalves, D.**, Ismail, M., and **Santos, L.L.**, Demographic, clinical and pathological characterisation of patients with colorectal and anal cancer followed between 2013 and 2016 at Maputo Central Hospital, Mozambique. *Ecancermedicalscience*. 15:1205, 2021. [IF: NA]
- Silva L.M., Correia V.G., Moreira A.S.P., Domingues M.R.M., Ferreira R.M., Figueiredo C., Azevedo N.F., Marcos-Pinto R., Carneiro F., Magalhães A., Reis C.A., Feizi T., **Ferreira J.A.**, Coimbra M.A., Palma A.S. Helicobacter pylori lipopolysaccharide structural domains and their recognition by immune proteins revealed with carbohydrate microarrays *Carbohydrate Polymers* 253, 2021. [IF: 9.381]
- Sousa Menezes, A., Fernandes, A., **Rocha Rodrigues, J., Salome, C.**, Machado, F., **Antunes, L., Castro Silva, J., Monteiro, E.**, and **Lara Santos, L.**, Optimizing classical risk scores to predict complications in head and neck surgery: a new approach. *Eur Arch Otorhinolaryngol* 278(1):191-202, 2021. [IF: 2.503]

- Tavares, P., Goncalves, D.M., **Santos, L.L.**, and Ferreira, R., Revisiting the clinical usefulness of C-reactive protein in the set of cancer cachexia. Porto Biomed J 6(1): e123, 2021. [IF:NA]
- Xavier C.P.R., Castro I., Caires H.R., **Ferreira D.**, Cavadas B., Pereira L., **Santos L.L.**, Oliveira M.J., Vasconcelos M.H. Chitinase 3-like-1 and fibronectin in the cargo of extracellular vesicles shed by human macrophages influence pancreatic cancer cellular response to gemcitabine Cancer Letters 501: 210-223, 2021. [IF: 8.679]

**b. Other outputs**

**Patents (National or international)**

Description	File number	Status	National/ international
Ferreira, JA; Gaiteiro, C; Silva, AMN; Ferreira, D; Relvas Santos, M; Soares, E; Peixoto, M; Santos, LL. Method for cancer detection, prognosis, and therapeutic selection based on short CD44 glycoproteoforms	20211000033741	Provisional	National
Ferreira, JA; Freitas, R; Relvas Santos; Gaiteiro, C; Peixoto, A; M; Silva, AMN; Santos, LL. CD44 glycoepitopes and chimeric vaccine glycoconjugates for cancer therapy and synthesis methods thereof	20211000033743	Provisional	National

**Oral Communications by Invitation**

- José Alexandre Ferreira. Glycomics and Glycoproteomics: Unravelling the cancer glycode towards precision oncology. 6th Latin American Glycobiology Congress. October 2021
- Palmeira, C. "The Application of Flow Cytometry in Testing New Therapeutics Strategies in Preclinical in vivo Models"; XVII Congress of the Iberian Society of Cytometry (Porto, Portugal), 2021

**Oral Communications in International Scientific meetings**

- Carneiro, Adriana; Piairo, Paulina; Teixeira, Alexandra; Chícharo, Alexandre; Abalde-Cela, Sara; Lima, Luís; Diéguez, Lorena. "Microfluidic-based Isolation of Gastrointestinal Circulating Tumour Cells". Trabalho apresentado em *EuroNanoForum Conference*, 2021
- Cotton, Sofia. "Molecular profiling of squamous cell carcinoma of the esophagus in Mozambique: a genoproteomic-assisted approach to improve oncologic care in Africa". Oral presentation presented in Virtual Cancer Genomics Conference: "African genomic diversity: A roadmap to global equity in cancer control", 2021
- Andreia Peixoto. Unravelling the Bladder tumour microenvironment using the Flow cytometry toolbox. XVII Congress of the Iberian Society of Cytometry. Oral presentation. 17/06/2021

**Posters in international conferences**

- Freitas, Rui; Relvas-Santos, Marta; Azevedo, Rita; Soares, Janine; Beatriz Teixeira; Fernandes, Elisabete; Silva, André M. N.; Ferreira, José Alexandre; Santos, Lúcio. "Single pot enzymatic synthesis of cancer associated MUC16 O glycopeptide libraries and multivalent protein glycoconjugates: a step towards cancer glycovaccines. Poster presented in 4th I3S PhDay: Break borders and build opportunities, 2021.
- Cotton, Sofia; Jotamo Come; Ferreira, Dylan; Fernandes, Elisabete; Carla Carrilho; Santos, Lúcio. "Molecular profiling of squamous cell carcinoma of the esophagus in Mozambique: a genoproteomic-assisted approach to improve oncologic care in Africa". Poster presented in Virtual Cancer Genomics Conference: "African genomic diversity: A roadmap to global equity in cancer control", 2021.
- Dylan Ferreira, Elisabete Fernandes, Rui Freitas, Cristiana Gaiteiro, Andreia Peixoto, Sara Oliveira, Sofia Cotton, Luís Pedro Afonso, Carlos Palmeira, Gabriela Martins, Maria José Oliveira, Lúcio Lara Santos, José Alexandre Ferreira. "Nucleolin-SLeA as E-Selectin Ligands and Potentially Targetable Biomarkers at the

Cell Surface of Gastric Cancer Cells: a flow cytometry-assisted approach". Poster presented in XVII Congress of the Iberian Society of Cytometry, 2021

- Andreia Miranda, Andreia Peixoto, Marta Relvas-Santos, José Alexandre Ferreira, Maria José Oliveira, Lúcio Lara Santos. "Decoding the Crosstalk Between Dendritic Cells and Bladder Cancer Associated Glycans: A Way to Identify Novel Immunotherapy Targets". Poster presented in IJUP-2021 - 14<sup>o</sup> Encontro de Investigação Jovem da Universidade do Porto, 2021.
- Andreia Peixoto, Rui Freitas, Dylan Ferreira, Marta Relvas-Santos, Paula Paulo, Marta Cardoso, Janine Soares, Cristiana Gaiteiro, Carlos Palmeira,
- Filipe Teixeira, Rita Ferreira, Maria José Oliveira, André M. N. Silva, Lúcio Lara Santos, José Alexandre Ferreira. Metabolomics, Transcriptomics and Functional Glycomics Reveals Bladder Cancer Cells Plasticity and Enhanced Aggressiveness Facing Hypoxia and Glucose Deprivation. 27th PORTO CANCER MEETING Stemness & Metastasis: Advances in Research and Clinical Translation. 20/06/2021
- Marta, A et al. "HEAVY-LIGHT CHAIN PAIR: CONTRIBUTION OF THIS BIOMARKER IN THE DIAGNOSIS AND FOLLOW-UP OF MULTIPLE MYELOMA". Annual Meeting of the Portuguese Society of Hematology, 2021.
- Trigo, C et al. "Study of immune system cell populations in peripheral blood of C57BL/6 wild type animals by flow cytometry". II Ibero-American Virtual Congress of Cytometry. Latinflow 2021, 2021.
- Silva, M et al. "A recurrent in-frame BUB1B germline variant in prostate cancer predisposition". Paper presented in EMBO Workshop Systems approaches in cancer, 2021.
- Rodrigues, P et al. "NODAL GAMMA-DELTA T CELL LYMPHOMA – CASE REPORT". XVII Congress of the Iberian Society of Cytometry, 2021.
- Malheiro, B et al. "CD200 EXPRESSION IN MANTLE CELL LYMPHOMA: A CASE REPORT". XVII Congress of the Iberian Society of Cytometry, 2021.
- Sousa, ME et al. "PERIPHERAL T.CELL LYMPHOMA OF FOLLICULAR HELPER T-CELL TYPE: A CASE REPORT". XVII Congress of the Iberian Society of Cytometry, 2021.
- Meneses, J et al. "CD123 EXPRESSION IN PEDIATRIC ACUTE MYELOID LEUKEMIA". XVII Congress of the Iberian Society of Cytometry, 2021.
- Couto, A et al. "BRAF MUTATION IN MATURE B-CELL NEOPLASMS NON HAIRY CELL LEUKEMIA". XVII Congress of the Iberian Society of Cytometry, 2021.
- Fernandes, B et al. "BRONCHOALVEOLAR LAVAGE ABNORMAL DNA CONTENT: WHAT CAN WE EXPECT?". XVII Congress of the Iberian Society of Cytometry, 2021.
- Faustino, A et al. "PERIPHERAL LYMPHOCYTE SUBPOPULATIONS IN PROSTATE CANCER - DATA FROM AN ANIMAL MODEL". XVII Congress of the Iberian Society of Cytometry, 2021.
- Faustino, A et al. "EFFECT OF EXERCISE TRAINING ON LYMPHOCYTE SUBPOPULATIONS IN CHEMICALLY AND HORMONALLY INDUCED PROSTATE CANCER: FLOW CYTOMETRY ANALYSIS". XVII Congress of the Iberian Society of Cytometry, 2021.
- Morais, M et al. "THE CYTOTOXIC POTENTIAL OF STARCH-CAPPED SILVER-NANOPARTICLES (AGNPS) AND THEIR ABILITY TO INDUCE CELL CYCLE ARREST IN PROSTATE CANCER CELLS". XVII Congress of the Iberian Society of Cytometry, 2021.
- Pires, A et al. "FREE LIGHT CHAIN: A MARKER OF DISEASE AND PROGNOSTIC IN INTACT IMMUNOGLOBULIN MULTIPLE MYELOMA". 7 th World Congress on Controversies in Multiple Myeloma (COMy), 2021.
- Rodrigues, C et al. "The role of microRNAs as biomarkers in liquid biopsies of oral cancer and oral potentially malignant disorders". Paper presented in 3rd National Meeting of Young Oncology Researchers - Porto, 2021, 2021.
- Santos, LL et al. HOSPITAL-BASED CANCER REGISTRY DATA FROM HOSPITAL AGOSTINHO NETO IN CAPE VERDE (2019 - 2020). AORTIC 2021. 2021
- Santos, LL et al. FELLOWSHIP IN SURGICAL ONCOLOGY: THE ANGOLAN FELLOWS OPINION. AORTIC 2021. 2021
- Santos, LL et al. DEMOGRAPHIC, CLINICAL AND PATHOLOGICAL CHARACTERISATION OF PATIENTS WITH COLORECTAL AND ANAL CANCER FOLLOWED BETWEEN 2013 AND 2016 AT MAPUTO CENTRAL HOSPITAL, MOZAMBIQUE. AORTIC 2021. 2021

- Santos, LL et al. EPIDEMIOLOGICAL PROFILE OF ESOPHAGEAL CANCER IN PATIENTS FOLLOWED AT DR. BAPTISTA DE SOUSA HOSPITAL IN S. VICENTE ISLAND, CAPE-VERDE, BETWEEN 2010 AND 2015. AORTIC 2021. 2021
- Santos, LL et al. BREAST CANCER IN ANGOLA - NEW IMMUNOHISTOCHEMICAL DATA. AORTIC 2021. 2021
- Santos, LL et al. THE ROLE OF DOCTORS WITH A PhD DEGREE IN CANCER CARE, TEACHING AND RESEARCH IN ANGOLA. AORTIC 2021. 2021
- Santos, LL et al. CLINICAL, PATHOLOGICAL AND THERAPEUTIC CHARACTERIZATION OF BREAST CANCER PATIENTS DIAGNOSED AT HOSPITAL AGOSTINHO NETO, CAPE VERDE FROM 2015 TO 2021. AORTIC 2021. 2021

**Editorial board Positions**

Journal	Publishing Company	Position	Researcher
Frontiers in Molecular Biosciences	Frontiers	Guest associate editor	José Alexandre Ferreira
Cancers	MDPI	Guest editor	José Alexandre Ferreira
Journal of the Portuguese Society of Surgery	Portuguese Society of Surgery	Executive editor	Lúcio Lara Santos

**Peer reviewer**

Ecancermedalscience

**Grant Reviewer**

Agency	Call	Country	Date	Researcher
EU	ERC Advanced Grants	Brussels	2021	José Alexandre Ferreira

**Participation as Opponent in MSc Evaluation Committees**

Student	Title	Program	Researcher
Paulo Sérgio do Valle	Hematological parameters as prognostic biomarkers in esophageal and gastric cancer	MSc in specialized clinical analysis Fernando Pessoa University, Faculty of Health Sciences.	Andreia Peixoto
Filipe Silva Alves	Malaria case study in Angola	School of Health - Fernando Pessoa University.	Carlos Palmeira
Diogo Francisco Martins Cunha	Proteomic profiling of the B cell immune synapse	MSc in Health Biochemistry; School of Health; Polytechnic Institute of Porto	José Alexandre Ferreira

**Participation as Opponent in PhD/ Aggregation Evaluation Committees**

Student	Title	Program	Researcher
Inês Afrodite Sá Glória Santiago	Contribution of Novel MR imaging methods to the staging and management of rectal cancer	Faculty of Medical Sciences   NOVA Medical School of the NOVA University of Lisbon	Lucio Lara Santos
Paula Pastrez	Analysis of the relationship of cytokines and TREX-1 with esophageal squamous cell carcinoma	Molecular Oncology Research Center. Pio XII Foundation - Barretos Cancer Hospital.	Lucio Lara Santos
Andreia Marina de Sousa Almeida	Mucoadhesive camptothecin polymeric micelles as nanodelivery systems for oral chemotherapy to treat colorectal cancer	PhD in Biomedical Sciences; ICBAS-UP	José Alexandre Ferreira

**Teaching Activity: Coordination of Curricular Units/Courses**

Member	Curricular Units	Programme	Position	Faculty/University
Lúcio Lara Santos	Clinical Anatomy	Integrated MSc in Medicine	Coordination and teaching	ICBAS; UP
Lúcio Lara Santos	Oncology	Integrated MSc in Dental Medicine	Coordination and teaching	School of Health; Fernando Pessoa University
Luis Lima	Laboratories in Pharmacy II	BSc in Pharmacy	Teaching	School of Health; Polytechnic Institute of Porto

**Prizes, Honors and Awards**

Researcher	Prize designation	Foundation/ Company	Date	Amount
Adriana Carneiro	LPPC-NRN fellowship	Portuguese League Against Cancer- North region	January 2021	12000€

**Scientific Appointments**

Organization	Researcher
Member of the Scientific Technical Board; Fernando Pessoa University, Faculty of Health Sciences.	Carlos Palmeira
The Human Proteome Organization (HUPO)	José Alexandre Ferreira

**National collaborations**

Title	Researchers	Collaborators	Funding	Period
RESOLVE: Rational Design of Multivalent Glycocode-Inspired Nanovaccines for Gastric Cancer Immunotherapy	Bruno Sarmento, Maria José Oliveira, Flávia Castro	José Alexandre Ferreira, Lúcio Santos, Luís Lima, Andreia Peixoto, Dylan Ferreira, Rui Freitas, Janine Soares, Cristiana Gaiteiro, Andreia Miranda, Sofia Cotton, Carlos Palmeira, Marta Relvas Santos	249.645,00€	2022-2024

**International collaborations**

Title	Researchers	Collaborators	Institute	Country	Funding
RESOLVE: Rational Design of Multivalent Glycocode-Inspired Nanovaccines for Gastric Cancer Immunotherapy	José Alexandre Ferreira, Lúcio Santos, Luís Lima, Andreia Peixoto, Dylan Ferreira, Rui Freitas, Janine Soares, Cristiana Gaiteiro, Andreia Miranda, Sofia Cotton, Carlos Palmeira, Marta Relvas Santos, Bruno Sarmento, Maria José Oliveira, Flávia Castro	Juan Lasarte, Pablo Sarobe, Helder Santos (consultant), Robert Kammerer (consultant)	CIMA at University of Navarra, University Medical Centre Groningen, Friedrich Loeffler Institute	Spain, The Netherlands, Germany,	249.645,00€

Phosphoproteomics of hypoxic and glucose deprived bladder cancer cells: the missing link towards systems oncology.	José Alexandre Ferreira (PI), Andreia Peixoto, Marta Relvas Santos	Albert Heck's laboratory	Utrecht university	The Netherlands	-
Envolv: Breast Cancer; Molecular lab organization	Lúcio Lara Santos	Hospital Agostinho Neto	Fundação Calouste Gulbenkian	Cape Verde	-

## Management, Outcomes Research, and Economics in Healthcare Group

### 1. Coordinator

Marina Borges, MSc

### 2. Research team (as of December 31<sup>st</sup> 2021)

Name	Academic Degree	Professional Situation	Category/position	Time %
Ana Salomé Gonçalves Monteiro	MSc	Contract	Data manager	10
Ana Sofia Dias de Oliveira	BSc	Contract	Management	10
Cecilia de Fátima dos Santos Gonçalves de Figueiredo Lopes	BSc	Contract	Law	10
Emanuel José da Costa Meireles de Melo	MSc	Fellowship	Research assistant	100
Inês Fortuna Alves da Silva	MSc	Fellowship	Research assistant	100
Isabel Vicência Franco Campos Matias da Veiga Malta	PhD	Contract	Biomedical Sciences	20
José Luís Simões da Cunha	MSc	Fellowship	Research assistant	100
Luisa Isabel Lopes Conceição	PhD	Contract	Junior Researcher; Public Health	100
Marina Andrea Marques Borges	MSc	Contract	Economics/Management	20
Patrícia Vagos Redondo	MSc	Contract	Management	10
Pedro Filipe da Silva Medeiros	BSc	Contract	Informatics Engineer	10
Sandra Rebelo Sarmiento	PhD	Contract	Medical Physicist	20

### 3. Group description and objectives

Given the level of challenges that healthcare systems face worldwide, established areas of knowledge such as applied management or economics are summoned to contribute to the resolution of prominent and delicate questions. Moreover, nowadays we can only conceptualize healthcare management with a strong component of clinical outcomes. Value-based health care is moving in a fast pace to be considered the golden standard in the field of healthcare management.

Health economics is a recent discipline in the field of economics, but already well established. Considering the increasing cost of cancer treatment, due to the introduction of new and expensive drugs, the tools provided by health technology assessment are critical to optimize the efficiency and effectiveness of the healthcare provided.

MOREHealth research group aims to impact healthcare local and globally by producing knowledge in the following areas:

- Healthcare management;
- Outcomes research;
- Health economics.

As IPO Porto Research Center is based in a cancer institute, we can leverage the role of a research group in these areas, because of the strong integration with the clinical practice.

The group will incorporate a multidisciplinary perspective; will seek national and international partnerships for the projects; will publish and communicate; will support observational studies at IPO Porto or with partner institutions; will enlarge the number of members with PhD.

### 4. Active projects and funding

Title	Principal Investigator	Funding
I-O Optimize initiative (Lung Cancer)	Marta Soares (Medical Oncology)	E-OEN
EU Breast Cancer Evidence Platform	Joana Bordalo e Sá (Oncologia médica)	E-OEN

Real-world response/survival and treatment patterns among patients with relapsed/refractory indolent Non-Hodgkin Lymphoma in USA, UK, France, Spain and Portugal oncology practices	Teresa Garcia (Onco-hematology)	E-OEN
Clinical characteristics, treatment patterns, and outcomes of Lenalidomide-refractory Multiple Myeloma patients in real-world settings: a multi-center retrospective cohort study	Eduarda Couto (Onco-hematology)	E-OEN
Real world evidence in Epithelial Ovarian Cancer. A retrospective multi-centre cohort study	Joana Bordalo e Sá (Medical Oncology)	E-OEN
CATERPILLAR-RWE study: Real-world contemporary systemic anti-cancer therapy effectiveness in patients with advanced/metastatic non-small cell lung cancer (NSCLC) harbouring epidermal growth factor receptor Ex20ins (i.e. external control cohort	Marta Soares (Medical Oncology)	E-OEN
Evaluation of the cost of treatment of pressure ulcers in oncological patients.	Marina Borges (MOREHealth RG)	N.a.
VOICE: Value based healthcare for Outcomes In breast and lung Cancer in Europe (lung cancer	Marta Soares (Oncologia médica)	N.a.
Neoadjuvant pertuzumab – HER2+ breast cancer	Cláudia Vieira (Medical Oncology)	N.a.
FIMDA: Evaluation of the cost of treatment and its aggressivity among oncology patients at end-of-life	Isabel Pereira (Medical Oncology)	N.a.
Comprehensive real-world evidence in stage III and IV melanoma – evaluation of a cohort of patients treated at a Portuguese institution	Ivo Julião (Medical Oncology)	Novartis
Retrospective cohort studies of real-world data (RWD) in Non-Small Cell Lung Cancer (NSCLC)	Marta Soares (Medical Oncology)	AatraZeneca
FAROL - implementation of a financing model based on the measurement of clinical and non-clinical outcomes and integrated disease management in lung cancer at IPO Porto	Marta Soares (Medical Oncology)	N.a.
ABC-Benchmarking - Achieving Best possible Cancer treatment outcomes in treatment pathways through Benchmarking in breast and prostate cancer	N.a.	N.a.

### 5. Major achievements in 2021 (based on the 2 most relevant publication for the group)

We would like to highlight the research group participation in the International Scholar-5 External Control Cohort of patients with Relapsed/Refractory Follicular Lymphoma. The comparison with the clinical outcomes from the updated Zuma-5 (Axicabtagene Ciloleucel) clinical trial demonstrated a clinically and statistically significant improvement in overall survival and progression free survival, highlighting that this CAR T-cell therapy addresses and important unmet need for these patients. Moreover, one PhD thesis ongoing by Marina Borges; Title: Breast cancer treatment cost; Program: Public Health; Area of expertise: Policy, Management and Health Administration; University: National School of Public Health (Nova University of Lisbon); Supervisor team: Prof. Carlos Manuel Morais da Costa, Prof. António da Silva Dias Alves and Prof. Maria Deolinda Paulino Pereira de Sousa Pereira.

**Soares, M., Antunes, L., Redondo, P., Borges, M., Grimson, F., Hermans, R., Chaib, C., Lacoïn, L., Juarez-Garcia, A., Daumont, M.J., Penrod, J.R., Bento, M.J., and Goncalves, F.R., Small cell lung cancer treatment and survival in Portugal: A retrospective analysis from the I-O Optimise initiative. *Eur J Cancer Care (Engl)*, 30(6):e13496, 2021 [IF: 2.520]**

Currently, there is a need to assess effectiveness in real-life clinical practice to fully evaluate the benefits of anticancer therapies. Moreover, in the context of assessing the impact of newer treatments, for example, immune checkpoint inhibitors, it is important to understand treatment patterns, patient outcomes and disease burden in the period before these treatments became available. I-O Optimise, a multinational,

observational research initiative, has been designed to utilise existing real-world data sources to provide valuable insights on the evolving treatment landscape for thoracic malignancies, including Small cell lung cancer (SCLC), across several countries in Europe. The database held by the IPO-Porto hospital is one of the data sources in this collaborative initiative. In this analysis, we describe the treatment patterns and survival outcomes among patients diagnosed with SCLC at IPO-Porto between 2012 and 2017. This real-world data analysis from IPO-Porto demonstrates a disease burden for patients diagnosed with SCLC, particularly those with ED, and highlights a need for more effective therapies

**Brandao, M., Morais, S., Guisseve, A., Bata, G., Borges, M., Tulsidas, S., Pereira, S., Carrilho, C., and Lunet, N., Comparing the cost of non-metastatic breast cancer care in a low-income vs a high-income country: A plea for an optimal allocation of health resources in Sub-Saharan Africa. *Breast*, 2021. 57:1-4 [IF: 4.380]**

Breast cancer (BC) is largely prevalent worldwide. HER2-positive BC account for roughly 20–25% of all BC cases and has an overall survival lower than other BC. Innovation on BC therapeutics is a constant, but novel therapies have higher costs. Therefore, cost-effectiveness research is essential to provide healthcare decision-makers with solid foundations for a resource allocation. This study aimed at estimating the average direct medical costs/ patient and cost-effectiveness of adding pertuzumab in neoadjuvant treatment (NeoT) for HER2-positive breast cancer (BC). ICER was more favourable in stage III HR negative BC patients compared to other patient profiles. Innovative treatments access is critical to deliver high-quality healthcare, but sustainability must be considered. These results suggest the importance of establishing a cost-effectiveness profile of Pertuzumab in NeoT for HER2- positive BC

## 6. Scientific output in 2021

### a. Peer-reviewed indexed publications (final publication date in 2021)

- **Borges, A., Pereira, F., Redondo, P., Antunes, L., Vieira, C., Antunes, P., Bento, M.J., Sousa, S., Lopes, J.M., Rocha-Goncalves, F., de Sousa, J.A., Pereira, D.S., and Borges, M., The addition of neoadjuvant pertuzumab for the treatment of HER2+ breast cancer: a cost estimate with real-world data. *Health Econ Rev* 11(1):33, 2021 [IF: 2.306]**
- **Brandao, M., Morais, S., Guisseve, A., Bata, G., Borges, M., Tulsidas, S., Pereira, S., Carrilho, C., and Lunet, N., Comparing the cost of non-metastatic breast cancer care in a low-income vs a high-income country: A plea for an optimal allocation of health resources in Sub-Saharan Africa. *Breast*, 2021. 57:1-4 [IF: 4.380]**
- O'Connor, U., Carinou, E., Clairand, I., Ciraj-Bjelac, O., De Monte, F., Domienik-Andrzejewska, J., Ferrari, P., Ginjaume, M., Hrsak, H., Hupe, O., Knezevic, Z., Sans Merce, M., **Sarmiento, S.**, Siiskonen, T., and Vanhavere, F., Recommendations for the use of active personal dosimeters (APDs) in interventional workplaces in hospitals. *Phys Med* 87:131-135, 2021. [IF:2.685]
- **Queiros, L., Redondo, P., Franca, M., Silva, S.E., Borges, P., de Melo, A.B., Pereira, N., da Costa, P.F., Carvalho, N., Borges, M., Sequeira, I., Goncalves, F.N.R., and Lemos, J., Implementing ICHOM standard set for cataract surgery at IPO-Porto (Portugal): clinical outcomes, quality of life and costs. *BMC Ophthalmol* 21(1):119, 2021 [IF: 2.209]**
- Reis-Mendes, A., Dores-Sousa, J.L., Padrao, A.I., Duarte-Araujo, M., Duarte, J.A., Seabra, V., **Goncalves-Monteiro, S.**, Remiao, F., Carvalho, F., Sousa, E., Bastos, M.L., and Costa, V.M., Inflammation as a Possible Trigger for Mitoxantrone-Induced Cardiotoxicity: An In Vivo Study in Adult and Infant Mice. *Pharmaceuticals (Basel)* 14(6), 2021 [IF: 5.863]
- Reis-Mendes, A., Padrao, A.I., Duarte, J.A., **Goncalves-Monteiro, S.**, Duarte-Araujo, M., Remiao, F., Carvalho, F., Sousa, E., Bastos, M.L., and Costa, V.M., Role of Inflammation and Redox Status on Doxorubicin-Induced Cardiotoxicity in Infant and Adult CD-1 Male Mice. *Biomolecules*, 2021. 11(11) [IF: 4.879]
- **Santos, J., Silva, S., and Sarmiento, S., Optimized method for in vivo dosimetry with small films in pelvic IOERT for rectal cancer. *Phys Med.* 81:20-30, 2021. [IF: 2.685]**
- **Soares, M., Antunes, L., Redondo, P., Borges, M., Grimson, F., Hermans, R., Chaib, C., Lacoïn, L., Juarez-Garcia, A., Daumont, M.J., Penrod, J.R., Bento, M.J., and Goncalves, F.R., Small cell lung cancer treatment and survival in Portugal: A retrospective analysis from the I-O Optimise initiative. *Eur J Cancer Care (Engl)*, 30(6):e13496, 2021 [IF: 2.520]**

- **Soares, M., Antunes, L., Redondo, P., Borges, M., Hermans, R., Patel, D., Grimson, F., Munro, R., Chaib, C., Lacoïn, L., Daumont, M., Penrod, J.R., O'Donnell, J.C., Bento, M.J., and Goncalves, F.R., Treatment and outcomes for early non-small-cell lung cancer: a retrospective analysis of a Portuguese hospital database. Lung Cancer Manag. 10(2):LMT46, 2021. [IF: NA]**

**b. Other outputs**

**Posters in international Conferences**

- Savva-Bordalo, J, Magalhães, M, Calisto, R, Redondo, P, Borges, M, Bento, MJ, Petiz, A and Pereira, D. **Real-world of ovarian cancer treatment outcomes in Northern Portugal.** E-poster presented at “22nd European Congress on Gynaecological Oncology” (23<sup>rd</sup>-25<sup>th</sup> and 30<sup>th</sup>-31<sup>st</sup>October 2021) ([https://ijgc.bmj.com/content/31/Suppl\\_3/A274.2](https://ijgc.bmj.com/content/31/Suppl_3/A274.2)).
- Soares, M, Gonçalves-Monteiro, S, Antunes, L, Bernardo, F, Figueiredo, S, Borges, M, Bento, MJ and Redondo, P. **EGFR mutated Non-Small Cell Lung Cancer Treatment Pathway – What is the best way?.** E-poster presented at “2021 World Conference on Lung Cancer” (8<sup>th</sup>-14<sup>th</sup> September 2021) ([https://www.jto.org/article/S1556-0864\(21\)02949-X/fulltext#relatedArticles](https://www.jto.org/article/S1556-0864(21)02949-X/fulltext#relatedArticles)).
- Vaz-Ferreira, A, Monteiro, S, Lopes, AR, Abreu, M, Ferreira, M, Sousa, S, Redondo, P, Pereira, D and Savva-Bordalo, J. **Bevacizumab in cervical cancer – the experience of a comprehensive cancer center in northern Portugal.** EPoster presented at “22nd European Congress on Gynaecological Oncology ” (23<sup>rd</sup>-25<sup>th</sup> and 30<sup>th</sup>-31<sup>st</sup>October 2021) ([https://ijgc.bmj.com/content/31/Suppl\\_3/A31.3](https://ijgc.bmj.com/content/31/Suppl_3/A31.3))
- Pinto, R, Monteiro, S, Lima, B, Lopes, AR, Abreu, M, Ferreira, M, Sousa, S, Redondo, P, Pereira, D and Savva-Bordalo, J. **Effectiveness of Bevacizumab in Platinum-Resistant Recurrent Epithelial Ovarian Cancer.** E-Poster presented at “22nd European Congress on Gynaecological Oncology ” (23<sup>rd</sup>-25<sup>th</sup> and 30<sup>th</sup>-31<sup>st</sup>October 2021) ([https://ijgc.bmj.com/content/ijgc/31/Suppl\\_3/A271.1.full.pdf](https://ijgc.bmj.com/content/ijgc/31/Suppl_3/A271.1.full.pdf))
- Savva-Bordalo, J, Cunha, J, Monteiro, S, Redondo, P, Sousa, S and Pereira, D. **Real World Effectiveness and Quality of Life of Ribociclib and Letrozole in Advanced Breast Cancer.** E-Poster presented at “Advanced Breast Cancer Sixth International Consensus Conference (ABC6)” (4<sup>th</sup>-6<sup>th</sup> November 2021) (<https://www.sciencedirect.com/science/article/pii/S0960977621005531>)
- Hall, G, Cheeseman, S, Levick, B, Nam, EJ, Lim, S, Classe, J-M, Martin, E, Kubelac, P, Achimaş-Cadariu, P, Savva-Bordalo, J, Borges, M, Becker, S, Shaid, S, Niklas, N and Guergova-Kuras, M. **An international, multicenter, real-world analysis of epithelial ovarian cancer treatment and outcomes.** E-poster presented at “2021 ASCO Annual Meeting” (4<sup>th</sup>-8<sup>th</sup> June 2021) ([https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15\\_suppl.5531](https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.5531)).
- Soares, M, Gonçalves-Monteio, S, Antunes, L, Bernardo, F, Figueiredo, S, Borges, M, Bento, MJ and Redondo, P. **Locally Advanced, Stage III Non-Small Cell Lung Cancer: A Highly Heterogenous Patient Population.** E-Poster presented at “European Lung Cancer Virtual Congress 2021” (25<sup>th</sup> to 27<sup>th</sup> March 2021) ([https://www.jto.org/article/S1556-0864\(21\)01917-1/fulltext](https://www.jto.org/article/S1556-0864(21)01917-1/fulltext))
- Soares, M, Antunes, L, Oliveira-Gomes, J, Paupério, GS, Cardia, J, Redondo, P, Borges, M, Chaib, C, Lacoïn, L, Grimson, F, Ralphy, E, Munro, R, Daumont, M, Penrod, JR, O'Donnell, JC, Bento, MJ and Rocha-Gonçalves, F. **Second-Line Immunotherapy Treatment Patterns in Non-Small Cell Lung Cancer in Portugal: An I-O Optimise Cohort Study.** Poster presented at “2020 World Conference on Lung Cancer” (28<sup>th</sup>-31<sup>th</sup> January 2021) ([https://www.jto.org/article/S1556-0864\(21\)00512-8/fulltext](https://www.jto.org/article/S1556-0864(21)00512-8/fulltext))
- Pereira, I, Gomes, J, Redondo, P, Antunes, L, Borges, M and Savva-Bordalo J. **Aggressiveness and economic impact of advanced cancer treatment near the end of life.** E-Poster Display presented at “ESMO Virtual Congress 2020”, (19<sup>th</sup>-21<sup>st</sup> September 2020) (<https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020/aggressiveness-and-economic-impact-of-advanced-cancer-treatment-near-the-end-of-life>)
- Couto, ME, Borges, M, Bento, MJ, Calisto, R, Magalhaes, M, Ajmal, A, Niklas, N, Dushkin, K, MacDougall, F, Wolf, A, Shaid, S, von Metzler, I. **Treatment Patterns and Outcomes in Lenalidomide-Exposed Multiple Myeloma Patients in Real-World Settings: A Multi-Center Retrospective Study.** Abstract published in Blood, Volume 138, Issue supplement 1, 23<sup>rd</sup> November 2021 (ASH Annual Meeting) (<https://ashpublications.org/blood/article/138/Supplement%201/5012/482048/Treatment-Patterns-and-Outcomes-in-Lenalidomide>)
- Julião, I, Cunha, JL, Redondo, P, Rodrigues, J, Figueiredo, T, Sousa, A, Antunes, L, Freitas, AS, Moital, I, Bento, MJ, Borges, M. **Comprehensive real-world evidence research in stage III and IV melanoma: Evaluation of a cohort of patients treated at a Portuguese institution.** Abstract published in Journal of Clinical Oncology, Volume 39, Issue 15\_suppl, 20<sup>th</sup> May 2021 (2021 ASCO Annual Meeting I) ([https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15\\_suppl.e18774](https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.e18774)).

**Posters in national Conferences**

- Lima B, Gonçalves-Monteiro, S, Pinto, R, Lopes, AR, Abreu, M, Ferreira, M, Sousa, S, Redondo, P, Pereira, D and Savva-Bordalo, J. **Efetividade da adição de Bevacizumab ao tratamento sistémico anti-neoplásico de 1ª linha no cancro epitelial do ovário**. E-Poster presented at “18º Congresso Nacional de Oncologia” (18th-20th November 2021)
- Julião, I, Redondo, P, Cunha, JL, Rodrigues, J, Antunes, L, Pardal, M, Freitas, AS, Bento, MJ and Borges, M. **Real world evidence em melanoma estágio III - avaliação de uma coorte de doentes tratados numa instituição portuguesa**. Oral communication at “17º Congresso Nacional Oncologia” (18<sup>th</sup>-22<sup>nd</sup> November 2020)
  - **Award:** Best oral communication award in Skin Cancer
  - Pereira, I, Gomes, J, Redondo, P, Antunes, L, Borges, M and Savva-Bordalo, J. **Aggressiveness and economic impact of advanced cancer treatment near the end of life**. E-Poster Display presented at “17º Congresso Nacional Oncologia” (18<sup>th</sup>-22<sup>nd</sup> November 2020)
  - **Award:** Best poster in Supportive Care

**Teaching Activity: Coordination of Curricular Units/Courses**

Researcher	Curricular Unit	Programme	Position	Faculty/University
Marina Borges	Cost-effectiveness in oncology	Postgraduation in Surgical Oncology	Teaching	Fernando Pessoa University

**International collaborations**

Acronym	Title	Aim	Coordinator
E-OEN	European Oncology Evidence Network	E-OEN is a research network of Europe’s larger cancer hospitals working with IQVIA to provide high-quality, real-world data reflecting the latest clinical practice.	NA
DigiCore	DiGital Institute for Cancer Outcomes REsearch	DIGICORE’s objectives are to help the cancer community for the digital revolution that will transform research through the routine use of electronic health records (EHR) and molecular diagnostic information (MDX) for trial automation, outcomes research, digital diagnostics, and care quality management.	NA
OECI-WGCEB	OECI Working Group on Cancer Economics and Benchmarking	The primary objectives of the WG is to demonstrate merits of cost-benefits analyses in oncology and to establish standards in budget impact analysis for OECI members.	Wim H. van Harten (Chairperson)
TDABC	TDABC in Healthcare Consortium	The TDABC in Healthcare Consortium is a collaborative group of researchers and institutions dedicated to improving the quality of projects that apply Time-driven Activity-based Costing (TDABC) method in healthcare and to sharing methodological advances for TDABC around the globe, to promote value-based healthcare (VBHC).	NA
EURADOS	EURADOS WorkGroup12	Assessment and improvement of patient and staff dosimetry in the medical field, excluding radiotherapy.	Željka Knežević (Chairperson)

## Medical Physics, Radiobiology and Radiation Protection Group

### 1. Coordinator

João Santos, PhD

### 2. Research team (as of December 31<sup>st</sup> 2021)

Name	Academic degree	Professional situation	Category/position	Time %
Alexandre Baptista Mendes Pereira	BSc	Contract	Medical Physicist	20
Anabela Gregório Dias	PhD	Contract	Medical Physicist	30
Bárbara Adélia Meireles Barbosa	MSc	Contract	Technologist	20
Bruno Miguel Ferreira Mendes	MSc	Contract	Medical Physicist	20
Carla Isabel Vaz Tavares Figueiredo Capelo	BSc	Contract	Radiopharmacist	20
Diana Jorge Pimparel Alves Nuno Pinto	BSc	Contract	Medical Physicist	20
Filipe Augusto Madeira Dias	MSc	Contract	Medical Physicist	20
Inês Magalhães da Silva de Lucena e Sampaio	BSc	Contract	Physician	20
Isabel Maria Guedes Bravo	PhD	Contract	Assistant Researcher, Radiobiologist	20
Joana Borges Lencart e Silva	BSc	Contract	Medical Physicist	20
João António Miranda dos Santos	PhD	Contract	Medical Physicist/ Group Leader	30
Jorge Barbosa Pereira	BSc	Contract	Medical Physicist	20
Jorge Eduardo Nunes Oliveira	MSc	Contract, Joaquim Chaves Saúde, Açores	Medical Physicist	20
José Pedro Amorim	MSc	PhD Fellowship	PhD Student	100
Laura Lopes Gonçalves da Providência e Costa	MSc	MSc Student	MSc Student	100
Leyla Ebrahimpour	PhD	Fellowship	Post-doctoral Research	100
Luís Hugo da Silva Trindade Duarte	BSc	Contract	Physician	20
Luís Paulo Teixeira Cunha	MSc	Contract	Medical Physicist	20
Margarida Macedo Freitas	BSc	MSc Student	MSc Student	100
Miriam Raquel Seoane Pereira Seguro Santos	MSc	PhD Fellowship	PhD Student	50
Pedro Filipe Conde Andrade Silva	MSc	Contract	Technologist	20
Pedro Peixoto Teles	PhD	Contract, FCUP	Physicist/Professor	50
Rogéria Maria Craveiro Pereira	MSc	Contract	Radiobiologist	20
Sara Patrícia de Almeida Pinto	MSc	Contract	Medical Physicist	20
Sofia Isabel de Castro e Silva	PhD	Contract	Medical Physicist	20
Susana Margarida Oliveira Gonçalves	MSc	Contract	Technologist/ Dosimetris	20

### 3. Group description and objectives

The Medical Physics, Radiobiology and Radiation Protection Group was formed in the beginning of 2008 housed by the IPO-Porto Research Center. Its members are mainly physicists and radiobiologists but also include other expertises such as radiopharmacy and clinical practitioners. It is the only Medical Physics and Radiobiology research group in Portugal whose activities are developed entirely in a hospital environment. The work of the group focuses on the application of the methodology of physics and radiobiology to solve specific problems related to health care, especially in the area of ionizing radiation, both from the perspective of the patient procedures optimization or in the perspective of the protection in the event of professional

exposure to ionizing radiation. Being focused in the interaction of ionizing radiation and biological tissues, the question of radiation protection arises immediately. The group embraced already critical personal exposure due to highly heterogeneous radiation fields during the project “Dose distribution mapping and Monte Carlo simulations in CT-fluoroscopy” (PTDC/SAU-ENB/115792/2009) and patient exposure during intra-operative radiotherapy during the project “IORT: the effect of shielding on dose distributions in intra-operative electron radiotherapy: a Monte Carlo simulations study.” (PTDC/SAU-ENB/117631/2010). Both these studies were complemented by Monte Carlo (MC) simulations. This methodology, with increasing computer power over the last years, is becoming a benchmark method to simulate “difficult-to-execute-in-practice” procedures in ionizing radiation physics, where exposure of subjects must be very well justified. Over the year of 2017, the group extended this methodology to external radiotherapy using Penelope based PRIMO software, which has become one of the main strategic lines of research. Monte Carlo methods are being used also in the field of Nuclear Medicine, both for imaging and radiation spectrum analysis and optimization.

The group is involved in several national and international collaborations such as Faculdade de Ciências da Universidade do Porto, Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto, Instituto Superior Técnico (IST/CTN), INESC Porto, Universidade de Aveiro (Dep. Eng. Mecânica), Universidade de Coimbra (Centro de Informática e Sistemas da Universidade de Coimbra; LIP), Faculdade de Ciências da Universidade de Lisboa, Universidade do Minho (MEMS), Institute of Nuclear Physics PAN, Radzikowskiego 152, PL 31-342 Krakow, Radiation Chemistry and Dosimetry Laboratory, Bijenička c. 54, HR-10000 Zagreb, Croatia, Greek Atomic Energy Commission (EEAE), Dosimetry and Calibration Department P.O. Box 60092, 153 10 Agia Paraskevi, Athens, Greece, SCK•CEN | Belgian Nuclear Research Centre, Unit Research in Dosimetric Applications, Boeretang 200 - BE-2400 Mol, among others.

The group has one Full Member (J.A.M. Santos) in the European Radiation Dosimetry Group (Eurados), and one Corresponding Member (J. Lencart), in the Workgroup 9, WG9 (Radiation Protection in Radiotherapy).

#### 4. Active projects and funding

- RAD3fRT- “Radiobiological effects of flattening filter free radiotherapy treatments” (CI-IPOP-119-2019), Budget: 15 000,00 € (2020-2023), PI: Isabel Bravo
- PRIMO- “Development of MC (PRIMO) tools for the optimization of EBRT workflows” (CI-IPOP-132-2020), Budget: 20 000,00 € (2020-2023), PI: João Santos
- TIPTOP- “Artificial intelligence applied to image-based oncological prognosis” (CI-IPOP-133-2020), Budget: 21 000,00 € (2020-2023), PI: Inês Domingues
- NVMAT - “Neuronal networking for VMAT failure probability determination” (CI-IPOP-134-2020), Budget: 34 000,00 € (2020-2023), PI: Sofia Silva
- CTOP - “CBCT dose measurement and optimization in image guided radiation therapy” (CI-IPOP-135-2020), Budget: 19 000,00 € (2020-2023), PI: Anabela Dias
- DOSIMAG- “Investigation of dose contribution in oncological population due to new imaging techniques” (CI-IPOP-136-2020), Budget: 17 000,00 € (2020-2023), PI: Pedro Teles

#### 5. Major achievements in 2021 (based on the 2 most relevant publications for the group)

##### A. Radiomic features in prostate cancer

Bruno Mendes, Inês Domingues, and João Santos. Prostate Cancer Aggressiveness Prediction Using CT Images. *Life*, 11(11):1164, 2021

Within this line of work, three main branches were explored. In the first line of work, radiomic features were analysed with the goal of predicting prostate cancer aggressiveness from CT images. The overall goal is to anticipate the prognosis and response to therapy using Artificial Intelligence methods, namely Machine Learning (and its Deep Learning component). This preliminary study focused on prostate cancer patients under the age of 55 treated at the IPO Porto between 2015 and 2019 (corresponding to a period of 5 years). Patients in this age group were chosen, as they typically present a more aggressive pathology, with a higher incidence of metastases, and with a lower average 5 year life expectancy. The fundamental motivation relies on the wide availability of CT images and the need to provide tools to assess EBRT effectiveness. Pyradiomics

and Local Image Features Extraction (LIFEx) were used to extract features and search for a radiomic signature within CT images. Promising results were found when applying Principal Component Analysis (PCA) to the features. Features need, however, to be extracted from previously delimited regions of interest. Several image segmentation methods were explored and compared to segment the bladder in CT images. To note that the bladder is one of the organs at risk in prostate cancer radiotherapy. Clustering, U-Net, Active Contours and Graph Based were experimented, being observed that U-Net presented the best results. In a different work, the same network, U-Net, was used in a multi-class setting to simultaneously segment the prostate and two organs at risk, namely the bladder and the rectum. The results suggest that training a model using a multi-class strategy, seems to improve the segmentation results for a previously challenging organ such as the rectum.

#### B. Hotspots detection in prostate cancer metastasis

Laura Providência, Inês Domingues, and João Santos. An iterative algorithm for semisupervised classification of hotspots on bone scintigraphies of patients with prostate cancer. *Journal of Imaging*, 7(8):148, 2021

A computational methodology was developed to detect hotspots in scintigraphy images. The first part consists of an image processing method that over-detects regions of interest. The number of false positives is then attenuated through two different methods: one using image analysis techniques and other using machine learning. For the machine learning method, an iterative semi-supervised classification algorithm was specially created for the purpose of hotspot classification, only requiring knowledge about the type of bone scan the hotspots were extracted from, and not about the hotspots themselves. The final assessment of the scintigraphic exam was accomplished by calculating the Bone Scan Index, a quantitative biomarker specially developed to improve the interpretation and clinical relevance of bone scans from patients with metastatic prostate cancer. Results from this line of work can be found in the following references.

## 6. Scientific output in 2021

### a. Peer-reviewed indexed publications (final publication date in 2021)

- **Bravo, I.**, Comment on a systematic review and meta-analysis on single fraction radiosurgery, fractionated radiosurgery, and conventional radiotherapy for spinal oligometastasis. *Radiother Oncol*, 154:e1, 2021 [IF: 6.280]
- Lima Ferreira, J., **Costa, C.**, Marques, B., **Castro, S.**, Victor, M., **Oliveira, J.**, **Santos, A.P.**, **Sampaio, I.L.**, **Duarte, H.**, Marques, A.P., and **Torres, I.**, Improved survival in patients with thyroid function test abnormalities secondary to immune-checkpoint inhibitors. *Cancer Immunol Immunother* 70(2)299-309, 2021. [IF: 6.968]
- **Lopes de Castro, C.**, Fundowicz, M., Rosello, A., Jove, J., Deantonio, L., Aguiar, A., Pisani, C., Villa, S., Boladeras, A., Konstanty, E., Kruszyna-Mochalska, M., Milecki, P., Jurado-Bruggeman, D., **Lencart, J.**, Modolell, I., Munoz-Montplet, C., Aliste, L., Torras, M.G., Puigdemont, M., **Carvalho, L.**, Krenkli, M., Guedea, F., and Malicki, J., Results of the IROCA international clinical audit in prostate cancer radiotherapy at six comprehensive cancer centres. *Sci Rep*, 2021. 11(1):12323 [IF: 4.380]
- **Mendes, B.**, **Domingues, I.**, Silva, A., and **Santos, J.**, Prostate Cancer Aggressiveness Prediction Using CT Images. *Life (Basel)*. 11(11), 2021. [IF: 3.817]
- **Providencia, L.**, **Domingues, I.**, and **Santos, J.**, An Iterative Algorithm for Semisupervised Classification of Hotspots on Bone Scintigraphies of Patients with Prostate Cancer. *J Imaging*. 7(8), 2021. [IF: NA]
- **Santos, J.**, **Silva, S.**, and **Sarmiento, S.**, Optimized method for in vivo dosimetry with small films in pelvic IOERT for rectal cancer. *Phys Med*. 81:20-30, 2021. [IF: 2.685]
- Strosberg, JR, Caplin, ME, Kunz, PL, Ruzniewski, PB, Bodei, L, Hendifar, A, Mittra, E, Wolin, EM, Yao, JC, Pavel, ME, Grande, E, Van Cutsem, E, Seregni, E, **Duarte, H**, Gericke, G, Bartalotta, A, Mariani, MF, Demange, A, Mutevelic, S, Krenning, EP and investigators, N- (177)Lu-Dotate plus long-acting octreotide versus highdose long-acting octreotide in patients with midgut neuroendocrine tumours (NETTER-1): final overall survival and long-term safety results from an open-label, randomised, controlled, phase 3 trial. *Lancet Oncol* 22(12):1752-63, 2021. [IF: 41.316]
- Viegas, L., **Domingues, I.**, and Mendes, M., Study on Data Partition for Delimitation of Masses in Mammography. *J Imaging*. 7(9), 2021. [IF: NA]

**b. Other outputs**

**Book Chapters**

M. El Amine Bechar, N. Settouti, and **I. Domingues**, *Deep Learning vs. Super Pixel Classification for Breast Masses Segmentation*, *Deep Learning for Biomedical Applications*, Boca Raton: CRC Press, 2021, pp. 121–156, eBook ISBN9780367855611

**Teaching activity & coordination positions by group members**

Researcher	Curricular Unit	Programme	Position	Faculty/ University
Isabel Bravo, João santos, Pero Teles	Dosimetry, Radiobiology and Radiation Protection	MSc in Medical Physics	Coordination and teaching	Faculty of Sciences-UP
João Santos	Radiological Physics and Nuclear Medicine	MSc in Medical Physics	Coordination and teaching	Faculty of Sciences-UP
Isabel Bravo	Radiobiology	EuropeanMSc in Medical Technology and Healthcare Business (EMMaH)	Teaching	School of Health of Polytechnic Institute of Porto, Health Hamburg University of Applied Sciences, Faculty of Life Sciences, HAW Faculté Ingénierie et Management de la Santé, ILIS

**International Consortia**

Organization	Researcher
European Consortia: Project Safe and Free Exchange of EU Radiography Professionals across Europe (SAFE EUROPE)- Work Package leaders (WP7)	Bárbara Barbosa, Isabel Bravo
European Radiation Dosimetry Group EURADOS ( <a href="https://eurados.sckcen.be/">https://eurados.sckcen.be/</a> )	João Santos

## Molecular Oncology and Viral Pathology Group

### 1. Coordinator

Rui Medeiros, PhD

### 2. Research team (as of December 31<sup>st</sup> 2021)

Name	Academic Degree	Professional Situation	Category/position	Time %
Alexandra de Castro e Costa	BSc	Student	MSc student MOM-FMUP	100
Ana Carina Martins Pereira	PhD	Fellowship	Postdoc FCT SFRH/BPD/114803/2016	50
Ana da Conceição Saraiva e Sousa	MSc	Contract	PhD student	20
Ana Luísa Pereira Teixeira	PhD	Contract	Junior researcher Art. 23.º D.L. 57/2016 + Lei 57/2017	100
Augusto José André Nogueira	PhD	TSS-Camara de VNGaia	Invited Researcher	20
Áurea Rosa Nunes Pereira Lima	PhD	Resident oncology HSS	Invited Researcher	20
Carla Manuela M Silva Campos	MSc	Contract	PhD student	20
Catarina Filipa Pereira Lopes	MSc	Fellowship	Research assistant SIRNAC	100
Cristina Sofia de Jesus Almeida	BSc	Student	MSc student MO-ICBAS	100
David Mata Martins	MD	Resident Internal Medicine	Clinical scientist	30
Francisca Guilherme Carvalho Dias	PhD	Contract	Junior researcher	100
Hugo Manuel Lopes de Sousa	PhD	Contract	Clinical scientist	20
Ines Cristiana Martins Nogueira	MSc	Fellowship	PhD student /FCT	100
Jani Viviana Alves Vital da Silva	PhD	Junior Researcher, AquaValor	Invited Researcher	20
Joana Maria de Oliveira Santos	MSc	Fellowship	PhD student/ FCT	100
Mara Sofia Aires Fernandes	MSc	Fellowship	PhD student LPCC	100
Maria de Fátima Araujo Magalhaes Cerqueira	PhD	Associate Professor UFP	Invited Researcher	20
Mariana Gomes Morais	MSc	Fellowship	PhD student/ FCT	100
Marlene Elisabete dos Santos	PhD	Adjunt professor CESPU	Invited Researcher	30
Mónica Patrícia Silva Gomes	PhD	Clinical scientist LPCC	Clinical scientist LPCC	100
Raquel Jorge Ferreira Catarino	PhD	Clinical Scientist/Resident Urology, HPH	Invited Researcher	20
Rui Manuel de Medeiros Melo Silva	Aggregation	Contract	Group coordinator/Assessor	50
Rui Miguel Gil da Costa Oliveira	PhD	Post-doctoral Researcher FEUP/Visiting Prof.Univ Maranhão	Invited Researcher	40
Setareh Satari	MD	Student	MSc student MOM-FMUP	100
Tânia Rôlo Dias	BSc	Student	MSc student MOM-FMUP	100
Tatiana Nunes Varandas	MSc	Contract	Lab Technician	100
Valéria Delgado Tavares	MSc	Fellowship	PhD student FCT	100

Vera Alexandra Pereira Machado	PhD	Contract	Junior researcher PTDC/MED-QUI/29800/2017	100
Alexandra de Castro e Costa	BSc	Student	MSc student MOM-FMUP	100
Ana Carina Martins Pereira	PhD	Fellowship	Postdoc FCT SFRH/BPD/114803/2016	50

### 3. Group description and objectives

The main goal of the Molecular Oncology and Viral Pathology Group, established in 2002, is the characterization of the molecular mechanisms associated with the cancer onset and with therapeutic outcome, through the identification of molecular biomarkers. Within the framework of Precision Medicine, the Group is especially focused on the study and validation of circulating cancer biomarkers with clinical relevance. Patients' stratification and optimization of current therapy approaches are important outcomes (Pharmacogenomics and Molecular Epidemiology) from this knowledge. Since the beginning, Molecular Oncology and Viral Pathology Group research on Pharmacogenomics and Comparative Personalized Medicine or Precision Medicine incorporated individualized genetic information to understand how this individuality may influence therapeutic responses, drug efficacy, drug side effects, and adverse events related to drug therapy. Furthermore, nowadays we try to clarify the dynamic network that is established between the host and tumor microenvironment, analyzing several types of molecular biomarkers (genetic polymorphisms, mRNAs, microRNAs, lncRNAs and viral genomes) to improve our predictive capacity. The goal of our research will be the development of rational therapeutic algorithms based on a patient's genomic profile in association with other molecular biomarkers, demographics factors, disease state, as well as other co-administered drugs to improve patient's management using mainly liquid biopsy approaches. The long-term goals of the research being conducted are not only identifying responders and non-responders to therapy, but also avoid adverse events, optimize drug dose, and understand the dynamic between the cells. Furthermore, considering the key role of several virus in oncobiology, the group also develops studies in the field of tumor virology, studying the association of viral pathogenesis (especially Human Papillomavirus, CMV and Epstein-Barr Virus) with carcinogenesis.

### 4. Active projects and funding

- ExomiR4RCC -Renal cell carcinoma-derived exosome: the microRNA content as a new disease predictive biomarker and an opportunity to invasive/metastatic disease management under the genetic background. CI-IPOP-21-2015; Budget: 87 500,00 € (2016-2025), PI: Rui Medeiros
- EUPICPHARMADCP-Pharmacogenomic determinants of therapeutic response of urogynecological cancer: (Eu-PIC). CI-IPOP-22-2015; Budget: 62 500,00 € (2016-2025), PI: Rui Medeiros
- VIRCIRCDNA-Circulating viral genomes in the blood of cervical cancer patients. CI-IPO- 37-2016; Budget: 12 500,00 € (2016-2025), PI: Rui Medeiros
- VIRALmiRNA- microRNA-mediated viral regulation of the tumor microenvironment.CI-IPO- 66-2017; Budget: 12 500,00 € (2018-2025), PI: Rui Medeiros
- NanoTEC: Sensitization of urologic tumors therapy driven by nanotechnology (PTDC/MED-QUI/29800/2017); FCT, Fundação para a Ciência e Tecnologia; Budget: 124 301,54 € (2018-2022), PI: Rui Medeiros
- SIRNAC- Novel Therapies Against Metastatic Colorectal Cancer (NORTE-01-0247-FEDER-033399); Fundos FEDER através do Sistema de Incentivos à Investigação e Desenvolvimento Tecnológico; Budget: 211 712,60 € (2018-2021), PI: Rui Medeiros

- GWASPHARMAGEN- GWAS and Data Science as putative approaches for identifying pharmacogenomics determinants of response to therapy. CI-IPOP-66-2017; Budget: 37 500,00 € (2019-2025), PI: Rui Medeiros
- NeutroSAC - Cachexia Anorexia Syndrome and its Clinical, Pharmacogenomic and Biochemical Characterization. CI-IPOP-118-2019; Budget: 40 000,00 € (2020-2025), PI: Rui Medeiros

## 5. Major achievements in 2021

The scientific output of Molecular Oncology and Viral Pathology Group from its beginning has achieved in 2020 a total of 406 international peer reviewed publications and 32 PhD Thesis concluded. During 2020, we published 27 manuscripts. The average impact factor of the 5 most relevant publications was 7.125. This scientific output is linked to the fundamental objective of the group that includes the molecular characterization of the mechanisms associated with the onset of cancer and the definition of new predictive circulating biomarkers that can contribute for a Comprehensive Comparative Precision Medicine. Under special relevance is to observe that the top 5 published manuscripts have as the first author a PhD/MSc Student of the Molecular Oncology and Viral Pathology Group.

We analyzed the applicability of an Extracellular vesicle (EV) derived miRNA profile as potential prognosis biomarkers in ccRCC, showing that the levels of EV-derived hsa-miR-25-3p, hsa-miR-126-5p, hsa-miR-200c-3p and hsa-miR-301a-3p decreased after surgery, whereas hsa-miR-1293 EV-levels increased. Metastatic patients also presented higher levels of hsa-miR-301a-3p and lower levels of hsa-miR-1293 when compared to patients with localized disease after surgery, showing that EVs content varies depending on the presence or absence of the disease and that an increase of EV-derived hsa-miR-301a-3p, and decrease of EV-derived hsa-miR-1293, may be potential biomarkers of metastatic ccRCC. The publication of these results was selected to be the cover of Volume 12, Issue 6 of *Cancers*, MDPI (<https://www.mdpi.com/2072-6694/12/6>). We also analyzed all the scientific literature available regarding green synthesized silver nanoparticles (AgNPs) application as cytotoxic agents in different cancer models. AgNPs potential as cytotoxic agents in cancer has been highlighted in the last years due to their green nature and to their biocompatibility in healthy tissues. Our paper analyzed, correlated, and summarized the AgNPs' main parameters and their influence in their cytotoxic ability showing their future potential in the oncology research. This review is relevant for our ongoing research in the scope of the funded FCT project (Nanowar2UrCancer- PTDC/MED-QUI/29800/2017). We also reviewed the interplay and the differences between cancer cachexia, sarcopenia, anorexia and asthenia as well as the molecular signaling pathways involved in cachexia, particularly those that can be explored as potential therapeutic opportunities. Additionally, we summarized recent data concerning the role of microRNAs and other ncRNAs in cancer cachexia pathogenesis and their possible clinical relevance. We have also showed that Venous Thromboembolism (VTE)-associated Single Nucleotide Polymorphisms (SNPs) reported by GWAS, can be potential Ovarian Cancer (OC)-related biomarkers and also predictive biomarkers of VTE.

## 6. Scientific output in 2021

### *a. Peer-reviewed indexed publications (final publication date in 2021)*

- **Abreu, SC, Tavares, V, Carneiro, F and Medeiros, R.** Venous thromboembolism and prostate cancer: what about genetic markers? *Pharmacogenomics* 22(6):365-73, 2021. [IF:2.533]
- Almeida, J., Ferreira, T., Santos, S., Pires, M.J., **da Costa, R.M.G., Medeiros, R.**, Bastos, M., Neuparth, M.J., Faustino-Rocha, A.I., Abreu, H., Pereira, R., Pacheco, M., Gaivao, I., Rosa, E., and Oliveira, P.A., The Red Seaweed *Grateloupia turuturu* Prevents Epidermal Dysplasia in HPV16-Transgenic Mice. *Nutrients* 13(12), 2021. [IF: 5.772]
- Caldas, A.R., Catita, J., Machado, R., Ribeiro, A., **Cerqueira, F., Horta, B., Medeiros, R.**, Lucio, M., and Lopes, C.M., Omega-3- and Resveratrol-Loaded Lipid Nanosystems for Potential Use as Topical Formulations in Autoimmune, Inflammatory, and Cancerous Skin Diseases. *Pharmaceutics*, 2021. 13(8) [IF: 6.321]
- Canadas-Sousa, A., Santos, M., **Medeiros, R.**, and Dias-Pereira, P., Single Nucleotide Polymorphism in Prolactin Gene Is Associated With Clinical Aggressiveness and Outcome of Canine Mammary Malignant Tumors. *Vet Pathol* 58(6):1051-1057, 2021. [IF: 2.221]

- Cardoso, J.V., **Medeiros, R., Dias, F.**, Costa, I.A., Ferrari, R., Berardo, P.T., and Perini, J.A., DROSHA rs10719 and DICER1 rs3742330 polymorphisms in endometriosis and different diseases: Case-control and review studies. *Exp Mol Pathol*. 119:104616, 2021. [IF: 3.362]
- Carvalho-Correia, E., Calçada, C., Branca, F., Estevez-Gomez, N., De Chiara, L., Varela, N., Gallego-Garcia, P., Posada, D., **Sousa, H.**, Sousa, J., Veiga, M.I., and Osorio, N.S., OmniSARS2: A Highly Sensitive and Specific RT-qPCR-Based COVID-19 Diagnostic Method Designed to Withstand SARS-CoV-2 Lineage Evolution. *Biomedicines* 9(10), 2021. [IF: 6.081]
- Castro, I., Sampaio-Marques, B., A, C.A., **Sousa, H.**, Fernandes, A., Sanchez-Maldonado, J.M., Cunha, C., Carvalho, A., Sainz, J., and Ludovico, P., Functional Genetic Variants in ATG10 Are Associated with Acute Myeloid Leukemia. *Cancers (Basel)* 13(6), 2021. [IF: 6.639]
- **Catarata M.J.**, Lourenço M., Martins M.F., Frade J., Pêgo A., Cordeiro C.R., **Medeiros R.**, Ribeiro R. Pharmacogenetics of advanced lung cancer: Predictive value of functional genetic polymorphism AGXT Pro11Leu in clinical outcome? *Pulmonology* 27(2): 116-123, 2021. [IF: 3.575]
- Cerqueira, F., Maia, M., Gabriel, C., **Medeiros, R.**, Cravo, S., Ribeiro, A.I., Dantas, D., Dias, A.M., Saraiva, L., Raimundo, L., and Pinto, E., Mechanism of Antifungal Activity by 5-Aminoimidazole-4-Carbohydrazonamide Derivatives against Candida albicans and Candida krusei. *Antibiotics (Basel)*, 2021. 10(2) [IF: 4.639]
- Cochicho, D., **Gil da Costa, R.**, and Felix, A., Exploring the roles of HPV16 variants in head and neck squamous cell carcinoma: current challenges and opportunities. *Virology* 18(1): p. 217, 2021. [IF:4.099]
- **Costa, A.C., Santos, J.M.O., Gil da Costa, R.M., and Medeiros, R.**, Impact of immune cells on the hallmarks of cancer: A literature review. *Crit Rev Oncol Hematol* 168: 103541, 2021. [IF: 6.312]
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- de Oliveira Neto, C.P., Medeiros-Fonseca, B., **Estevao, D.**, Mestre, V.F., **Costa, N.R.**, de Andrade, F.E., Oliveira, P.A., Bastos, M., **Medeiros, R.**, Assis, D., Felix, A., Ferreira Lopes, F., **Gil da Costa, R.M.**, Brito, H.O., and Brito, L.M.O., Differential Incidence of Tongue Base Cancer in Male and Female HPV16-Transgenic Mice: Role of Female Sex Hormone Receptors. *Pathogens*. 10(10), 2021. [IF: 3.492]
- **Dias, F., Almeida, C., Teixeira, A.L., Morais, M., and Medeiros, R.**, LAT1 and ASCT2 Related microRNAs as Potential New Therapeutic Agents against Colorectal Cancer Progression. *Biomedicines* 9(2), 2021. [IF: 6.081]
- **Dias, T.R., Santos, J.M.O., Gil da Costa, R.M., and Medeiros, R.**, Long non-coding RNAs regulate the hallmarks of cancer in HPV-induced malignancies. *Crit Rev Oncol Hematol* 161: 103310, 2021. [IF: 6.312]
- **Fernandes, M.**, Marques, H., **Teixeira, A.L.**, and **Medeiros, R.**, Competitive Endogenous RNA Network Involving miRNA and lncRNA in Non-Hodgkin Lymphoma: Current Advances and Clinical Perspectives. *Biomedicines* 9(12), 2021. [IF: 6.081]
- **Fernandes, M.**, Marques, H., **Teixeira, A.L.**, and **Medeiros, R.**, miRNA- and lncRNA-Based Therapeutics for Non-Hodgkin's Lymphoma: Moving towards an RNA-Guided Precision Medicine. *Cancers (Basel)* 13(24), 2021. [IF:6.639]
- **Fernandes, R.**, Dos Santos, J., Reis, F., and Monteiro, S., Cushing Syndrome as a Manifestation of Neuroendocrine Prostate Cancer: A Rare Presentation Within a Rare Tumor. *Cureus*. 13(9):e18160, 2021. [IF: NA]
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- Freitas-Silva, M., **Medeiros, R.**, and Nunes, J.P.L., Risk factors among stroke subtypes and its impact on the clinical outcome of patients of Northern Portugal under previous aspirin therapy. Clin Neurol Neurosurg, 2021. 203:106564 [IF: 1.876]
- **Gil da Costa, R.M.** and Abreu-Silva, A.L., Editorial: Biology and Pathology of Tumor Viruses in Animals. Front Vet Sci. 8:797596, 2021 [IF: 3.412]
- Goncalves, H.M., **Silva, J.**, Pintado Maury, I., **Tavares, A.**, **Campos, C.**, **Sousa, H.**, Jacinto, A., Aguiar, P., Caldeira, L., and **Medeiros, R.**, The prevalence and risk-factors of oral HPV DNA detection among HIV-infected men between men who have sex with men and heterosexual men. Infect Dis (Lond). 53(1):19-30, 2021. [IF: 3.404]
- **Lima, A.**, Peixoto, I, **Sarandao, S.**, Melo, D, **Rodrigues, A** and **Pereira, H.** Breast Cancer Metastasis in a Renal Carcinoma Pulmonary Metastasis: A Rare Example of Tumor-to-Tumor Metastasis. Case Rep Oncol Med. 2021:3054232, 2021. [IF: NA]
- **Lima, A.**, **Sousa, H.**, Nobre, A., Faria, A.L., and Machado, M., The Impact of COVID-19 Pandemic in Portuguese Cancer Patients: A Retrospective Study. Int J Environ Res Public Health. 18(16), 2021. [IF: 3.390]
- **Lopes, C.**, **Pereira, C.**, **Farinha, M.**, **Medeiros, R.**, and **Dinis-Ribeiro, M.**, Genetic Variations in Prostaglandin E2 Pathway Identified as Susceptibility Biomarkers for Gastric Cancer in an Intermediate Risk European Country. Int J Mol Sci 22(2), 2021. [IF: 5.923]
- **Lopes, C.**, **Pereira, C.**, and **Medeiros, R.**, ASCT2 and LAT1 Contribution to the Hallmarks of Cancer: From a Molecular Perspective to Clinical Translation. Cancers (Basel) 13(2), 2021. [IF:6.639]
- Lopez-Labrador, F.X., Brown, J.R., Fischer, N., Harvala, H., Van Boheemen, S., Cinek, O., Sayiner, A., Madsen, T.V., Auvinen, E., Kufner, V., Huber, M., Rodriguez, C., Jonges, M., Honemann, M., Susi, P., **Sousa, H.**, Klapper, P.E., Perez-Cataluna, A., Hernandez, M., Molenkamp, R., der Hoek, L.V., Schuurman, R., Couto, N., Leuzinger, K., Simmonds, P., Beer, M., Hoper, D., Kamminga, S., Feltkamp, M.C.W., Rodriguez-Diaz, J., Keyaerts, E., Nielsen, X.C., Puchhammer-Stockl, E., Kroes, A.C.M., Buesa, J., Breuer, J., Claas, E.C.J., de Vries, J.J.C., and Sequencing, E.N.o.N.-G., Recommendations for the introduction of metagenomic high-throughput sequencing in clinical virology, part I: Wet lab procedure. J Clin Virol 134: 104691, 2021. [IF:3.168]
- **Medeiros, R.**, **Horta, B.**, Freitas-Silva, J., **Silva, J.**, **Dias, F.**, Sousa, E., Pinto, M., and **Cerqueira, F.**, Effect of 1-Carbaldehyde-3,4-dimethoxyxanthone on Prostate and HPV-18 Positive Cervical Cancer Cell Lines and on Human THP-1 Macrophages. Molecules, 2021. 26(12) [IF: 4.411]
- Medeiros-Fonseca, B., Abreu-Silva, A.L., **Medeiros, R.**, Oliveira, P.A., and **Gil da Costa, R.M.**, Pteridium spp. and Bovine Papillomavirus: Partners in Cancer. Front Vet Sci 8:758720, 2021. [IF:3.412]
- Medeiros-Fonseca, B., Cubilla, A., Brito, H., Martins, T., **Medeiros, R.**, Oliveira, P., and **Gil da Costa, R.M.**, Experimental Models for Studying HPV-Positive and HPV-Negative Penile Cancer: New Tools for An Old Disease. Cancers (Basel) 13(3), 2021. [IF:6.639]
- Milho, C., **Silva, J.**, Guimarães, R., Ferreira, I.C.F.R., Barros, L., and Alves, M.J., Antimicrobials from Medicinal Plants: An Emergent Strategy to Control Oral Biofilms. Applied Sciences 11(9) , 2021. [IF:2.679]
- **Morais, M.**, **Dias, F.**, **Nogueira, I.**, **Leao, A.**, **Goncalves, N.**, **Araujo, L.**, Granja, S., Baltazar, F., **Teixeira, A.L.**, and **Medeiros, R.**, Cancer Cells' Metabolism Dynamics in Renal Cell Carcinoma Patients' Outcome: Influence of GLUT-1-Related hsa-miR-144 and hsa-miR-186. Cancers (Basel) 13(7), 2021. [IF: 6.639]
- **Morais, M.**, **Machado, V.**, **Dias, F.**, **Palmeira, C.**, **Martins, G.**, Fonseca, M., Martins, C.S.M., **Teixeira, A.L.**, Prior, J.A.V., and **Medeiros, R.**, Starch-Capped AgNPs' as Potential Cytotoxic Agents against Prostate Cancer Cells. Nanomaterials (Basel) 11(2), 2021. [IF: 5.076]
- Petrucci, G., Henriques, J., Gregorio, H., Vicente, G., Prada, J., Pires, I., Lobo, L., **Medeiros, R.**, and Queiroga, F., Metastatic feline mammary cancer: prognostic factors, outcome and comparison of different treatment modalities - a retrospective multicentre study. J Feline Med Surg, 2021. 23(6):549-556 [IF: 2.015]

- **Pita, I., Libanio, D., Dias, F., Teixeira, A.L., Nogueira, I., Medeiros, R., Dinis-Ribeiro, M., and Pimentel-Nunes, P.**, Original Article: MicroRNA Dysregulation in the Gastric Carcinogenesis Cascade: Can We Anticipate Its Role in Individualized Care? Pathobiology, 88(5):338-350, 2021 [IF: 4.342]
- **Roumani, F., Azinheiro, S., Sousa, H., Sousa, A., Timoteo, M., Varandas, T., Fonseca-Silva, D., Baldaque, I., Carvalho, J., Prado, M., and Garrido-Maestu, A.**, Optimization and Clinical Evaluation of a Multi-Target Loop-Mediated Isothermal Amplification Assay for the Detection of SARS-CoV-2 in Nasopharyngeal Samples. Viruses 13(5) , 2021. [IF: 5.048]
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- **Santos, J.M.O., Costa, A.C., Dias, T.R., Satari, S., Costa, E.S.M.P., da Costa, R.M.G., and Medeiros, R.**, Towards Drug Repurposing in Cancer Cachexia: Potential Targets and Candidates. Pharmaceuticals (Basel), 2021. 14(11). [IF: 5.863]
- **Silva, J., Cerqueira, F., Teixeira, A.L., Campinha, R., Amorim, J., and Medeiros, R.**, Prevalence of Neisseria gonorrhoeae and Trichomonas vaginalis in Portuguese women of childbearing age. J Obstet Gynaecol 41(2):254-258, 2021 [IF: 1.246]
- **Tavares, V., Pinto, R., Assis, J., Coelho, S., Brandao, M., Alves, S., Pereira, D., and Medeiros, R.**, Implications of venous thromboembolism GWAS reported genetic makeup in the clinical outcome of ovarian cancer patients. Pharmacogenomics J. 21(2):222-232, 2021. [IF: 3.550]
- **Teixeira, A.L., Patrao, A.S., Dias, F., Silva, C., Vieira, I., Silva, J.F., Ferreira, M., Morais, A., Mauricio, J., and Medeiros, R.**, AGO2 expression levels and related genetic polymorphisms: influence in renal cell progression and aggressive phenotypes. Pharmacogenomics, 2021. 22(16):1069-1079 [IF: 2.533]
- **Timoteo, M., Tavares, A., Cruz, S., Campos, C., Medeiros, R., and Sousa, H.**, Association of Murine Double Minute 2 polymorphisms with gastric cancer: A systematic review with meta-analysis. Biomed Rep. 15(2):69, 2021. [IF: NA]

**b. Other Outputs**

**Editorial Board Positions**

Journal	Publishing Company	Position	Researcher
Cancers	MDPI	Guest Editors: "Non-codingRNAs in Renal Cell Carcinoma Landscape"	Ana Luísa Teixeira, Francisca Dias, Rui Medeiros
Cancers	MDPI	Guest Editor: "Basic and translational research on HPV-related malignancies";	Rui Gil da Costa
Revista Portuguesa de Oncologia- Portuguese Journal of Oncology (ISSN 2182-8067)	Portuguese Society of Oncology/ Sociedade Portuguesa de Oncologia	Member of the Editorial Board	Ana Luísa Teixeira, Rui Medeiros
Journal of Visualized Experiments (JoVE)	MyLove Corp.	Guest Editor "Current methods for preclinical research in genitourinary malignancies"	Rui Gil da Costa
Frontiers in Veterinary Science	Frontiers	Guest Editor "Biology and pathology of tumor viruses in animals"	Rui Gil da Costa
Frontiers of Genetics	Frontiers	Member of the Editorial Board	Rui Medeiros
eLife	eLife Sciences	Member of the Editorial Board	Rui Medeiros
Int. J Molecular Sciences	MDPI	Member of the Editorial Board	Rui Medeiros

**Peer review**

Researchers from the group have been invited to participate as reviewers/referees for leading journals in their working field as follows: Archives of Virology, Journal of Medical Virology, Annals of Human Genetics, Biomedicine, BMC Cancer, BMC Medical Genetics, Brazilian Journal Biological Research, Cancers, Carcinogenesis, Cancer Detection and Prevention, Cancer Genetics and Cytogenetics, Cancer Letters, Cancer Drugs, Cancer Research, Disease Biomarkers, European Journal of Cancer, Gynecologic Oncology, Human Mutation, Human Reproduction, International Journal of Obesity, Indian Journal of Cancer, International Journal of Cancer, International Journal of Gynecologic Cancer, Journal of Clinical Pathology, Molecular Human Reproduction, Oncotarget, Pharmacogenomics, Pharmacogenomics Journal, PLOS One, Tumour Biology and Virology

**Grant Reviewer**

Agency	Call	Country	Date	Researcher
•FAF Grants 2021- Belgian Foundation against cancer	Fundamental research	Belgium	2021	Rui Medeiros

**Teaching Activity: Coordination of Curricular Units/Courses**

Researchers from the group actively participate in teaching activities for undergraduate, MSc or PhD Programs lecturing curricular units as Virology, Pharmacogenomics, Pharmacogenomics and Molecular Epidemiology, and Forensic Biology and Forensic Anthropology. Participation in the master’s in Pharmacy; and Master’s in health Biochemistry – ESS – IPP. Participation in the BSc in Biosciences and MSc in Applied Microbiology), Superior School of Biotechnology (ESB-UCP). Participation in the MSc and PhD Program on Medicine and Molecular Oncology, Faculty of Medicine at University of Porto. Participation in the MSc in Oncology and in the PhD Program on Pathology and Molecular Genetics, ICBAS, Biomedical School, Faculty of Medicine at University of Porto.

**Scientific Appointments**

Organization	Researcher
Vice-President of ECL- Association of the European Cancer Leagues, Brussels, Belgium	Rui Medeiros
Scientific Board ECL Annual Meeting ECL European Cancer Leagues	Rui Medeiros
HPV Action Network of the European Cancer Organization	Rui Medeiros
Scientific Board of the LPCC, Portuguese League Against Cancer-North	Rui Medeiros

**National collaborations**

Title	Researcher	Collaborators	Funding	Period
Nanowar2UrCancer: Sensitization of urologic tumors therapy driven by nanotechnology	Rui Medeiros, Ana Luísa Teixeira, Francisca Dias, Mónica Gomes, Mariana Morais, Vera Machado, Deolinda Pereira, Carla Castro, Tiago Ramos, Angelo Oliveira, Carolina Ferreira	REQUIMTE Team: João Prior, Universidade do Porto Team: Alberto Araujo	FCT: PTDC/MED-QUI/29800/2017	2018-2021
SIRNAC- Novel Therapies Against Metastatic Colorectal Cancer	Rui Medeiros, Ana Luísa Teixeira, Francisca Dias, Catarina Lopes, Carina Pereira, Mário Dinis Ribeiro, Rui Henrique, Mónica Farinha, Rita Guimarães, Mariana Ferreira	PHYZAT Biopharmaceuticals Patrício Soares da Silva, INEB	NORTE-01-0247-FEDER-033399	

**International collaborations**

Title	Researchers	Collaborators	Funding
Project staR: European Network on the Study of Germline Genetics of Gastric Cancer   Identifikation von Risikogenen für das Adenokarzinom des Magens   SCHU 2596/6-1	Carina Pereira, Rui Medeiros, Mário Dinis-Ribeiro	Center for Human Genetics, University Hospital of Marburg, Germany,	SCHU 2596/6-1

## Clinical Research Unit

### 1. Coordinator

José Dinis, MD

### 2. Research team (as of December 31<sup>st</sup> 2021)

Name	Academic Degree	Professional Situation	Category/position	Time %
Alina Isabel Miranda Silva Pereira	BSc	Contract	Clinical Trials Assistant	100
Ana Maria Sancas Finisterra	BSc	Contract	Clinical Trials Technician	100
António Eliseu de Carvalho Pereira Osório	MSc	Contract	Clinical Trials Assistant	100
Inês Matos França de Carvalho	MSc	Contract	Clinical Trials Technician	100
Joana dos Santos Soares Harper Maia	BSc	Contract	Manager of Good Clinical Practices and Quality	100
Joana Isabel Gomes Assis	PhD	Contract	Junior Researcher	100
Joana Isabel Valentim Ferreira	BSc	Contract	PhD student	100
Jorge André Anacleto Ribeiro	BSc	Contract	Clinical Trials Assistant	100
José Dinis Bastos Lima da Silva	BSc	Contract	Senior Researcher, Oncologist	10
Juliana Maria Salsa Ferreira	BSc	Contract	Clinical Trials Technician	100
Júlio Manuel Ramos Maia de Oliveira	MSc	Contract	Oncologist, PhD Student	20
Liliana Maria Almeida Azevedo	BSc	Contract	Clinical Trials Assistant	100
Pedro Miguel Fernandes Calvão	BSc	Contract	Clinical Trials Technician	100

### 3. Group description and objectives

IPO-Porto's Clinical Research Unit was created in 2006; its activities are supported by a professionalized team of over 50 MDs, 50 Nurses, 15 pharmacists and several technicians of a wide variety of areas of expertise. Moreover, the Clinical Research Unit has a full-time dedicated team of 11, whose daily activity includes supporting Clinical Trials recruitment and conduct, assist in protocols compliance and support all related procedures involving the multidisciplinary professionals of the institution. IPO-Porto is considered as a reference center for Clinical Trials conducted in Portugal, in most pathologies treated in the institution. Although most of the clinical trials are Phase IIb/Phase III, in early 2019 a subunit- Early phase clinical trials-dedicated to Phase I /Phase IIa trials was created.

### 4. Major achievements in 2021

In 2021, 3 early phase clinical trials were started and 7 were ongoing, being one investigator-initiated and 6 sponsored by Pharma.

#### Early phase clinical trials started in 2021

- A phase 1b study of ASP1948, targeting an immune modulatory receptor, as a single agent and in combination with a PD-I inhibitor (nivolumab or pembrolizumab) in subjects with advanced solid tumors (1948-CL-0101, PI: José Dinis)
- Tumor-agnostic precision immuno-oncology and somatic targeting rational for you (TAPISTRY) phase II platform trial (BO41932 TAPISTRY, PI Júlio Oliveira)
- A Phase 1b/2 clinical study of intratumoral administration of V937 in combination with pembrolizumab (MK-3475) in participants with advanced/metastatic solid tumors (V937-013, PI: Júlio Oliveira)

### Early phase clinical trials ongoing in 2021

- Neoadjuvant Immunotherapy with Durvalumab (MEDI4736) in Non-Surgical Early Stage or Locally Advanced Non-Small Cell Lung Cancer (NSCLC) Followed by Radical Radiotherapy or Chemoradiotherapy (IDEAR) (CI-IPOP 74/2017 IDEAR; Promotor: IPO Porto; PI Julio Oliveira)
- A phase 1, open-label, dose-escalation and dose-expansion study to evaluate the safety, tolerability pharmacokinetics immunogenicity, and antitumor activity of MEDI5752 in subjects with advanced solid tumors (D7980C00001, PI: Dr. Júlio Oliveira)
- A phase 1b study of ASP8374, an immune checkpoint inhibitor, as a single agent and in combination with pembrolizumab in subjects with advanced solid tumors (8374-CL-0101, PI: Dr. Júlio Oliveira)
- A phase II basket study of the oral TRK inhibitor LOXO-101 in subjects with NTRK fusion-positive tumors (LOXO-TRK-15002 NAVIGATE, PI: Dr. Nuno Sousa)
- A phase II, randomized, active-controlled multi-center study comparing the efficacy and safety of targeted therapy or cancer immunotherapy guided by genomic profiling versus platinum-based chemotherapy in patients with cancer of unknown primary site who have received three cycles of platinum doublet chemotherapy (MX39795 CUPISCO, PI: Dr. Ana Ferreira)
- An open-label study to investigate the tolerability, pharmacokinetics and anti-tumour effect following photodynamic therapy (PDT) with single-ascending doses of LUZ11 in patients with advanced head and neck cancer (LUZ11-CDU-001, PI: Prof. Dr. Lúcio Lara Santos)
- Open-label, single-arm trial to evaluate antitumor activity, safety, and pharmacokinetics of SAR408701 used in combination with ramucirumab in metastatic, nonsquamous, non-small-cell lung cancer (NSQ NSCLC) patients with CEACAM5-positive tumors, previously treated with platinum-based chemotherapy and an immune checkpoint inhibitor (ACT16525 CARMEN-LC04, PI: Dr. Júlio Oliveira)

**In 2021, 30 Phase IIb/Phase III Clinical trials were started joining to the 86 already ongoing.**

### Phase IIb/Phase III clinical trials started in 2021

- A phase 3, randomized, open-label study to compare adjuvant immunotherapy of bempegaldesleukin combined with nivolumab versus nivolumab after complete resection of melanoma in patients at high risk for recurrence (20-214-29/CA045-022 PIVOT-12, PI: Dr. Paula Ferreira)
- An open-label, single arm, roll-over study to provide continued treatment with darolutamide in participants who were enrolled in previous Bayer-sponsored studies (20321, PI: Dr. Alina Rosinha)
- Phase 1b/2 study of carfilzomib in combination with induction chemotherapy in children with relapsed or refractory Acute Lymphoblastic Leukemia (20140106, PI: Dr. Vitor Costa)
- Randomized, double-blind, multicenter study comparing magrolimab in combination with azacitidine versus azacitidine plus placebo in treatment-naïve patients with higher risk myelodysplastic syndrome (5F9009 ENHANCE, PI: Dr. Cláudia Moreira)
- A randomized, open-label phase 3 study of combination amivantamab and carboplatin-pemetrexed therapy, compared with carboplatin-pemetrexed, in patients with EGFR Exon 20ins mutated locally advanced or metastatic non-small cell lung cancer (61186372NSC3001 PAPHILLON, PI: Dr. Isabel Azevedo)
- A phase 3, randomized study of amivantamab and lazertinib combination therapy versus osimertinib versus lazertinib as first-line treatment in patients with EGFR-mutated locally advanced or metastatic non-small cell lung cancer (73841937NSC3003 MARIPOSA, PI: Dr. Sara Alves)

- A phase 3, randomized, double-blind, placebo-controlled study of acalabrutinib in combination with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in subjects ≤65 years with previously untreated non-germinal center Diffuse Large B-Cell Lymphoma (ACE-LY-312 (D8227C00001) ESCALADE, PI: Dr. Nelson Domingues)
- A phase 3 randomized, open-label, multicenter study comparing zanubrutinib (BGB-3111) plus rituximab versus bendamustine plus rituximab in patients with previously untreated Mantle Cell Lymphoma who are ineligible for stem cell transplantation (BGB-3111-306 MANGROVE, PI: Dr. Ângelo Martins)
- A phase III randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of GDC-9545 combined with palbociclib compared with letrozole combined with palbociclib in patients with estrogen receptor-positive, HER2-negative locally advanced or metastatic breast cancer (BO41843 PersevERA, PI: Dr. Maria Cassiano Neves)
- A phase III, randomized, open-label study of pralsetinib versus standard of care for first-Line treatment of RET fusion-positive, metastatic non-small cell lung cancer (BO42864 AcceleRET-Lung, PI: Dr. Ana Rodrigues)
- A phase 3, randomized, study of neoadjuvant chemotherapy alone versus neoadjuvant chemotherapy plus nivolumab or nivolumab and BMS-986205, followed by continued post-surgery therapy with nivolumab or nivolumab and BMS-986205 in participants with muscle-invasive bladder cancer (CA017-078, PI: Dr. Nuno Sousa)
- A randomized, multicenter, double-blind, placebo-controlled phase 3 study of Nivolumab versus placebo in combination with neoadjuvant chemotherapy and adjuvant endocrine therapy in patients with high-risk, estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-) primary breast cancer (CA209-7FL CheckMate 7FL, PI: Dr. João Dias)
- A phase III, multi-center, randomized (1:1), open-label, active-controlled study to assess the efficacy and safety of alpelisib (BYL719) in combination with olaparib as compared to single agent cytotoxic chemotherapy, in participants with no germline BRCA mutation detected, platinum-resistant or refractory, high-grade serous ovarian cancer (CBYL719K12301 EPIK-O, PI: Dr. Miguel Abreu)
- A phase III, randomized, controlled, open-label, multicenter, global study of capmatinib versus SoC docetaxel chemotherapy in previously treated patients with EGFR wt, ALK negative, locally advanced or metastatic (stage IIIB/IIIC or IV) NSCLC harboring MET exon 14 skipping mutation (MET $\Delta$ ex14) (CINC280A2301 GEOMETRY III, PI: Dr. Maria Cassiano Neves)
- A phase 3 randomized, double-blind, multicenter, global study of monalizumab or placebo in combination with cetuximab in participants with recurrent or metastatic squamous cell carcinoma of the head and neck previously treated with an immune checkpoint inhibitor (D7310C00001 INTERLINK-1, PI: Dr. João Dias)
- A randomized, double-blind placebo-controlled, phase 3 study of Debio 1143 in combination with platinum-based chemotherapy and standard fractionation intensity-modulated radiotherapy in patients with locally advanced squamous cell carcinoma of the head and neck, suitable for definitive chemoradiotherapy (Debio 1143-SCCHN-301 TRILYNX, PI: Dr. José Dinis)
- A phase II study of adjuvant palbociclib as an alternative to chemotherapy in elderly patients with high-risk ER+/HER2- early breast cancer (EORTC-1745-ETF-BCG APPALACHES, PI: Dr. Inês Pousa)
- A phase III, open-label, randomized study of atezolizumab and tiragolumab compared with durvalumab in patients with locally advanced, unresectable stage III non-small cell lung cancer who have not progressed after concurrent platinum-based chemoradiation (GO41854 SKYSCRAPER-03, PI: Dr. João Dias)

- A randomized open-label phase III study of sacituzumab govitecan versus treatment of physician's choice in subjects with metastatic or locally advanced unresectable urothelial cancer (IMMU-132-13 TROPiCS-04, PI: Dr. Filipa Carneiro)
- An open-label, multicenter, phase 1b/2 study of the safety and efficacy of KRT-232 in combination with acalabrutinib in subjects with relapsed/refractory Diffuse Large B-cell Lymphoma or relapsed/refractory Chronic Lymphocytic Leukemia (KRT-232-111, PI: Dr. Cláudia Moreira)
- A phase 3, multicenter, randomized, open-label trial to compare the efficacy and safety of pembrolizumab (MK-3475) in combination with lenvatinib (E7080/MK-7902) versus docetaxel in previously treated participants with metastatic non-small cell lung cancer (NSCLC) and progressive disease (PD) after platinum doublet chemotherapy and immunotherapy (MK7902-008 LEAP-008, PI: Dr. Isabel Azevedo)
- A phase 2, randomized, open-label three-arm clinical study to evaluate the safety and efficacy of lenvatinib (E7080/MK-7902) in combination with pembrolizumab (MK-3475) versus standard of care chemotherapy and lenvatinib monotherapy in participants with recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) that have progressed after platinum therapy and immunotherapy (PD-1/PD-L1 inhibitors) (MK7902-009 LEAP-009, PI: Dr. Cláudia Vieira)
- A multicenter, open-label, non-comparative, three-arm, phase IIa trial of ipatasertib (GDC-0068) in combination with non-taxane chemotherapy agents for taxane-pretreated unresectable locally advanced or metastatic triple-negative breast cancer patients (MedOPP253 PATHFINDER, PI: Dr. Cláudia Vieira)
- A randomized, multicenter, double-blind, placebo-controlled phase III study of the efficacy and safety of trastuzumab emtansine in combination with atezolizumab or placebo in patients with HER2-positive and PD-L1-positive locally advanced or metastatic breast cancer who have received prior trastuzumab- (+/-pertuzumab) and taxane-based therapy (MO42319 KATE3, PI: Dr. Susana Sousa)
- A phase 3 multicenter, open-label, randomized, controlled study of oral infigratinib versus gemcitabine with cisplatin in subjects with advanced/metastatic or inoperable cholangiocarcinoma with FGFR2 gene fusions/translocations (QBGJ398-301 PROOF 301, PI: Dr. Dânia Marques)
- Targeting EGFR/ERBB2 with neratinib in hormone receptor (HR)-positive/HER2-negative HER2-enriched advanced/metastatic breast cancer (SOLTI-1718 NEREA, PI: Dr. Sara Alves)
- A phase 2 study of TAS-120 in metastatic breast cancers harboring fibroblast growth factor receptor (FGFR) amplifications (TAS-120-201 FOENIX MBC2, PI: Dr. Marta Ferreira)
- A phase III, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of GDC-0074 plus palbociclib and fulvestrant versus placebo plus palbociclib and fulvestrant in patients with PIK3CA-mutant, hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer (WO41554 INAVO120, PI: Dr. Joana Bordalo e Sá)
- A phase III, randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of adjuvant atezolizumab or placebo and trastuzumab emtansine for HER2-positive breast cancer at high risk of recurrence following preoperative therapy (WO42633 ASTEFANIA, PI: Dr. Ana Ferreira)
- A phase III, randomized, double-blind, placebo-controlled study of atezolizumab with or without tiragolumab (anti-TIGIT antibody) in patients with unresectable locally advanced esophageal squamous cell carcinoma (YO42137 SKYSCRAPER-07, PI: Dr. Paula Ferreira)

## Ongoing Phase IIb/Phase III clinical trials

- A 2-part phase III randomized, open label, multicenter study of LGX818 plus MEK162 versus vemurafenib and LGX818 monotherapy in patients with unresectable or metastatic BRAF V600 mutant melanoma (CMEK162B2301 COLUMBUS, PI: Dr. Paula Ferreira)
- A multicenter, randomized, double-blind, placebo-controlled phase 3 study of the Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib, in combination with rituximab versus placebo in combination with rituximab in treatment naïve subjects with follicular lymphoma (PCYC-1141-CA, PI: Dr. José Mário Mariz)
- A multicenter, randomized, open-label phase 2 study evaluating the safety and efficacy of three different regimens of oral panobinostat in combination with subcutaneous bortezomib and oral dexamethasone in patients with relapsed or relapsed/refractory multiple myeloma who have been previously exposed to immunomodulatory agents (CLBH589D2222 PANORAMA-3, PI: Dr. José Mário Mariz)
- A phase 1/2 open-label, multi-center, safety, preliminary efficacy and pharmacokinetic (PK) study of isatuximab in combination with other anti-cancer therapies in participants with lymphoma (ACT15320, PI: Dr. Ilídia Moreira)
- A phase 1/2 study for the safety, efficacy, pharmacokinetic and pharmacodynamics evaluation of SAR439859, administered orally as monotherapy, then in combination with palbociclib in postmenopausal women with estrogen receptor-positive advanced breast cancer (TED14856, PI: Dr. Ana Rodrigues)
- A phase 2, multi-center, open-label, randomized study of oral asciminib added to imatinib versus continued imatinib versus switch to nilotinib in patients with CML-CP who have been previously treated with imatinib and have not achieved deep molecular response (CABL001E2201 ASC4MORE, PI: Dr. Isabel Oliveira)
- A phase 3 multicenter, randomized, double-blind, placebo-controlled trial of the FLT3 inhibitor gilteritinib (ASP2215) administered as maintenance therapy following induction/consolidation therapy for subjects with FLT3/ITD AML in first complete remission (2215-CL-0302 GOSSAMER, PI: Dr. Ana Espirito Santo)
- A phase 3 multicenter, randomized, double-blinded, active-controlled, clinical study to evaluate the safety and efficacy of lenvatinib (E7080/MK-7902) with pembrolizumab (MK-3475) in combination with transarterial chemoembolization (TACE) versus TACE in participants with incurable/non-metastatic hepatocellular carcinoma (MK7902-012 LEAP-012, PI: Dr. Maria Frago)
- A phase 3 multicenter, randomized, open label, active-controlled, study of AMG 510 versus docetaxel for the treatment of previously treated locally advanced and unresectable or metastatic NSCLC subjects with mutated KRAS p.G12C (20190009 CodeBreak 200, PI: Dr. Marta Soares)
- A phase 3 randomized, double-blind, controlled study evaluating FPA144 and modified FOLFOX6 in patients with previously untreated advanced gastric and gastroesophageal cancer: phase 3 preceded by dose-finding in phase 1 (FPA144-004 FIGHT, PI: Dr. Alina Rosinha)
- A phase 3 randomized, open-label, multicenter study assessing the clinical benefit of isatuximab (SAR650984) in combination with bortezomib (Velcade®), lenalidomide (Revlimid®) and dexamethasone versus bortezomib, lenalidomide and dexamethasone in patients with newly diagnosed multiple myeloma not eligible for transplant (EFC12522 IMROZ, PI: Dr. Ângelo Martins)
- A phase 3 study of erdafitinib compared with vinflunine or docetaxel or pembrolizumab in subjects with advanced urothelial cancer and selected FGFR gene aberrations (42756493BLC3001 THOR, PI: Dr. Cátia Faustino)
- A phase 3, double-Blind, placebo-controlled study of quizartinib (AC220) administered in combination with induction and consolidation chemotherapy, and administered as maintenance therapy in subjects 18 to 75 years old with newly diagnosed FLT3-ITD (+) Acute Myeloid Leukemia (QuANTUM-First) (AC220-A-U302 QuANTUM-First, PI: Dr. Ângelo Martins)
- A phase 3, double-blind, randomized study to compare the efficacy and safety of rituximab Plus lenalidomide (CC-5013) versus rituximab plus placebo in subjects with relapsed/refractory indolent lymphoma (CC-5013-NHL-007 AUGMENT, PI: Dr. Cláudia Moreira)

- A phase 3, global, multi-center, double-blind, randomized, efficacy study of zolbetuximab (IMAB362) plus CAPOX compared with placebo plus CAPOX as first-line treatment of subjects with claudin (CLDN) 18.2-Positive, HER2-negative, locally advanced unresectable or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma (8951-CL-0302 GLOW, PI: Dr. Cátia Faustino)
- A phase 3, multicenter, randomized, open-label, active-controlled trial of DS-8201a, an anti-HER2-antibody drug conjugate (ADC), versus treatment of physician's choice for HER2-low, unresectable and/or metastatic breast cancer subjects (DS8201-A-U303 DESTINY, PI: Dr. Ana Rodrigues)
- A phase 3, multicenter, randomized, open-label, parallel-group study of the efficacy and safety of lenalidomide (REVLIMID®) versus chlorambucil as first-line therapy for previously untreated elderly patients with B-cell chronic lymphocytic leukemia (The ORIGIN Trial) (CC-5013-CLL-008 ORIGIN, PI: Dr. Nelson Domingues)
- A phase 3, open-label, randomized study to compare the efficacy and safety of luspaterecept (ACE-536) versus epoetin alfa for the treatment of anemia due to IPSS-R very low, low or intermediate risk myelodysplastic syndromes (MDS) in ESA naïve subjects who require red blood cell transfusions (ACE-536-MDS-002 COMMANDS, PI: Dr. Dulcineia Pereira)
- A phase 3, randomized, comparator-controlled clinical trial to study the efficacy and safety of pembrolizumab (MK-3475) in combination with Bacillus Calmette-Guerin (BCG) in participants with high-risk non-muscle invasive bladder cancer (HR NMIBC) that is persistent or recurrent following BCG induction (MK3475-676 KEYNOTE-676, PI: Dr. Rui Freitas)
- A phase 3, randomized, double-blind, placebo-controlled study of talazoparib with enzalutamide in metastatic castration-resistant prostate cancer (C3441021 TALAPRO-2, PI: Dr. Alina Rosinha)
- A phase 3, randomized, double-blind, placebo-controlled study to evaluate pembrolizumab versus placebo as adjuvant therapy following surgery and radiation in participants with high-risk locally advanced cutaneous squamous cell carcinoma (LA cSCC) (MK3475-630 KEYNOTE-630, PI: Dr. Paula Ferreira)
- A phase 3, randomized, open-label study of NKTR-214 combined with nivolumab versus nivolumab in participants with previously untreated unresectable or metastatic melanoma (CA045-001, PI: Dr. Dânia Marques)
- A phase 3, randomized, placebo-controlled, double-blind study of oral ixazomib citrate (MLN9708) maintenance therapy in patients with multiple myeloma following autologous stem cell transplant (C16019, PI: Dr. Luís Cláudio Leite)
- A phase 3, randomized, placebo-controlled, double-blind study of oral ixazomib maintenance therapy after initial therapy in patients with newly diagnosed multiple myeloma not treated with stem cell transplantation (C16021, PI: Dr. Nelson Domingues)
- A phase 3b, multicenter, open-label, PCI-32765 (Ibrutinib) long-term extension study (PCI-32765CAN3001, PI: Dr. Ana Espírito Santo)
- A phase 4, open-label, single-arm study of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma (C25006, PI: Dr. Ana Espírito Santo)
- A phase Ib, open-label, randomized study to assess safety and preliminary efficacy of tafasitamab in addition to R-CHOP or tafasitamab plus lenalidomide in addition to R-CHOP in patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL) – First-MIND (MOR208C107 First-MIND, PI: Dr. Dulcineia Pereira)
- A phase II, multicenter, randomized, open-label study to evaluate the safety and efficacy of 400 mg of ribociclib in combination with non-steroidal aromatase inhibitors for the treatment of pre- and postmenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer who received no prior therapy for advanced disease (CLEE011A2207 AMALEE, PI: Dr. Ana Ferreira)
- A phase II/III, randomised, multicentre study of MOR00208 with bendamustine versus rituximab with bendamustine in patients with relapsed or refractory diffuse large B-cell lymphoma (R-R DLBCL) who are not eligible for high-dose chemotherapy (HDC) and autologous stem-cell transplantation (ASCT) – B-MIND (MOR208C204 B-MIND, PI: Dr. Dulcineia Pereira)
- A phase III randomized, double-blind, placebo-controlled study of LEE011 or placebo in combination with tamoxifen and goserelin or a non-steroidal aromatase inhibitor (NSAI) and goserelin for the

- treatment of premenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer (CLEE011E2301 MONALEESA-7, PI: Dr. Susana Sousa)
- A phase III randomized, placebo-controlled trial of carboplatin and paclitaxel with or without the PARP inhibitor veliparib (ABT-888) in HER-2 negative metastatic or locally advanced unresectable BRCA-associated breast cancer (M12-914, PI: Dr. Miguel Abreu)
  - A phase III, double-blinded, randomized, placebo-controlled study of atezolizumab plus cobimetinib and vemurafenib versus placebo plus cobimetinib and vemurafenib in previously untreated BRAFV600 mutation-positive patients with unresectable locally advanced or metastatic melanoma (CO39262 TRILOGY, PI: Dr. Paula Ferreira)
  - A phase III, multicenter, randomized, double-blind, placebo-controlled study of atezolizumab (anti-PD-L1 antibody) as adjuvant therapy after definitive local therapy in patients with high-risk locally advanced squamous cell carcinoma of the head and neck (WO40242 IMvoke010, PI: Dr. José Dinis)
  - A phase III, multicenter, randomized, open-label, controlled study to evaluate the efficacy, safety, and pharmacokinetics of atezolizumab given in combination with cabozantinib versus docetaxel monotherapy in patients with metastatic non-small cell lung cancer previously treated with an anti-PD-L1/PD-1 antibody and platinum-containing chemotherapy (GO41892 Contact-1, PI: Dr. Inés Pousa)
  - A phase III, multicenter, randomized, placebo-controlled study of atezolizumab (anti-PD-L1 antibody) as monotherapy and in combination with platinum-based chemotherapy in patients with untreated locally advanced or metastatic urothelial carcinoma (WO30070 IMvigor130, PI: Dr. Nuno Sousa)
  - A phase III, open-label, multicenter trial of avelumab (MSB0010718C) versus platinum based doublet as a first line treatment of recurrent or stage IV PD L1+ non small cell lung cancer (EMR 100070-005 JAVELIN Lung 100, PI: Dr. Marta Soares)
  - A phase III, open-label, multicenter, randomized study to investigate the efficacy and safety of atezolizumab compared with chemotherapy in patients with treatment-naïve advanced or recurrent (stage IIIB not amenable for multimodality treatment) or metastatic (stage IV) non-small cell lung cancer who are deemed unsuitable for platinum-containing therapy (MO29872 IPSOS, PI: Dr. Júlio Oliveira)
  - A phase III, open-label, randomized study to investigate the efficacy and safety of atezolizumab (anti-PD-L1 antibody) compared with best supportive care following adjuvant cisplatin-based chemotherapy in PD-L1-selected patients with completely resected stage IB–IIIA non-small cell lung cancer (GO29527, PI: Dr. Júlio Oliveira)
  - A phase III, randomized, double-blind study to evaluate pembrolizumab plus chemotherapy vs placebo plus chemotherapy as neoadjuvant therapy and pembrolizumab vs placebo as adjuvant therapy for triple negative breast cancer (TNBC) (MK3475-522, PI: Dr. Marta Ferreira)
  - A phase III, randomized, double-blind, controlled, multicenter study of intravenous PI3K inhibitor copanlisib in combination with standard immunochemotherapy versus standard immunochemotherapy in patients with relapsed indolent non-Hodgkin's lymphoma (iNHL) - CHRONOS-4 (17833 CHRONOS-4, PI: Dr. Cláudia Moreira)
  - A phase III, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of copanlisib in combination with rituximab in patients with relapsed indolent B-cell non-Hodgkin's lymphoma (iNHL) - CHRONOS-3 (17067 CHRONOS-3, PI: Dr. Sérgio Chacim)
  - A phase III, randomized, double-blind, placebo-controlled, multicenter trial testing ipatasertib plus abiraterone plus prednisone/prednisolone, relative to placebo plus abiraterone plus prednisone/prednisolone in adult male patients with asymptomatic or mildly symptomatic, previously untreated, metastatic castrate-resistant prostate cancer (CO39303 IPATential 150, PI: Dr. Cátia Faustino)
  - A phase III, randomized, double-blind, placebo-controlled, multicenter study of the efficacy and safety of atezolizumab plus chemotherapy for patients with early relapsing recurrent (inoperable locally advanced or metastatic) triple-negative breast cancer (MO39193 IMPassion132, PI: Dr. Joana Bordalo e Sá)

- A phase III, randomized, open-label study to evaluate pembrolizumab as neoadjuvant therapy and in combination with standard of care as adjuvant therapy for stage III-IVA resectable locoregionally advanced head and neck squamous cell carcinoma (LA HNSCC) (MK3475-689 KEYNOTE-689, PI: Dr. Cláudia Vieira)
- A phase IIIb, single-arm, open-label multicentre study of olaparib maintenance monotherapy in platinum sensitive relapsed non germline BRCA mutated ovarian cancer patients who are in complete or partial response following platinum based chemotherapy (D0816C00020 OPINION, PI: Dr. Marta Ferreira)
- A randomised, double-blind, parallel group, placebo-controlled multi-centre phase III study to assess the efficacy and safety of olaparib versus placebo as adjuvant treatment in patients with germline BRCA1/2 mutations and high risk HER2 negative primary breast cancer who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy (D081CC00006 OLYMPIA, PI: Prof. Dr. Miguel Abreu)
- A randomized double-blind, placebo controlled study of ribociclib in combination with fluevestrant for the treatment of postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who have received no or only one line of prior endocrine treatment (CLEE011F2301 MONALEESA-3, PI: Dr. Ana Ferreira)
- A randomized phase 3 study of nivolumab plus ipilimumab or nivolumab combined with fluorouracil plus cisplatin versus fluorouracil plus cisplatin in subjects with unresectable advanced, recurrent or metastatic previously untreated esophageal squamous cell carcinoma (CheckMate 648: CHECKpoint pathway and nivoluMab clinical Trial Evaluation 648) (CA209648 CheckMate 648, PI: Dr. Ivo Julião)
- A randomized phase II study of fulvestrant in combination with the dual mTOR inhibitor AZD2014 or everolimus or fulvestrant alone in estrogen receptor positive advanced or metastatic breast cancer (009175QM MANTA, PI: Dr. Marta Ferreira)
- A randomized, double-blind, active-controlled, phase 3 study evaluating the efficacy and safety of ABP 959 compared with eculizumab in adult subjects with paroxysmal nocturnal hemoglobinuria (PNH) (20150168 Dahlia, PI: Dr. Cláudia Moreira)
- A randomized, double-blind, adaptive, phase II/III study of GSK3359609 or placebo in combination with pembrolizumab for first-Line treatment of PD-L1 positive recurrent/metastatic head and neck squamous cell carcinoma (209229 INDUCE-3, PI: Prof. Dr. Cláudia Vieira)
- A randomized, double-blind, phase III study of pembrolizumab versus placebo in combination with neoadjuvant chemotherapy and adjuvant endocrine therapy for the treatment of high-risk early-stage estrogen receptor-positive, human epidermal growth factor receptor 2-negative (ER+/HER2-) breast cancer (MK3475-756 KEYNOTE-756, PI: Dr. Marta Ferreira)
- A randomized, double-blind, placebo controlled phase 3 study of venetoclax in combination with azacitidine versus azacitidine in treatment naïve subjects with acute myeloid leukemia who are ineligible for standard induction therapy (M15-656, PI: Dr. Ângelo Martins)
- A randomized, double-blind, placebo-controlled clinical trial to evaluate the safety, tolerability, pharmacokinetics, and efficacy of a single infusion of bezlotoxumab (MK-6072, human monoclonal antibody to C. difficile toxin B) in children aged 1 to <18 Years receiving antibacterial drug treatment for C. difficile infection (MODIFY III) (MK6072-001 MODIFY III, PI: Dr. Ana Maia Ferreira)
- A randomized, double-blind, placebo-controlled phase 3 study of rovalpituzumab tesirine as maintenance therapy following first-line platinum-based chemotherapy in subjects with extensive stage small cell lung cancer (MERU) (M16-298 MERU, PI: Dr. Inés Pousa)
- A randomized, double-blind, placebo-controlled phase 3 trial of pembrolizumab (MK-3475) versus placebo in participants with esophageal carcinoma receiving concurrent definitive chemoradiotherapy (MK3475-975 KEYNOTE-975, PI: Dr. Dânia Marques)
- A randomized, double-blind, placebo-controlled phase III multi-center study of azacitidine with or without MBG453 for the treatment of patients with intermediate, high or very high risk myelodysplastic syndrome (MDS) as per IPSS-R, or chronic myelomonocytic leukemia-2 (CMML-2) (CMBG453B12301 STIMULUS MDS 2, PI: Dr. Ana Espírito Santo)

- A randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of vedolizumab in the prophylaxis of intestinal acute graft-versus-host disease in subjects undergoing allogeneic hematopoietic stem cell transplantation (Vedolizumab-3035 Graphite, PI: Dr. Luís Cláudio Leite)
- A randomized, double-blind, placebo-controlled, phase III study evaluating the efficacy and safety of pembrolizumab plus platinum-based doublet chemotherapy with or without canakinumab as first line therapy for locally advanced or metastatic non-squamous and squamous non-small cell lung cancer subjects (CACZ885U2301 CANOPY-1, PI: Dr. Marta Soares)
- A randomized, multicenter, open-label cross-over study to evaluate patient preference and satisfaction of subcutaneous administration of the fixed-dose combination of pertuzumab and trastuzumab in patients with HER2-positive early breast cancer (MO40628 PHranceSCa, PI: Dr. Susana Sousa)
- A randomized, multicenter, open-label, phase 3 study of nivolumab plus ipilimumab or nivolumab in combination with oxaliplatin plus fluoropyrimidine versus oxaliplatin plus fluoropyrimidine in subjects with previously untreated advanced or metastatic gastric or gastroesophageal junction cancer (CheckMate 649: CHECKpoint pathway and nivoluMab clinical Trial Evaluation 649) (CA209649 CheckMate 649, PI: Dr. Nuno Sousa)
- A randomized, open label, phase III trial to evaluate the efficacy and safety of palbociclib + anti-HER2 therapy + endocrine therapy vs. anti-HER2 therapy + endocrine therapy after induction treatment for hormone receptor positive (HR+)/HER2-positive metastatic breast cancer (AFT-38 PATINA, PI: Prof. Dr. Cláudia Vieira)
- A randomized, open-label, controlled phase 3 adaptive trial to investigate the efficacy, safety, and tolerability of the BiTE<sup>®</sup> antibody blinatumomab as consolidation therapy versus conventional consolidation chemotherapy in pediatric subjects with high-risk first relapse B-precursor acute lymphoblastic leukemia (ALL) (20120215, PI: Dr. Ana Maia Ferreira)
- A randomized, open-label, multicenter, phase 3 study of rovalpituzumab tesirine compared with topotecan for subjects with advanced or metastatic DLL3high small cell lung cancer (SCLC) who have first disease progression during or following front-line platinum-based chemotherapy (TAHOE) (M16-289 TAHOE, PI: Dr. Ana Rodrigues)
- A randomized, open-label, phase 3 study of abemaciclib combined with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone in patients with high risk, node positive, early stage, hormone receptor positive, human epidermal receptor 2 negative, breast cancer (I3Y-MC-JPCF MonarchE, PI: Dr. Miguel Abreu)
- A randomized, phase 3 trial with anti-PD-1 monoclonal antibody pembrolizumab (MK-3475) versus placebo for patients with early stage NSCLC after resection and completion of standard adjuvant therapy (MK3475-091 PEARLS, PI: Dr. Marta Soares)
- A single-arm open-label multi-centre extension study of pertuzumab administered as a single agent or in combination with other anti-cancer therapies in patients previously enrolled in a Hoffmann-La Roche-sponsored pertuzumab study (MO29406 PereX, PI: Dr. Ana Ferreira)
- Adjuvant immunotherapy with anti-PD-1 monoclonal antibody pembrolizumab (MK-3475) versus placebo after complete resection of high-risk stage III melanoma: A randomized, double-blind phase 3 trial of the EORTC Melanoma Group (MK3475-054 EORTC 1325, PI: Dr. Paula Ferreira)
- An open-label early access phase IIIb study of trifluridine / tipiracil (S 95005/TAS-102) in patients with a pretreated metastatic colorectal cancer (CL3-95005-004 SOLSTICE, PI: Dr. Dânia Marques)
- An open-label, multicenter extension study of trastuzumab emtansine administered as a single agent or in combination with other anti-cancer therapies in patients previously enrolled in a Genentech and /or F. Hoffmann-La Roche Ltd. - sponsored trastuzumab emtansine study (BO25430, PI: Dr. Inés Pousa)
- An open-label, multicenter, phase IIIb study to assess the safety and efficacy of ribociclib (LEE011) in combination with letrozole for the treatment of men and pre/postmenopausal women with hormone receptor-positive (HR+) HER2-negative (HER2-) advanced breast cancer (aBC) with no prior hormonal therapy for advanced disease (CLEE011A2404 COMPLEEMENT-1, PI: Dr. Ana Ferreira)

- An open-label, phase IIIB, single arm multicenter safety study of atezolizumab (Tecentriq) plus nabpaclitaxel or paclitaxel in the treatment of unresectable locally advanced or metastatic triple-negative breast cancer (MO39874 EL1SSAR, PI: Dr. Miguel Abreu)
- An open-label, randomized phase 3 study to evaluate enfortumab vedotin vs chemotherapy in subjects with previously treated locally advanced or metastatic urothelial cancer (EV-301) (7465-CL-0301, PI: Dr. Filipa Carneiro)
- An open-label, randomized phase 3 trial of combinations of nivolumab, elotuzumab, pomalidomide and dexamethasone in relapsed and refractory multiple myeloma (CheckMate 602: CHECKpoint pathway and nivoluMAB clinical Trial Evaluation 602) (CA209602 CheckMate 602, PI: Dr. José Mário Mariz)
- Double-blind, randomised, placebo-controlled, phase IIa trial on the efficacy and tolerability of an 8-week treatment with two different doses of budesonide orodispersible tablets vs. placebo for prevention of oesophageal strictures in adult patients after endoscopic submucosal dissection for squamous cell carcinoma (BUL-5/ESD PEGASUS-1, PI: Dr. Diogo Libânio)
- Elacestrant monotherapy vs. standard of care for the treatment of patients with ER+/HER2- advanced breast cancer following CDK4/6 inhibitor therapy: a phase 3 randomized, open-label, active-controlled, multicenter trial (RAD1901-308 EMERALD, PI: Dr. Susana Sousa)
- INtegratiON of trastuzumab, with or without pertuzumab, into periOperatiVe chemotherApy of HER-2 posiTIve stOmach caNcer: the INNOVATION-TRIAL (EORTC-1203-GITCG INNOVATION, PI: Dr. Cátia Faustino)
- International study for treatment of standard risk childhood relapsed ALL 2010: A randomized phase III study conducted by the Resistant Disease Committee of the International BFM study group (IntReALL SR 2010, PI: Dr. Vitor Costa)
- Multicenter, randomized, double-blind, placebo-controlled, phase 3 trial of fulvestrant (FASLODEX) with or without PD-0332991 (PALBOCICLIB) ± goserelin in women with hormone receptor-positive, HER2-negative metastatic breast cancer whose disease progressed after prior endocrine therapy (A5481023 PALOMA, PI: Dr. Joana Bordalo e Sá)
- Open-label, phase IIb study of dabrafenib in COMBination with trametinib in the Adjuvant treatment of stage III BRAF V600 mutation-positive melanoma after complete resection to evaluate the impact on pyrexia related outcomes of an adapted pyrexia AE-management algorithm (Plus) (CDRB436F2410 COMBI-APlus, PI: Dr. Ivo Julião)
- Open-Label, single arm, phase 3b, multi-center study evaluating the efficacy of venetoclax (ABT-199) in relapsed/refractory subjects with chronic lymphocytic leukemia (CLL) (VENICE I) (M15-550 VENICE-I, PI: Dr. José Mário Mariz)
- Open-label, single-arm trial to evaluate antitumor activity, safety, and pharmacokinetics of isatuximab used in combination with chemotherapy in pediatric patients from 28 days to less than 18 years of age with relapsed/refractory B or T acute lymphoblastic leukemia or acute myeloid leukemia in first or second relapse (ACT15378 ISAKIDS, PI: Dr. Vitor Costa)
- PALbociclib CoLLaborative Adjuvant Study: A randomized phase III trial of Palbociclib with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone for hormone receptor positive (HR+) / human epidermal growth factor receptor 2 (HER2)-negative early breast cancer (ABGSG 42 PALLAS, PI: Dr. Susana Sousa)
- Phase 2 study of MCLA-128-based combinations in metastatic breast cancer (MBC): MCLA-128/trastuzumab/chemotherapy in HER2-positive MBC and MCLA-128/endocrine therapy in estrogen receptor positive and low HER2 expression MBC (MCLA-128-CL02, PI: Dr. Ana Ferreira)
- Randomized phase 3 multicenter open-label study to compare the efficacy of TAK-788 as first-line treatment versus platinum-based chemotherapy in patients with non-small cell lung cancer with EGFR exon 20 insertion mutations (TAK-788-3001, PI: Dr. Ana Rodrigues)
- Randomized, multicenter, phase III, open label study of alectinib versus crizotinib in treatment naïve anaplastic lymphoma kinase-positive advanced non-small cell lung cancer (BO28984 ALEX, PI: Dr. Júlio Oliveira)

**5. Scientific output in 2021 (Publications of clinical trials)**

- Barata, F., Queiroga, H., Teixeira, E., Almodovar, T., Soares, M., Parente, B., Mellidez, J.C., Alves, P., and Antunes, A., Results from phase II, open-label study of anti-tumoral activity of first-line erlotinib in advanced/metastatic NSCLC patients with EGFR activating mutations, in Portugal: The MuTAR study. *Pulmonology*, 2021. 27(2): p. 175-177.DOI: 10.1016/j.pulmoe.2020.08.007. <https://www.ncbi.nlm.nih.gov/pubmed/32972881>
- Dent, S., Cortes, J., Im, Y.H., Dieras, V., Harbeck, N., Krop, I.E., Wilson, T.R., Cui, N., Schimmoller, F., Hsu, J.Y., He, J., De Laurentiis, M., Sousa, S., Drullinsky, P., and Jacot, W., Phase III randomized study of tasisib or placebo with fulvestrant in estrogen receptor-positive, PIK3CA-mutant, HER2-negative, advanced breast cancer: the SANDPIPER trial. *Ann Oncol*, 2021. 32(2): p. 197-207.DOI: 10.1016/j.annonc.2020.10.596. <https://www.ncbi.nlm.nih.gov/pubmed/33186740>
- Harrington, K.J., Soulieres, D., Le Tourneau, C., Dinis, J., Licitra, L.F., Ahn, M.J., Soria, A., Machiels, J.H., Mach, N., Mehra, R., Burtness, B., Ellison, M.C., Cheng, J.D., Chirovsky, D.R., Swaby, R.F., and Cohen, E.E.W., Quality of Life With Pembrolizumab for Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinoma: KEYNOTE-040. *J Natl Cancer Inst*, 2021. 113(2): p. 171-181.DOI: 10.1093/jnci/djaa063. <https://www.ncbi.nlm.nih.gov/pubmed/32407532>
- Laubach, J.P., Schjesvold, F., Mariz, M., Dimopoulos, M.A., Lech-Maranda, E., Spicka, I., Hungria, V.T.M., Shelekhova, T., Abdo, A., Jacobasch, L., Polprasert, C., Hajek, R., Illes, A., Wrobel, T., Sureda, A., Beksac, M., Goncalves, I.Z., Blade, J., Rajkumar, S.V., Chari, A., Lonial, S., Spencer, A., Maison-Blanche, P., Moreau, P., San-Miguel, J.F., and Richardson, P.G., Efficacy and safety of oral panobinostat plus subcutaneous bortezomib and oral dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma (PANORAMA 3): an open-label, randomised, phase 2 study. *Lancet Oncol*, 2021. 22(1): p. 142-154.DOI: 10.1016/S1470-2045(20)30680-X. <https://www.ncbi.nlm.nih.gov/pubmed/33301738>
- O'Shaughnessy, J., Sousa, S., Cruz, J., Fallowfield, L., Auvinen, P., Pulido, C., Cvetanovic, A., Wilks, S., Ribeiro, L., Burotto, M., Klingbiel, D., Messeri, D., Alexandrou, A., Trask, P., Fredriksson, J., Machackova, Z., Stamatovic, L., and group, P.H.s., Preference for the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection in patients with HER2-positive early breast cancer (PHranceSCa): A randomised, open-label phase II study. *Eur J Cancer*, 2021. 152: p. 223-232.DOI: 10.1016/j.ejca.2021.03.047. <https://www.ncbi.nlm.nih.gov/pubmed/34147014>
- Rodrigues, A.T., Romano, S., Romao, M., Figueira, D., Bulhosa, C., Madeira, A., Rocha, L., and Alves, J., Effectiveness of a pharmacist-led intervention on inhalation technique for asthma and COPD patients: The INSPIRA pilot cluster-randomized controlled trial. *Respir Med*, 2021. 185: p. 106507.DOI: 10.1016/j.rmed.2021.106507. <https://www.ncbi.nlm.nih.gov/pubmed/34166959>

## V. LIST OF PUBLICATIONS WITH ABSTRACTS

The list of the 280 publications of CI-IPOP in indexed journals in 2021, including the respective abstract whenever available, is indicated below (only those with final date of publication in 2021 are included):

### 1. Venous thromboembolism and prostate cancer: what about genetic markers?

*Abreu, SC, Tavares, V, Carneiro, F and Medeiros, R. Pharmacogenomics. 2021;22(6):365-73 [IF: 2.533]*

**Aim & methods:** To review the existing literature concerning the relationship between venous thromboembolism (VTE) and prostate cancer (PC) and explore the putative biological and clinical implications of VTE genetic markers on PC patients by screening the PubMed database. **Results:** Considering the roles of VTE genome-wide association studies-identified genetic determinants in disease development in the general population, these variants might also underlie the susceptibility for PC-related VTE. Therefore, they could help to identify those with a positive benefit-to-harm ratio for thromboprophylaxis approaches during cancer therapy management, thereby improving patient's prognosis. **Conclusion:** Future studies are mandatory to explore the relationship between VTE and PC and dissect the predictive value of VTE genome-wide association studies-identified genetic determinants in PC patients, given their clinical implications.

### 2. Identification of a Two-MicroRNA Signature in Plasma as a Novel Biomarker for Very Early Diagnosis of Breast Cancer.

*Adam-Artigues, A, Garrido-Cano, I, Carbonell-Asins, JA, Lameirinhas, A, Simon, S, Ortega-Morillo, B, Martinez, MT, Hernando, C, Constancio, V, Burgues, O, Bermejo, B, Henrique, R, Lluch, A, Jeronimo, C, Eroles, P and Cejalvo, JM. Cancers (Basel). 2021;13(11) [IF: 6.639]*

The early diagnosis of breast cancer is essential to improve patients' survival rate. In this context, microRNAs have been described as potential diagnostic biomarkers for breast cancer. Particularly, circulating microRNAs have a strong value as non-invasive biomarkers. Herein, we assessed the potential of a microRNA signature based on miR-30b-5p and miR-99a-5p levels in plasma as a diagnostic biomarker for breast cancer. This two-microRNA signature was constructed by Principal Component Analysis and its prognostic value was assessed in a discovery cohort and blindly validated in a second cohort from an independent institution. ROC curve analysis and biomarker performance parameter evaluation demonstrated that our proposed signature presents a high value as a non-invasive biomarker for very early detection of breast cancer. In addition, pathway enrichment analysis identified three of the well-known pathways involved in cancer as targets of the two microRNAs.

### 3. Circulating miR-30b-5p levels in plasma as a novel potential biomarker for early detection of breast cancer.

*Adam-Artigues, A, Garrido-Cano, I, Simon, S, Ortega, B, Moragon, S, Lameirinhas, A, Constancio, V, Salta, S, Burgues, O, Bermejo, B, Henrique, R, Lluch, A, Jeronimo, C, Eroles, P and Cejalvo, JM. ESMO Open. 2021;6(1):100039 [IF: 6.540]*

**BACKGROUND:** Recently, microRNAs have been demonstrated to be potential non-invasive biomarkers for diagnosis, prognosis assessment or prediction of response to treatment in cancer. In this study, we evaluate the potential of miR-30b-5p as a biomarker for early diagnosis of breast cancer (BC) in tissue and plasma. **METHODS:** Expression of miR-30b-5p was determined in a series of 112 BC and 40 normal breast tissues. Circulating miR-30b-5p levels in plasma samples were determined in a discovery cohort of 38 BC patients and 40 healthy donors and in a validation cohort of 83 BC patients and 83 healthy volunteers. miR-30b-5p expression was measured by quantitative real-time PCR and receiver operating characteristics curve analysis was carried out. **RESULTS:** The miR-30b-5p expression was significantly lower in BC tissue than in healthy breast samples. In contrast, circulating miR-30b-5p levels were significantly higher in BC patients compared with healthy donors. Furthermore, circulating miR-30b-5p levels were significantly higher in patients with positive axillary lymph node and de novo metastatic patients. Receiver operating characteristics curve analysis demonstrated a good diagnostic potential of miR-30b-5p to detect BC even at an early stage of the disease. **CONCLUSION:** Thus, we highlight the potential of miR-30b-5p as a non-invasive, fast, reproducible and cost-effective diagnostic biomarker of BC.

#### 4. Comprehensive Review of Numerical Chromosomal Aberrations in Chromophobe Renal Cell Carcinoma Including Its Variant Morphologies.

*Alaghehbandan, R, Trpkov, K, Tretiakova, M, Luis, AS, Rogala, JD and Hes, O. Adv Anat Pathol. 2021;28(1):8-20 [IF: 3.875]*

Chromophobe renal cell carcinoma (ChRCC) accounts for 5% to 7% of all renal cell carcinomas. It was thought for many years that ChRCC exhibits a hypodiploid genome. Recent studies using advanced molecular genetics techniques have shown more complex and heterogenous pattern with frequent chromosomal gains. Historically, multiple losses of chromosomes 1, 2, 6, 10, 13, 17, and 21 have been considered a genetic hallmark of ChRCC, both for classic and eosinophilic ChRCC variants. In the last 2 decades, multiple chromosomal gains in ChRCCs have also been documented, depicting a considerably broader genetic spectrum than previously thought. Studies of rare morphologic variants including ChRCC with pigmented microcystic adenomatoid/multicystic growth, ChRCC with neuroendocrine differentiation, ChRCC with papillary architecture, and renal oncocytoma-like variants also showed variable chromosomal numerical aberrations, including multiple losses (common), gains (less common), or chromosomal changes overlapping with renal oncocytoma. Although not the focus of the review, The Cancer Genome Atlas (TCGA) data in ChRCC show TP53, PTEN, and CDKN2A to be the most mutated genes. Given the complexity of molecular genetic alterations in ChRCC, this review analyzed the existing published data, aiming to present a comprehensive up-to-date survey of the chromosomal abnormalities in classic ChRCC and its variants. The potential role of chromosomal numerical aberrations in the differential diagnostic evaluation may be limited, potentially owing to its high variability.

#### 5. Circulating extracellular vesicles release oncogenic miR-424 in experimental models and patients with aggressive prostate cancer.

*Albino, D, Falcione, M, Uboldi, V, Temilola, DO, Sandrini, G, Merulla, J, Civenni, G, Kokanovic, A, Sturchler, A, Shinde, D, Garofalo, M, Mestre, RP, Constancio, V, Wium, M, Burrello, J, Baranzini, N, Grimaldi, A, Theurillat, JP, Bossi, D, Barile, L, Henrique, RM, Jeronimo, C, Zerbini, LF, Catapano, CV and Carbone, GM. Commun Biol. 2021;4(1):119 [IF: 6.268]*

Extracellular vesicles (EVs) are relevant means for transferring signals across cells and facilitate propagation of oncogenic stimuli promoting disease evolution and metastatic spread in cancer patients. Here, we investigated the release of miR-424 in circulating small EVs or exosomes from prostate cancer patients and assessed the functional implications in multiple experimental models. We found higher frequency of circulating miR-424 positive EVs in patients with metastatic prostate cancer compared to patients with primary tumors and BPH. Release of miR-424 in small EVs was enhanced in cell lines (LNCaP(abl)), transgenic mice (Pb-Cre4;Pten(flox/flox);Rosa26(ERG/ERG)) and patient-derived xenograft (PDX) models of aggressive disease. EVs containing miR-424 promoted stem-like traits and tumor-initiating properties in normal prostate epithelial cells while enhanced tumorigenesis in transformed prostate epithelial cells. Intravenous administration of miR-424 positive EVs to mice, mimicking blood circulation, promoted miR-424 transfer and tumor growth in xenograft models. Circulating miR-424 positive EVs from patients with aggressive primary and metastatic tumors induced stem-like features when supplemented to prostate epithelial cells. This study establishes that EVs-mediated transfer of miR-424 across heterogeneous cell populations is an important mechanism of tumor self-sustenance, disease recurrence and progression. These findings might indicate novel approaches for the management and therapy of prostate cancer.

#### 6. Anal cancer and precancerous lesions: a call for improvement.

*Albuquerque, A, Nathan, M, Cappello, C and Dinis-Ribeiro, M. Lancet Gastroenterol Hepatol. 2021;6(4):327-34 [IF: 18.486]*

Anal squamous cell carcinoma is the most common type of anal cancer and is largely associated with anal human papillomavirus infection. The incidence of anal squamous cell carcinoma is increasing, and although still uncommon in the general population, a high incidence has been noted in specific population groups (eg, patients with HIV, men who have sex with men [MSM], recipients of solid organ transplants, women with genital neoplasia, and patients with systemic lupus erythematosus or inflammatory bowel disease). The higher incidence among individuals who are HIV-positive makes anal squamous cell carcinoma one of

the most common non-AIDS-defining cancers among HIV-positive individuals. Anal cancer screening in high-risk groups aims to detect high-grade squamous intraepithelial lesions, which are considered anal precancerous lesions, and for which identification can provide an opportunity for prevention. A blind anal cytology is normally the first screening method, and for patients with abnormal results, this approach can be followed by an examination of the anal canal and perianal area under magnification, along with staining—a technique known as high-resolution anoscopy. Digital anorectal examination can enable early anal cancer detection. Several societies are in favour of screening for HIV-positive MSM and recipients of transplants. There are no current recommendations for screening of anal precancerous lesions via endoscopy, but in high-risk groups, a careful observation of the squamocolumnar junction should be attempted. Several treatments can be used to treat high-grade squamous intraepithelial lesions, including argon plasma coagulation or radiofrequency ablation, which are largely limited by high recurrence rates. Gastroenterologists need to be aware of anal squamous cell carcinoma and anal precancerous lesions, given that patients at high risk are frequently encountered in the gastroenterology department. We summarise simple procedures that can help in early anal squamous cell carcinoma detection.

### **7. Mining Pre-Surgical Patterns Able to Discriminate Post-Surgical Outcomes in the Oncological Domain.**

*Alexandre, L, Costa, RS, Santos, LL and Henriques, R. IEEE J Biomed Health Inform. 2021;25(7):2421-34 [IF: 5.772]*

Understanding the individualized risks of undertaking surgical procedures is essential to personalize preparatory, intervention and post-care protocols for minimizing post-surgical complications. This knowledge is key in oncology given the nature of interventions, the fragile profile of patients with comorbidities and cytotoxic drug exposure, and the possible cancer recurrence. Despite its relevance, the discovery of discriminative patterns of post-surgical risk is hampered by major challenges: i) the unique physiological and demographic profile of individuals, as well as their differentiated post-surgical care; ii) the high-dimensionality and heterogeneous nature of available biomedical data, combining non-identically distributed risk factors, clinical and molecular variables; iii) the need to generalize tumors have significant histopathological differences and individuals undertake unique surgical procedures; iv) the need to focus on non-trivial patterns of post-surgical risk, while guaranteeing their statistical significance and discriminative power; and v) the lack of interpretability and actionability of current approaches. Biclustering, the discovery of groups of individuals correlated on subsets of variables, has unique properties of interest, being positioned to satisfy the aforementioned challenges. In this context, this work proposes a structured view on why, when and how to apply biclustering to mine discriminative patterns of post-surgical risk with guarantees of usability, a subject remaining unexplored up to date. These patterns offer a comprehensive view on how the patient profile, cancer histopathology and entailed surgical procedures determine: i) post-surgical complications, ii) survival, and iii) hospitalization needs. The gathered results confirm the role of biclustering in comprehensively finding interpretable, actionable and statistically significant patterns of post-surgical risk. The found patterns are already assisting healthcare professionals at IPO-Porto to establish specialized pre-habilitation protocols and bedside care.

### **8. Patient-Reported Outcomes in Sarcoma: A scoping review.**

*Almeida, A, Martins, T and Lima, L. Eur J Oncol Nurs. 2021;50:101897 [IF: 2.398]*

**PURPOSE:** Sarcoma is a heterogeneous group of tumours, usually affecting young patients and related to both endogenous and exogenous risk factors. The importance of obtaining the patient's perspective of the illness experience is imperative. Patient-reported outcomes (PROs) are the outcomes that come directly from the patient. They include symptoms, functional health, well-being, quality of life, psychological issues, among other indicators reported by the patients. The objective of this scoping review was to map the PROs in sarcoma patients and how they are measured. **METHODS:** The review process was guided by the Joanna Briggs Institute (JBI) checklist for scoping reviews. **RESULTS:** The search identified 116 potentially relevant studies, with 27 articles meeting the inclusion criteria. The most common PRO evaluated in the selected studies were health-related quality of life (HRQoL), followed by functional outcome, aspects of mental health, and specific symptoms. Generic HRQoL questionnaires were widely used. Quantitative studies usually applied more than one type of Patient-Reported Outcome Measures (PROMs) to measure different PROs. **CONCLUSIONS:** PROs should be carefully analysed to better understand the sarcoma patient's needs.

The PROMs used in the selected studies about sarcoma were not specific to sarcoma, therefore, to better reflect on the perceptions of sarcoma patients, a different new and specific measurement strategy should be considered.

#### 9. The Impact of Routine Transvaginal Ultrasound Measurement of the Cervical Length on the Prediction of Preterm Birth: A Retrospective Study in a Tertiary Hospital.

Almeida, J, *Bartosch, CMM* and Macedo, A. *Rev Bras Ginecol Obstet.* 2021;43(4):264-74 [IF: NA]

Preterm birth (PTB) is a major obstetric problem associated with high rates of neonatal morbidity and mortality. The prevalence of PTB has not changed in the last decade; thus, the establishment of a screening test and effective treatment are warranted. Transvaginal ultrasound measurement of the cervical length (TUCL) has been proposed as an effective method to screen pregnant women at a higher risk of experiencing PTB. OBJECTIVE: To evaluate the applicability and usefulness of second-trimester TUCL to predict PTB in a cohort of Portuguese pregnant women. METHODS: Retrospective cross-sectional cohort study including all singleton pregnant women who performed their second-trimester ultrasound (between weeks 18 and 22 + 6 days) from January 2013 to October 2017 at Centro Hospitalar Universitario Sao Joao. RESULTS: Our cohort included 4,481 women. The prevalence of spontaneous PTB was of 4.0%, with 0.7% occurring before the 34th week of gestation. The mean TUCL was of 33.8 mm, and percentiles 3, 5 and 10 corresponded to TUCLs of 25.0 mm, 27.0 mm and 29.0 mm respectively. The multiple logistic regression analysis, including maternal age, previous PTB and cervical surgery showed a significant negative association between TUCL and PTB, with an odds ratio (OR) of 0.92 (95% confidence interval [95%CI]: 0.90-0.95;  $p < 0.001$ ). The use of a TUCL of 20 mm is the best cut-off, when compared with the 25-mm cut-off, improving the prediction of risk. CONCLUSION: The present study showed an inverse association between TUCL and PTB, and that the inclusion of other risk factors like maternal age, previous PTB and cervical surgery can improve the screening algorithm. Furthermore, it emphasizes that the TUCL cut-off that defines short cervix can differ according to the population.

#### 10. The Red Seaweed *Grateloupia turuturu* Prevents Epidermal Dysplasia in HPV16-Transgenic Mice.

Almeida, J, Ferreira, T, Santos, S, Pires, MJ, *da Costa, RMG, Medeiros, R, Bastos, M, Neuparth, MJ, Faustino-Rocha, AI, Abreu, H, Pereira, R, Pacheco, M, Gaivao, I, Rosa, E and Oliveira, PA.* *Nutrients.* 2021;13(12) [IF: 5.717]

The role of dietary profiles in promoting or reducing the risk of multiple types of cancer is increasingly clear, driving the search for balanced foods and nutraceuticals. The red seaweed *Grateloupia turuturu* has been used as human food showing a balanced nutritional profile. This study aims to test in vivo chemopreventive effects of *G. turuturu* against cutaneous pre-malignant lesions in transgenic mice for the human papillomavirus type 16 (HPV16). Forty-four female HPV(+/-) or HPV(-/-) mice received a standard diet or were supplemented with 10% *G. turuturu* for 22 consecutive days. Cutaneous lesions (ear and chest skin) were identified histologically. Complementarily, the weights and histology of internal organs as well as blood biochemical and DNA integrity parameters were also assessed. *G. turuturu* consistently reduced the incidence of epidermal dysplasia induced by HPV16 on both cutaneous sites. Moreover, biochemical, DNA integrity and histological analyses confirmed *G. turuturu* edibility as no signs of toxicity were found. Dietary supplementation with *G. turuturu* is an effective and safe chemopreventive strategy in this model.

#### 11. Dealing with missing information on covariates for excess mortality hazard regression models - Making the imputation model compatible with the substantive model.

Antunes, L, Mendonca, D, Bento, MJ, Njagi, EN, Belot, A and Rachet, B. *Stat Methods Med Res.* 2021;30(10):2256-68 [IF: 3.021]

Missing data is a common issue in epidemiological databases. Among the different ways of dealing with missing data, multiple imputation has become more available in common statistical software packages. However, the incompatibility between the imputation and substantive model, which can arise when the associations between variables in the substantive model are not taken into account in the imputation models or when the substantive model is itself nonlinear, can lead to invalid inference. Aiming at analysing population-based cancer survival data, we extended the multiple imputation substantive model compatible-fully conditional specification (SMC-FCS) approach, proposed by Bartlett et al. in 2015 to

accommodate excess hazard regression models. The proposed approach was compared with the standard fully conditional specification multiple imputation procedure and with the complete-case analysis using a simulation study. The SMC-FCS approach produced unbiased estimates in both scenarios tested, while the fully conditional specification produced biased estimates and poor empirical coverages probabilities. The SMC-FCS algorithm was then used for handling missing data in the evaluation of socioeconomic inequalities in survival from colorectal cancer patients diagnosed in the North Region of Portugal. The analysis using SMC-FCS showed a clearer trend in higher excess hazards for patients coming from more deprived areas. The proposed algorithm was implemented in R software and is presented as Supplementary Material.

## 12. Interchangeability of two versions of the Montreal Cognitive Assessment for the longitudinal evaluation of patients with breast cancer.

*Araujo, N, Lopes-Conceicao, L, Morais, S, Fontes, F, Dias, T, Cruz, VT, Ruano, L, Pereira, S and Lunet, N. Support Care Cancer. 2022;30(3):2639-47 [IF: 3.603]*

**PURPOSE:** The cognitive performance of patients with breast cancer (BCa) may be affected by cancer and its treatments. The Montreal Cognitive Assessment (MoCA) is a widely used cognitive impairment screening tool, but practice effects must be considered for longitudinal assessments. Since learning effects could be overcome through the alternate use of two versions of the MoCA, we aimed to explore their interchangeability by comparing their overall, and domain- and task-specific, scores among patients with BCa. **METHODS:** BCa patients from the NEON-BC cohort were evaluated with the MoCA, version 7.1, after diagnosis and after 1 year. At the 3-year follow-up (n = 422), the 7.1 and 7.3 versions were applied at the beginning and at the end (approximately 1 h later) of this evaluation, respectively. Agreements between versions, regarding total, sub-domain, and task scores, were assessed using Bland-Altman plots and intraclass correlation coefficients (ICC). **RESULTS:** The mean total scores were not statistically different between versions and the ICC was 0.890. The Bland-Altman limits of agreement were - 3.70 to 3.88. For women with midrange scores, total scores were significantly higher in version 7.1. There were significant differences in the percentage of correct answers in 7 out of 12 tasks, being the highest for the copy of a geometric figure (more than twofold higher with version 7.3). In version 7.1, the language and memory domains presented higher scores and lower visuospatial ability. **CONCLUSION:** Despite similar overall scores being obtained with the two versions of the MoCA, there were item-specific differences that may compromise their interchangeable use.

## 13. Cognitive decline in patients with prostate cancer: study protocol of a prospective cohort, NEON-PC.

*Araujo, N, Morais, S, Costa, AR, Braga, R, Carneiro, AF, Cruz, VT, Ruano, L, Oliveira, J, Figueiredo, LP, Pereira, S and Lunet, N. BMJ Open. 2021;11(2):e043844 [IF: 2.692]*

**INTRODUCTION:** Prostate cancer is the most prevalent oncological disease among men in industrialised countries. Despite the high survival rates, treatments are often associated with adverse effects, including metabolic and cardiovascular complications, sexual dysfunction and, to a lesser extent, cognitive decline. This study was primarily designed to evaluate the trajectories of cognitive performance in patients with prostate cancer, and to quantify the impact of the disease and its treatments on the occurrence of cognitive decline. **METHODS:** Participants will be recruited from two main hospitals providing care to approximately half of the patients with prostate cancer in Northern Portugal (Portuguese Institute of Oncology of Porto and Sao Joao Hospital Centre), and will comprise a cohort of recently diagnosed patients with prostate cancer proposed for different treatment plans, including: (1) radical prostatectomy; (2) brachytherapy and/or radiotherapy; (3) radiotherapy in combination with androgen deprivation therapy and (4) androgen deprivation therapy (with or without chemotherapy). Recruitment began in February 2018 and is expected to continue until the first semester of 2021. Follow-up evaluations will be conducted at 1, 3, 5, 7 and 10 years. Sociodemographic, behavioural and clinical characteristics, anxiety and depression, health literacy, health status, quality of life, and sleep quality will be assessed. Blood pressure and anthropometrics will be measured, and a fasting blood sample will be collected. Participants' cognitive performance will be evaluated before treatments and throughout follow-up (Montreal Cognitive Assessment and Cube Test as well as Brain on Track for remote monitoring). All participants suspected of cognitive impairment will undergo neuropsychological tests and clinical observation by a neurologist. **ETHICS AND DISSEMINATION:** The study was approved by the Ethics Committee of the hospitals involved.

All participants will provide written informed consent, and study procedures will be developed to ensure data protection and confidentiality. Results will be disseminated through publication in peer-reviewed journals and presentation in scientific meetings.

**14. Trajectories of cognitive performance over five years in a prospective cohort of patients with breast cancer (NEON-BC).**

*Araujo, N, Severo, M, Lopes-Conceicao, L, Fontes, F, Dias, T, Branco, M, Morais, S, Cruz, VT, Ruano, L, Pereira, S and Lunet, N. Breast. 2021;58:130-7 [IF: 4.380]*

**PURPOSE:** To identify trajectories of cognitive performance up to five years since diagnosis and their predictors, in a cohort of patients with breast cancer (BCa). **METHODS:** A total of 464 women with BCa admitted to the Portuguese Institute of Oncology, Porto, during 2012, were evaluated with the Montreal Cognitive Assessment (MoCA) before any treatment, and after one, three and five years. Probable cognitive impairment (PCI) at baseline was defined based on normative age- and education-specific reference values. Mclust was used to define MoCA trajectories. Receiver Operating Characteristic curves were used to assess the predictive accuracy for cognitive trajectories. **RESULTS:** Two trajectories were identified, one with higher scores and increasing overtime, and the other, including 25.9% of the participants, showing a continuous decline. To further characterize each trajectory, participants were also classified as scoring above or below the median baseline MoCA scores. This resulted in four groups: 1) highest baseline scores, stable overtime (0.0% with PCI); 2) lowest baseline scores (29.5% with PCI); 3) mid-range scores at baseline, increasing overtime (10.5% with PCI); 4) mid-range scores at baseline, decreasing overtime (0.0% with PCI). Adding the change in MoCA during the first year to baseline variables significantly increased the accuracy to predict the downward trajectory (area under the curve [AUC] = 0.732 vs. AUC = 0.841, P < 0.001). **CONCLUSION:** Four groups of patients with BCa with different cognitive performance trends were identified. The assessment of cognitive performance before treatments and after one year allows for the identification of patients more likely to have cognitive decline in the long term.

**15. A new path for the UEG Journal.**

*Archibugi, L, Pawlak, KM and Libanio, D. United European Gastroenterol J. 2021;9(1):9-10 [IF: 4.623]*

**16. Early gastric cancer and Artificial Intelligence: Is it time for population screening?**

*Arribas Anta, J and Dinis-Ribeiro, M. Best Pract Res Clin Gastroenterol. 2021;52-53:101710 [IF: 3.043]*

Gastric cancer is a common cause of death worldwide and its early detection is crucial to improve its prognosis. Its incidence varies throughout countries, and screening has been found to be cost-effective at least in high-incidence regions. Identification of individuals harbouring preneoplastic lesions and their surveillance or of those with early gastric cancer are extremely important processes and endoscopy play a key role for this purpose. Unfortunately, also quality and accuracy for endoscopic detection varies among centres and endoscopists. Recent studies about Artificial Intelligence applied to endoscopic imaging show that these technologies perform very well and could be extremely useful for endoscopists to achieve the accuracy needed for gastric cancer screening. Nonetheless, as its introduction in this field is very recent, most studies are carried out offline and its results in clinical practice need to be further validated namely by incorporating all the components/dimensions of endoscopy from pre to post-assessment.

**17. A prospective prostate cancer screening programme for men with pathogenic variants in mismatch repair genes (IMPACT): initial results from an international prospective study.**

*Bancroft, EK, Page, EC, Brook, MN, Thomas, S, Taylor, N, Pope, J, McHugh, J, Jones, AB, Karlsson, Q, Merson, S, Ong, KR, Hoffman, J, Huber, C, Maehle, L, Grindedal, EM, Stormorken, A, Evans, DG, Rothwell, J, Lalloo, F, Brady, AF, Bartlett, M, Snape, K, Hanson, H, James, P, McKinley, J, Mascarenhas, L, Syngal, S, Ukaegbu, C, Side, L, Thomas, T, Barwell, J, Teixeira, MR, Izatt, L, Suri, M, Macrae, FA, Poplawski, N, Chen-Shtoyerman, R, Ahmed, M, Musgrave, H, Nicolai, N, Greenhalgh, L, Brewer, C, Pachter, N, Spigelman, AD, Azzabi, A, Helfand, BT, Halliday, D, Buys, S, Ramon, YCT, Donaldson, A, Cooney, KA, Harris, M, McGrath, J, Davidson, R, Taylor, A, Cooke, P, Myhill, K, Hogben, M, Aaronson, NK, Ardern-Jones, A, Bangma, CH, Castro, E, Dearnaley, D, Dias, A, Dudderidge, T, Eccles, DM, Green, K, Eyfjord, J, Falconer, A, Foster, CS, Gronberg, H, Hamdy, FC,*

Johannsson, O, Khoo, V, Lilja, H, Lindeman, GJ, Lubinski, J, Axcrona, K, Mikropoulos, C, Mitra, AV, Moynihan, C, Ni Raghallaigh, H, Rennert, G, Collier, R, Collaborators, IS, Offman, J, Kote-Jarai, Z and Eeles, RA. *Lancet Oncol.* 2021;22(11):1618-31 [IF: 41.316]

**BACKGROUND:** Lynch syndrome is a rare familial cancer syndrome caused by pathogenic variants in the mismatch repair genes MLH1, MSH2, MSH6, or PMS2, that cause predisposition to various cancers, predominantly colorectal and endometrial cancer. Data are emerging that pathogenic variants in mismatch repair genes increase the risk of early-onset aggressive prostate cancer. The IMPACT study is prospectively assessing prostate-specific antigen (PSA) screening in men with germline mismatch repair pathogenic variants. Here, we report the usefulness of PSA screening, prostate cancer incidence, and tumour characteristics after the first screening round in men with and without these germline pathogenic variants.

**METHODS:** The IMPACT study is an international, prospective study. Men aged 40-69 years without a previous prostate cancer diagnosis and with a known germline pathogenic variant in the MLH1, MSH2, or MSH6 gene, and age-matched male controls who tested negative for a familial pathogenic variant in these genes were recruited from 34 genetic and urology clinics in eight countries, and underwent a baseline PSA screening. Men who had a PSA level higher than 3.0 ng/mL were offered a transrectal, ultrasound-guided, prostate biopsy and a histopathological analysis was done. All participants are undergoing a minimum of 5 years' annual screening. The primary endpoint was to determine the incidence, stage, and pathology of screening-detected prostate cancer in carriers of pathogenic variants compared with non-carrier controls. We used Fisher's exact test to compare the number of cases, cancer incidence, and positive predictive values of the PSA cutoff and biopsy between carriers and non-carriers and the differences between disease types (ie, cancer vs no cancer, clinically significant cancer vs no cancer). We assessed screening outcomes and tumour characteristics by pathogenic variant status. Here we present results from the first round of PSA screening in the IMPACT study. This study is registered with ClinicalTrials.gov, NCT00261456, and is now closed to accrual.

**FINDINGS:** Between Sept 28, 2012, and March 1, 2020, 828 men were recruited (644 carriers of mismatch repair pathogenic variants [204 carriers of MLH1, 305 carriers of MSH2, and 135 carriers of MSH6] and 184 non-carrier controls [65 non-carriers of MLH1, 76 non-carriers of MSH2, and 43 non-carriers of MSH6]), and in order to boost the sample size for the non-carrier control groups, we randomly selected 134 non-carriers from the BRCA1 and BRCA2 cohort of the IMPACT study, who were included in all three non-carrier cohorts. Men were predominantly of European ancestry (899 [93%] of 953 with available data), with a mean age of 52.8 years (SD 8.3). Within the first screening round, 56 (6%) men had a PSA concentration of more than 3.0 ng/mL and 35 (4%) biopsies were done. The overall incidence of prostate cancer was 1.9% (18 of 962; 95% CI 1.1-2.9). The incidence among MSH2 carriers was 4.3% (13 of 305; 95% CI 2.3-7.2), MSH2 non-carrier controls was 0.5% (one of 210; 0.0-2.6), MSH6 carriers was 3.0% (four of 135; 0.8-7.4), and none were detected among the MLH1 carriers, MLH1 non-carrier controls, and MSH6 non-carrier controls. Prostate cancer incidence, using a PSA threshold of higher than 3.0 ng/mL, was higher in MSH2 carriers than in MSH2 non-carrier controls (4.3% vs 0.5%;  $p=0.011$ ) and MSH6 carriers than MSH6 non-carrier controls (3.0% vs 0%;  $p=0.034$ ). The overall positive predictive value of biopsy using a PSA threshold of 3.0 ng/mL was 51.4% (95% CI 34.0-68.6), and the overall positive predictive value of a PSA threshold of 3.0 ng/mL was 32.1% (20.3-46.0).

**INTERPRETATION:** After the first screening round, carriers of MSH2 and MSH6 pathogenic variants had a higher incidence of prostate cancer compared with age-matched non-carrier controls. These findings support the use of targeted PSA screening in these men to identify those with clinically significant prostate cancer. Further annual screening rounds will need to confirm these findings.

**FUNDING:** Cancer Research UK, The Ronald and Rita McAulay Foundation, the National Institute for Health Research support to Biomedical Research Centres (The Institute of Cancer Research and Royal Marsden NHS Foundation Trust; Oxford; Manchester and the Cambridge Clinical Research Centre), Mr and Mrs Jack Baker, the Cancer Council of Tasmania, Cancer Australia, Prostate Cancer Foundation of Australia, Cancer Council of Victoria, Cancer Council of South Australia, the Victorian Cancer Agency, Cancer Australia, Prostate Cancer Foundation of Australia, Asociacion Espanola Contra el Cancer (AECC), the Instituto de Salud Carlos III, Fondo Europeo de Desarrollo Regional (FEDER), the Institut Catala de la Salut, Autonomous Government of Catalonia, Fundacao para a Ciencia e a Tecnologia, National Institutes of Health National Cancer Institute, Swedish Cancer Society, General Hospital in Malmo Foundation for Combating Cancer.

**18. The Extremely Rare Hypopharyngeal Fetal Rhabdomyoma in an Adult.**

*Baracas, C, Farinha, M, Afonso, LP and Bacelar, MT. Cureus. 2021;13(9):e18096 [IF: NA]*

Extracardiac rhabdomyomas are rare benign tumors showing skeletal muscle differentiation. They can be divided into adult, fetal, and genital subtypes. Fetal rhabdomyomas are rarer than the adult subtype and although usually diagnosed at birth, the diagnosis is based on histology rather than patient age. We present a rare case of a 25-year-old man with a cellular fetal (juvenile) rhabdomyoma, found in the postcricoid region of the hypopharynx.

**19. Results from phase II, open-label study of anti-tumoral activity of first-line erlotinib in advanced/metastatic NSCLC patients with EGFR activating mutations, in Portugal: The MuTAR study.**

*Barata, F, Queiroga, H, Teixeira, E, Almodovar, T, Soares, M, Parente, B, Mellidez, JC, Alves, P and Antunes, A. Pulmonology. 2021;27(2):175-7 [IF: 3.575]*

**20. Next Generation Sequencing of Tumor and Matched Plasma Samples: Identification of Somatic Variants in ctDNA From Ovarian Cancer Patients.**

*Barbosa, A, Pinto, P, Peixoto, A, Guerra, J, Pinheiro, M, Santos, C, Pinto, C, Escudeiro, C, Bartosch, C, Santos, R, Brandao, A, Silva, J and Teixeira, MR. Front Oncol. 2021;11:754094 [IF: 6.244]*

Genetic testing to detect somatic alterations is usually performed on formalin-fixed paraffin-embedded tumor samples. However, tumor molecular profiling through ctDNA analysis may be particularly interesting with the emergence of targeted therapies for ovarian cancer (OC), mainly when tumor is not available and biopsy is not viable, also allowing representation of multiple neoplastic subclones. Using a custom panel of 27 genes, next-generation sequencing (NGS) was performed on tumor and matched plasma samples from 96 OC patients, which were combined in two groups (treatment naive and post-treatment). Overall, at least one somatic variant present in the tumor sample was also detected in the matched plasma sample in 35.6% of the patients, a percentage that increased to 69.6% of the treatment naive patients and 83.3% of those with stage IV disease, showing the potential of ctDNA analysis as an alternative to identify somatic variants in these patients, namely those that have predictive value for targeted therapy. In fact, of the two treatment-naive patients with somatic BRCA1 variants identified in tumor samples, in one of them we detected in ctDNA a BRCA1 somatic variant that was present in the tumor with a VAF of 53%, but not in the one that had a VAF of 5.4%. We also showed that ctDNA analysis has a complementary role to molecular unraveling of inter- and intra-tumor heterogeneity, as exemplified by one patient diagnosed with bilateral OC in which different somatic variants from both tumors were detected in ctDNA. Interestingly, as these bilateral tumors shared a rare combination of two of the three variants identified in ctDNA, we could conclude that these morphologically different tumors were clonally related and not synchronous independent neoplasias. Moreover, in the post-treatment group of patients with plasma samples collected after surgery, those with detectable somatic variants had poor prognosis when compared with patients with no detectable somatic variants, highlighting the potential of ctDNA analysis to identify patients at higher risk of recurrence. Concluding, this study demonstrated that somatic variants can be detected in plasma samples of a significant proportion of OC patients, supporting the use of NGS-based ctDNA testing for noninvasive tumor molecular profiling and to stratify patients according to prognosis.

**21. Repeated Administration of Clinically Relevant Doses of the Prescription Opioids Tramadol and Tapentadol Causes Lung, Cardiac, and Brain Toxicity in Wistar Rats.**

*Barbosa, J, Faria, J, Garcez, F, Leal, S, Afonso, LP, Nascimento, AV, Moreira, R, Pereira, FC, Queiros, O, Carvalho, F and Dinis-Oliveira, RJ. Pharmaceuticals (Basel). 2021;14(2) [IF: 5.863]*

Tramadol and tapentadol, two structurally related synthetic opioid analgesics, are widely prescribed due to the enhanced therapeutic profiles resulting from the synergistic combination between mu-opioid receptor (MOR) activation and monoamine reuptake inhibition. However, the number of adverse reactions has been growing along with their increasing use and misuse. The potential toxicological mechanisms for these drugs are not completely understood, especially for tapentadol, owing to its shorter market history. Therefore, in the present study, we aimed to comparatively assess the putative lung, cardiac, and brain cortex toxicological damage elicited by the repeated exposure to therapeutic doses of both prescription opioids. To this purpose, male Wistar rats were intraperitoneally injected with single daily doses of 10, 25, and 50

mg/kg tramadol or tapentadol, corresponding to a standard analgesic dose, an intermediate dose, and the maximum recommended daily dose, respectively, for 14 consecutive days. Such treatment was found to lead mainly to lipid peroxidation and inflammation in lung and brain cortex tissues, as shown through augmented thiobarbituric acid reactive substances (TBARS), as well as to increased serum inflammation biomarkers, such as C reactive protein (CRP) and tumor necrosis factor-alpha (TNF-alpha). Cardiomyocyte integrity was also shown to be affected, since both opioids incremented serum lactate dehydrogenase (LDH) and alpha-hydroxybutyrate dehydrogenase (alpha-HBDH) activities, while tapentadol was associated with increased serum creatine kinase muscle brain (CK-MB) isoform activity. In turn, the analysis of metabolic parameters in brain cortex tissue revealed increased lactate concentration upon exposure to both drugs, as well as augmented LDH and creatine kinase (CK) activities following tapentadol treatment. In addition, pneumo- and cardiotoxicity biomarkers were quantified at the gene level, while neurotoxicity biomarkers were quantified both at the gene and protein levels; changes in their expression correlate with the oxidative stress, inflammatory, metabolic, and histopathological changes that were detected. Hematoxylin and eosin (H & E) staining revealed several histopathological alterations, including alveolar collapse and destruction in lung sections, inflammatory infiltrates, altered cardiomyocytes and loss of striation in heart sections, degenerated neurons, and accumulation of glial and microglial cells in brain cortex sections. In turn, Masson's trichrome staining confirmed fibrous tissue deposition in cardiac tissue. Taken as a whole, these results show that the repeated administration of both prescription opioids extends the dose range for which toxicological injury is observed to lower therapeutic doses. They also reinforce previous assumptions that tramadol and tapentadol are not devoid of toxicological risk even at clinical doses.

## 22. Assessment of the Safety and Therapeutic Benefits of Convalescent Plasma in COVID-19 Treatment: A Systematic Review and Meta-Analysis.

*Barreira, DF, Lourenco, RA, Calisto, R, Moreira-Goncalves, D, Santos, LL and Videira, PA. Front Med (Lausanne). 2021;8:660688 [IF: 5.091]*

Background: The coronavirus disease (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), prompted a global health crisis, with no available specific treatments. Convalescent plasma (CP) with neutralizing antibodies could be a promising therapeutic approach to reduce mortality. Objectives: To evaluate the therapeutic potential of CP for COVID-19 and to assess its safety and efficacy in reducing the patients' mortality. Methods: We retrieved clinical trial references from multiple Databases (e.g., PubMed, B-On, SCOPUS), for complete studies until November 26th 2020. We included Randomized controlled trials (RCT) and controlled non-randomized trials (CNRT), that assessed the efficacy of CP to treat hospitalized COVID-19 patients. Trials were included regardless of concomitant medications in the intervention's arms. Eleven trials met our eligibility criteria. This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. We defined a methodological protocol to extract and evaluate all pertinent baseline demographics and interventions' characteristics from trials. The primary outcomes were the safety profile of CP, measured by the type, frequency and severity of adverse events, and CP effectiveness in reducing mortality, measured by the number of deaths registered for this therapy. Results: We assessed 11 trials (5 RCT and 6 CNRT) with 3,098 participants, of whom 923 patients were treated with CP. Only 32 (3.5%) of the treated patients suffered adverse events (from which 9.4% serious transfusion-related adverse events). The overall mortality rates were significantly decreased by CP administration {risk ratio (RR) 0.71,  $p = 0.005$ , 95% confidence interval (CI) [0.57-0.90]}, with low heterogeneity. In the sub-analysis by period of transfusion, CP transfusion within a week of hospitalization contributed to diminished mortality rate (RR = 0.71,  $p = 0.03$ , 95%CI [0.53-0.96]). CP therapy also led to significantly reduced viral loads at 72 h after transfusion (RR = 0.61,  $p = 0.04$ , 95%CI [0.38-0.98]), despite high heterogeneity due to disease severity. Conclusion: This meta-analysis established CP as a safe and potentially effective therapy for COVID-19, decreasing the mortality rates and promoting a swift viral clearance. Further studies are necessary to provide stronger evidence.

## 23. The role of OncoSnoRNAs and Ribosomal RNA 2'-O-methylation in Cancer.

*Barros-Silva, D, Klavert, J, Jenster, G, Jeronimo, C, Lafontaine, DLJ and Martens-Uzunova, ES. RNA Biol. 2021;18(sup1):61-74 [IF: 4.652]*

Ribosomes are essential nanomachines responsible for all protein production in cells. Ribosome biogenesis and function are energy costly processes, they are tightly regulated to match cellular needs. In cancer, major pathways that control ribosome biogenesis and function are often deregulated to ensure cell survival and to accommodate the continuous proliferation of tumour cells. Ribosomal RNAs (rRNAs) are abundantly modified with 2'-O-methylation (Nm, ribomethylation) being one of the most common modifications. In eukaryotic ribosomes, ribomethylation is performed by the methyltransferase Fibrillarin guided by box C/D small nucleolar RNAs (snoRNAs). Accumulating evidences indicate that snoRNA expression and ribosome methylation profiles are altered in cancer. Here we review our current knowledge on differential snoRNA expression and rRNA 2'-O methylation in the context of human malignancies, and discuss the consequences and opportunities for cancer diagnostics, prognostics, and therapeutics.

#### 24. Deciphering RNA Methylation in Cancer.

*Barros-Silva, D, Martens-Uzunova, ES and Jerónimo, C. In: S. Jurga and J. Barciszewski, editors.*

*Epitranscriptomics. RNA Technologies. Cham: Springer International Publishing; 2021. p. 247-66 [IF: NA]*

Every single RNA nucleotide may undergo a variety of (post-)transcriptional chemical modifications. Historically, the inefficiency of detection methods and the difficulties in chemical structure elucidation have been a rate-limiting step in the discovery and functional analysis of ribonucleotide modifications. The current substantial progress in RNA modification profiling techniques launched epitranscriptomics as a new research field investigating this additional layer of information influencing cell physiology and disease development. RNA methylation is one of the most common and versatile chemical alterations found in the epitranscriptome, indicating a previously invisible code outside DNA and RNA sequences. Herein, we portray the historical evolution of strategies commonly used for overall and site-specific detection of methylated nucleotides in RNA and provide an overview of the relevance of these approaches for cancer biology research. We also discuss the potential of third-generation sequencing methods for direct detection of RNA methylation and prospects of RNA methylation for anticancer therapy.

#### 25. Treatment optimization of locally advanced and metastatic pancreatic cancer (Review).

*Barros, AG, Pulido, CF, Machado, M, Brito, MJ, Couto, N, Sousa, O, Melo, SA and Mansinho, H. Int J Oncol. 2021;59(6) [IF: 5.650]*

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignant tumor types, being the sixth leading cause of mortality worldwide and the fourth in Europe. Globally, it has a mortality/incidence ratio of 98%, and the 5year survival rate in Europe is only 3%. Although risk factors, such as obesity, diabetes mellitus, smoking, alcohol consumption and genetic factors, have been identified, the causes of PDAC remain elusive. Additionally, the only curative treatment for PDAC is surgery with negative margins. However, upon diagnosis, ~30% of the patients already present with locally advanced disease. In these cases, a multidisciplinary approach is required to improve diseaserelated symptoms and prolong patient survival. In the present article, a comprehensive review of PDAC epidemiology, physiology and treatment is provided. Moreover, guidelines on patient treatment are suggested. Among the different available therapeutic options for the treatment of advanced PDAC, results are modest, most likely due to the complexity of the disease, and so the prognostic remains poor. Molecular approaches based on multiomics research are promising and will contribute to groundbreaking personalized medicine. Thus, economic investment that promotes research of pancreatic cancer will be critical to the development of more efficient diagnostic and treatment strategies.

#### 26. Association Between Estrogen Receptors and GATA3 in Bladder Cancer: A Systematic Review and Meta-Analysis of Their Clinicopathological Significance.

*Bernardo, C, Monteiro, FL, Direito, I, Amado, F, Afreixo, V, Santos, LL and Helguero, LA. Front Endocrinol (Lausanne). 2021;12:684140 [IF: 5.555]*

Background: Estrogen receptors alpha (ERalpha) and beta (ERbeta) and the cooperating protein GATA-binding factor 3 (GATA3) have been implicated in bladder carcinogenesis and tumour progression. GATA3 and ER have been functionally linked in the establishment of luminal fate in breast tissue, but to date their relationship in bladder cancer has not been established. This information will be useful to advance diagnostic and prognostic markers. Aim: To determine the relationship between the expression of ERalpha,

ERbeta and GATA3 in bladder cancer, disclose their prognostic and diagnostic value and their association with clinicopathological characteristics. Methods: A comprehensive literature search in PubMed database was performed for all immunohistochemical studies of ERalpha, ERbeta and/or GATA3 in bladder cancer patients. We selected eligible studies in accordance with the PRISMA guidelines and evaluated methodological quality and risk of bias based on quality criteria from the reporting recommendations for tumour MARKer (REMARK) prognostic studies. Risk of bias assessment was performed using Review Manager 5. R software was used for all statistical analysis, the packages used were meta and dmetar for the standard meta-analysis, and netmeta for the network meta-analysis. Results: Thirteen studies were eligible for ERalpha, 5 for ERbeta and 58 for GATA3 meta-analysis. Low grade tumours showed significantly lower ERalpha expression. GATA3 was widely expressed in bladder tumours, especially urothelial carcinomas, with higher expression of GATA3 in low grade and low stage tumours. Data was insufficient to determine the prognostic value of either ERalpha or ERbeta, but GATA3-positivity was associated with higher recurrence free survival. A negative correlation between ERalpha or ERbeta positivity and GATA3 expression was disclosed. Additionally, several sources of heterogeneity were identified, which can be used to improve future studies. Conclusion: The clinicopathological value of ERalpha and ERbeta was inconclusive due to low availability of studies using validated antibodies. Still, this meta-analysis supports GATA3 as good prognostic marker. On the contrary, ERalpha-positivity was associated to higher grade tumours; while ERalpha and ERbeta were inversely correlated with GATA3 expression. Considering that it has previously been shown that bladder cancer cell lines have functional ERs, this suggests that ERalpha could be activated in less differentiated cells and independently of GATA3. Therefore, a comprehensive analysis of ERalpha and ERbeta expression in BlaCa supported by complete patient clinical history is required for the identification of BlaCa subtypes and subgroups of patients expressing ERalpha, to investigate if they could benefit from treatment with hormonal therapy. Systematic Review Registration: Prospero, CRD42021226836.

#### 27. Revising the European Society of Gastrointestinal Endoscopy (ESGE) research priorities: a research progress update.

*Bhandari, P, Longcroft-Wheaton, G, Libanio, D, Pimentel-Nunes, P, Albeniz, E, Pioche, M, Sidhu, R, Spada, C, Anderloni, A, Repici, A, Haidry, R, Barthet, M, Neumann, H, Antonelli, G, Testoni, A, Ponchon, T, Siersema, PD, Fuccio, L, Hassan, C and Dinis-Ribeiro, M. Endoscopy. 2021;53(5):535-54 [IF: 10.093]*

BACKGROUND: One of the aims of the European Society of Gastrointestinal Endoscopy (ESGE) is to encourage high quality endoscopic research at a European level. In 2016, the ESGE research committee published a set of research priorities. As endoscopic research is flourishing, we aimed to review the literature and determine whether endoscopic research over the last 4 years had managed to address any of our previously published priorities. METHODS: As the previously published priorities were grouped under seven different domains, a working party with at least two European experts was created for each domain to review all the priorities under that domain. A structured review form was developed to standardize the review process. The group conducted an extensive literature search relevant to each of the priorities and then graded the priorities into three categories: (1) no longer a priority (well-designed trial, incorporated in national/international guidelines or adopted in routine clinical practice); (2) remains a priority (i. e. the above criterion was not met); (3) redefine the existing priority (i. e. the priority was too vague with the research question not clearly defined). RESULTS: The previous ESGE research priorities document published in 2016 had 26 research priorities under seven domains. Our review of these priorities has resulted in seven priorities being removed from the list, one priority being partially removed, another seven being redefined to make them more precise, with eleven priorities remaining unchanged. This is a reflection of a rapid surge in endoscopic research, resulting in 27 % of research questions having already been answered and another 27 % requiring redefinition. CONCLUSIONS: Our extensive review process has led to the removal of seven research priorities from the previous (2016) list, leaving 19 research priorities that have been redefined to make them more precise and relevant for researchers and funding bodies to target.

#### 28. Disseminated Tuberculosis With Cardiac Tamponade in an Immunocompetent Individual.

*Bibi, M, Monteiro, J, Oliveira, N and Pereira, M. Cureus. 2021;13(7):e16088*

We report a case of disseminated tuberculosis with cardiac tamponade in a 26-year-old man from northern

Portugal. He was imprisoned for one year before the diagnosis and had no known immunosuppressing conditions. A high level of suspicion with a detailed review of risk factors and exposure history (e.g., in this case, imprisonment is a risk factor for tuberculosis) is necessary when pursuing a diagnosis of extrapulmonary tuberculosis and treatment should be started as soon as possible when life-threatening manifestations occur. We used a 12-month course of antituberculosis agents associated with steroids, in our case. The patient had a good clinical response and no signs of disease at the end of the treatment.

**29. ESGE quality parameters in colonoscopy: How to ensure their adoption?**

*Bisschops, R and Dinis-Ribeiro, M. Endosc Int Open. 2021;9(10):E1463-E5*

**30. Overcoming the barriers to dissemination and implementation of quality measures for gastrointestinal endoscopy: European Society of Gastrointestinal Endoscopy (ESGE) and United European Gastroenterology (UEG) position statement.**

*Bisschops, R, Rutter, MD, Areia, M, Cristiano, S, Domagk, D, Kaminski, MF, Veitch, A, Khanoussi, W, Gralnek, IM, Hassan, C, Messmann, H, Ponchon, T, Fockens, P, Dignass, A and Dinis-Ribeiro, M. United European Gastroenterol J. 2021;9(1):120-6 [IF: 4.623]*

The European Society of Gastrointestinal Endoscopy (ESGE) has developed performance measures and established a framework for quality assessment for gastrointestinal endoscopy in Europe. Most national societies actively undertake initiatives to implement and explicitly endorse these quality indicators. Given this, the ESGE proposes that, at a national level, strong leadership should exist to disseminate and implement quality parameters. Thus, understanding the potential barriers that may vary locally is of paramount importance. The ESGE suggests that each national society should prioritise quality and standards of care in gastrointestinal endoscopy in their activities and should survey/understand which measures are a local priority to their members and make measuring quality intrinsic to daily endoscopy practice.

**31. Overcoming the barriers to dissemination and implementation of quality measures for gastrointestinal endoscopy: European Society of Gastrointestinal Endoscopy (ESGE) and United European Gastroenterology (UEG) position statement.**

*Bisschops, R, Rutter, MD, Areia, M, Spada, C, Domagk, D, Kaminski, MF, Veitch, A, Khannoussi, W, Gralnek, IM, Hassan, C, Messmann, H, Ponchon, T, Fockens, P, Dignass, A and Dinis-Ribeiro, M. Endoscopy. 2021;53(2):196-202 [IF: 10.093]*

The European Society of Gastrointestinal Endoscopy (ESGE) has developed performance measures and established a framework for quality assessment for gastrointestinal endoscopy in Europe. Most national societies actively undertake initiatives to implement and explicitly endorse these quality indicators. Given this, ESGE proposes that, at a national level, strong leadership should exist to disseminate and implement quality parameters. Thus, understanding the potential barriers that may vary locally is of paramount importance. ESGE suggests that each national society should prioritize quality and standards of care in gastrointestinal endoscopy in their activities and should survey/understand which measures are a local priority to their members and make measuring quality intrinsic to daily endoscopy practice.

**32. The Impact of Vitamin D in Non-Alcoholic Fatty Liver Disease: A Cross-Sectional Study in Patients with Morbid Obesity.**

*Borges-Canha, M, Neves, JS, Mendonca, F, Silva, MM, Costa, C, Cabral, PM, Guerreiro, V, Lourenco, R, Meira, P, Salazar, D, Ferreira, MJ, Pedro, J, Leite, AR, von-Hafe, M, Vale, C, Viana, S, Sande, A, Belo, S, Lau, E, Freitas, P and Carvalho, D. Diabetes Metab Syndr Obes. 2021;14:487-95 [IF: 3.168]*

Purpose: We aimed to evaluate the association between vitamin D status and hepatic function parameters and scores: Fatty Liver Index (FLI, predictor of hepatic steatosis) and BARD (BMI, AST/ALT ratio and DM, predictor of hepatic fibrosis) in patients with morbid obesity. Patients and Methods: Cross-sectional study including patients with morbid obesity followed in our centre between January 2010 and July 2018. Patients with missing vitamin D levels or hepatic profile parameters were excluded. We divided the population according to two cut-offs of vitamin D levels (12ng/mL and 20ng/mL). Results: The included

population (n=1124) had an average age of 43.3+/-10.7 years and 84.3% were female. Seventy-point eight percent of the population had vitamin D levels lower than 20ng/mL and 34.8% lower than 12ng/dL. Patients with lower vitamin D levels (<12ng/mL) had higher BMI, hip and waist circumferences and higher prevalence of hypertension. Higher FLI scores [OR= 0.77 (0.07), p<0.01] and ALP levels [beta= -0.03 (-0.06, -0.01), p<0.01] associated to lower vitamin D levels. Conclusion: Vitamin D deficiency is associated with a higher risk of hepatic steatosis in individuals with morbid obesity. Correction of vitamin D deficiency may have a beneficial role in the management of NAFLD in patients with morbid obesity.

### 33. Beta Cell Function as a Baseline Predictor of Weight Loss After Bariatric Surgery.

*Borges-Canha, M, Neves, JS, Mendonca, F, Silva, MM, Costa, C, P, MC, Guerreiro, V, Lourenco, R, Meira, P, Salazar, D, Ferreira, MJ, Pedro, J, Barkoudah, E, Sande, A, Lau, E, S, BS, Preto, J, Freitas, P and Carvalho, D. Front Endocrinol (Lausanne). 2021;12:714173 [IF: 5.555]*

Background: Obesity is a multifactorial disease, which is strongly associated to other metabolic disorders. Bariatric surgery is the most effective treatment of morbid obesity. The role of beta cell function in weight loss after bariatric surgery is uncertain. Aim: To evaluate the association between beta cell function and percentage of total body weight loss (TBWL%) 1, 2, 3, and 4 years after bariatric surgery in patients with morbid obesity. Methods: Retrospective longitudinal study in patients with morbid obesity followed in our center between January 2010 and July 2018. Patients were excluded if they had diabetes at baseline or missing data on the needed parameters. We evaluated baseline Homeostatic Model Assessment of IR, Homeostatic Model Assessment of beta-cell function (HOMA-beta), Quantitative Insulin Sensitivity Check Index, and Matsuda and DeFronzo index, and TBWL% at years 1 to 4. Linear regression models were used to evaluate the association of indexes of insulin resistance with TBWL% (unadjusted and adjusted for age, sex, BMI, and type of surgery). Results: There were 1,561 patients included in this analysis. HOMA-beta was negatively associated with TBWL% at second, third, and fourth years post-surgery (beta = -1.04 [-1.82 to -0.26], p<0.01; beta = -1.16 [-2.13 to -0.19], p=0.02; beta = -1.29 [-2.64 to 0.06], p=0.061, respectively). This was not observed in the first year post-surgery nor for the other indexes. Glycemia at baseline was positively associated to EWL% at second and third years post-surgery. Conclusion: beta-cell function at baseline seems to be associated to long-term weight loss, explicitly after the first year post bariatric surgery. This might be a helpful predictor of weight loss in clinical practice.

### 34. The addition of neoadjuvant pertuzumab for the treatment of HER2+ breast cancer: a cost estimate with real-world data.

*Borges, A, Pereira, F, Redondo, P, Antunes, L, Vieira, C, Antunes, P, Bento, MJ, Sousa, S, Lopes, JM, Rocha-Goncalves, F, de Sousa, JA, Pereira, DS and Borges, M. Health Econ Rev. 2021;11(1):33 [IF: 2.306]*

BACKGROUND: Breast cancer (BC) is largely prevalent worldwide. HER2-positive BC account for roughly 20-25% of all BC cases and has an overall survival lower than other BC. Innovation on BC therapeutics is a constant, but novel therapies have higher costs. Therefore, cost-effectiveness research is essential to provide healthcare decision-makers with solid foundations for a resource allocation. This study aims to estimate the average direct medical costs/patient and cost-effectiveness of adding pertuzumab in neoadjuvant treatment (NeoT) for HER2-positive breast cancer (BC). METHODS: Two retrospective real-world consecutive cohorts of >=18yo female patients diagnosed with HER2-positive BC treated with NeoT at the Breast Clinic of IPO-Porto were studied. The AC-DH regimen (2012-2015) comprised 8 cycles of neoadjuvant therapy (4 cycles of doxorubicin + cyclophosphamide followed by 4 cycles of docetaxel + trastuzumab), while the AC-DHP regimen (2015-2017) included also pertuzumab as NeoT. NeoT was followed by surgery and adjuvant trastuzumab. Micro-costing technique and a bottom-up approach was used comprising all medical direct costs from the hospital perspective. Unit costs were obtained from government official prices or from IPO-Porto costing system. Costs were adjusted to 2017 and are expressed in euros. Multivariable logistic regression models were used for effectiveness assessment, while generalized linear models with gamma distribution were used for costs. ICER was calculated using the pathological complete response (pCR) as the preferential measure of effectiveness. Sensitivity analysis was also performed. RESULTS: AC-DHP (n = 40) and AC-DH (n = 54) cohorts had heterogenous patient profiles (median age 43y/53y; 67.5%/59.3% positive HR; 60.0%/27.8% operable; 25.0%/24.1% inflammatory, respectively). The AC-DHP average total cost/patient was 56,375euro, with pertuzumab accounting for

13,978euro (24.79%) and increasing in 15,982euro the average cost/patient ( $p < 0.001$ ). Clinical staging and hormone receptors (HR) were significantly associated with pCR. ICER was 1.370euro per percentage point of pCR. CONCLUSIONS: ICER was more favourable in stage III HR negative BC patients compared to other patient profiles. Innovative treatments access is critical to deliver high-quality healthcare, but sustainability must be considered. These results suggest the importance of establishing a cost-effectiveness profile of Pertuzumab in NeOT for HER2-positive BC.

### 35. Radical hysterectomy in early cervical cancer in Europe: characteristics, outcomes and evaluation of ESGO quality indicators.

*Boria, F, Chiva, L, Zanagnolo, V, Querleu, D, Martin-Calvo, N, Capilna, ME, Fagotti, A, Kucukmetin, A, Mom, C, Chakalova, G, Shamistan, A, Malzoni, M, Narducci, F, Arencibia, O, Raspagliesi, F, Toptas, T, Cibula, D, Kaidarova, D, Meydanli, MM, Tavares, M, Golub, D, Perrone, AM, Poka, R, Tsolakidis, D, Vujic, G, Jedryka, MA, Zusterzeel, PLM, Beltman, JJ, Goffin, F, Haidopoulos, D, Haller, H, Jach, R, Yezhova, I, Berlev, I, Bernardino, M, Bharathan, R, Lanner, M, Maenpaa, MM, Sukhin, V, Feron, JG, Fruscio, R, Kukk, K, Ponce, J, Alonso-Espias, M, Minguez, JA, Vazquez-Vicente, D, Manzour, N, Jurado, M, Castellanos, T, Chacon, E and Alcazar, JL. Int J Gynecol Cancer. 2021;31(9):1212-9 [IF: 3.437]*

INTRODUCTION: Comprehensive updated information on cervical cancer surgical treatment in Europe is scarce. OBJECTIVE: To evaluate baseline characteristics of women with early cervical cancer and to analyze the outcomes of the ESGO quality indicators after radical hysterectomy in the SUCCOR database.

METHODS: The SUCCOR database consisted of 1272 patients who underwent radical hysterectomy for stage IB1 cervical cancer (FIGO 2009) between January 2013 and December 2014. After exclusion criteria, the final sample included 1156 patients. This study first described the clinical, surgical, pathological, and follow-up variables of this population and then analyzed the outcomes (disease-free survival and overall survival) after radical hysterectomy. Surgical-related ESGO quality indicators were assessed and the accomplishment of the stated recommendations was verified. RESULTS: The mean age of the patients was 47.1 years (SD 10.8), with a mean body mass index of 25.4 kg/m<sup>2</sup> (SD 4.9). A total of 423 (36.6%) patients had a previous cone biopsy. Tumor size (clinical examination) <2 cm was observed in 667 (57.7%) patients. The most frequent histology type was squamous carcinoma (794 (68.7%) patients), and positive lymph nodes were found in 143 (12.4%) patients. A total of 633 (54.8%) patients were operated by open abdominal surgery. Intra-operative complications occurred in 108 (9.3%) patients, and post-operative complications during the first month occurred in 249 (21.5%) patients, with bladder dysfunction as the most frequent event (119 (10.3%) patients). Clavien-Dindo grade III or higher complication occurred in 56 (4.8%) patients. A total of 510 (44.1%) patients received adjuvant therapy. After a median follow-up of 58 months (range 0-84), the 5-year disease-free survival was 88.3%, and the overall survival was 94.9%. In our population, 10 of the 11 surgical-related quality indicators currently recommended by ESGO were fully fulfilled 5 years before its implementation. CONCLUSIONS: In this European cohort, the rate of adjuvant therapy after radical hysterectomy is higher than for most similar patients reported in the literature. The majority of centers were already following the European recommendations even 5 years prior to the ESGO quality indicator implementations.

### 36. Differences in the management and survival of metastatic colorectal cancer in Europe. A population-based study.

*Bouvier, AM, Jooste, V, Sanchez-Perez, MJ, Bento, MJ, Rocha Rodrigues, J, Marcos-Gragera, R, Carmona-Garcia, MC, Luque-Fernandez, MA, Minicozzi, P, Bouvier, V, Innos, K, Sant, M and Working Group on, C. Dig Liver Dis. 2021;53(5):639-45 [IF: 4.088]*

BACKGROUND: The management regarding metastatic colorectal cancer throughout Europe is not well known. AIMS: To draw a European comparison of the management and prognosis of metastatic colorectal cancers. METHODS: Factors associated with chemotherapy administration were identified through logistic regressions. Net survival was estimated and crude probabilities of death related to cancer and other causes using a flexible cumulative hazard model. RESULTS: Among the 13 227 patients with colorectal cancer diagnosed between 2010 and 2013 in cancer registries from 10 European countries, 3140 were metastatic. 62% of metastatic patients received chemotherapy. Compared to Spain, the related adjusted odds ratios ranged from 0.7 to 4.0 ( $P < 0.001$ ) according to country. The 3-year net survival by country ranged between

16% and 37%. The survival gap between countries diminished from 21% to 10% when adjusting for chemotherapy, age and sex. Geographical differences in the crude probability of death related to cancer were large for patients <70 or >/=80 years at diagnosis. CONCLUSION: Heterogeneity in the application of European guidelines partly explain these differences. General health between populations, accessibility to a reference centre, or provision of health care could also be involved. Further population-based studies are warranted to disentangle between these possible explanations.

**37. A nonviral, nonintegrating DNA nanovector platform for the safe, rapid, and persistent manufacture of recombinant T cells.**

*Bozza, M, De Roia, A, Correia, MP, Berger, A, Tuch, A, Schmidt, A, Zornig, I, Jager, D, Schmidt, P and Harbottle, RP. Sci Adv. 2021;7(16):eabf1333 [IF: 14.136]*

The compelling need to provide adoptive cell therapy (ACT) to an increasing number of oncology patients within a meaningful therapeutic window makes the development of an efficient, fast, versatile, and safe genetic tool for creating recombinant T cells indispensable. In this study, we used nonintegrating minimally sized DNA vectors with an enhanced capability of generating genetically modified cells, and we demonstrate that they can be efficiently used to engineer human T lymphocytes. This vector platform contains no viral components and is capable of replicating extrachromosomally in the nucleus of dividing cells, providing persistent transgene expression in human T cells without affecting their behavior and molecular integrity. We use this technology to provide a manufacturing protocol to quickly generate chimeric antigen receptor (CAR)-T cells at clinical scale in a closed system and demonstrate their enhanced anti-tumor activity in vitro and in vivo in comparison to previously described integrating vectors.

**38. The role of the hospital pharmacist in immunocellular therapy with chimeric antigen receptor (CAR) T cells.**

*Braga, F, Morgado, S, Roque, F and Morgado, M. Drugs & Therapy Perspectives. 2021;37(9):433-8 [IF: NA]*

The development and commercialization of genetically modified T-cell medicines using chimeric antigen receptor (CAR) T cells represents a new challenge for European Union hospital pharmacies. The aim of this article was to review the key aspects of these medicines, particularly those already available in the European Union (axicabtagene ciloleucel and tisagenlecleucel), and to describe the hospital pharmacist's role within the multidisciplinary health team. Because CAR T-cell medicines are exclusively used at the hospital level, hospital pharmacists have a responsibility to contribute to their rational use, assuming technical responsibility for their ordering, product receipt, storage, preservation, and dispensing, as well as establishing an effective and safe system that ensures correct administration to the patient. This should also include the short- and long-term follow-up of patients treated with this type of therapy, emphasizing on the management of the main adverse effects of this therapy. CAR T-cell therapy offers hospital pharmacists the opportunity to work closely with other health professionals involved in the process, allowing their contribution to the development of procedures, clinical practice guidelines of global use, establishing starting points when facing future therapies of similar complexity, and even improving previously established basic processes in the various phases of this type of medication.

**39. Comparing the cost of non-metastatic breast cancer care in a low-income vs a high-income country: A plea for an optimal allocation of health resources in Sub-Saharan Africa.**

*Brandao, M, Morais, S, Guisseve, A, Bata, G, Borges, M, Tulsidas, S, Pereira, S, Carrilho, C and Lunet, N. Breast. 2021;57:1-4 [IF: 4.380]*

Breast cancer incidence is rising in low-income countries, but there is limited information regarding health resource allocation for its care. We assessed the cost of care during the first three years after diagnosis in a low-income country (Mozambique; n = 162 women) and compared it with a high-income country (Portugal, n = 703 women). Local currency prices were converted to 2019 international dollars (Int\$). In Mozambique, the median cost was lower than in Portugal (2888 vs 18,533 Int\$, respectively) and did not vary across stage or tumor subtype. These findings may help improving resource allocation for breast cancer care in Sub-Saharan Africa, despite reflecting an underfunding of treatment in this setting.

**40. Comment on a systematic review and meta-analysis on single fraction radiosurgery, fractionated**

**radiosurgery, and conventional radiotherapy for spinal oligometastasis.**

*Bravo, I. Radiother Oncol. 2021;154:e1 [IF: 6.280]*

**41. Omega-3- and Resveratrol-Loaded Lipid Nanosystems for Potential Use as Topical Formulations in Autoimmune, Inflammatory, and Cancerous Skin Diseases.**

*Caldas, AR, Catita, J, Machado, R, Ribeiro, A, Cerqueira, F, Horta, B, Medeiros, R, Lucio, M and Lopes, CM. Pharmaceutics. 2021;13(8) [IF: 6.321]*

Resveratrol (RSV) and omega 3 (omega3), because of their biological favorable properties, have become subjects of interest for researchers in dermocosmetic and pharmaceutical industries; however, these bioactives present technological limitations that hinder their effective delivery to the target skin layer. To overcome the stability and skin permeation limitations of free bioactives, this work proposes a combined strategy involving two different lipid nanosystems (liposomes and lipid nanoparticles) that include omega3 in their lipid matrix. Additionally, RSV is only encapsulated in liposomes that provide an adequate amphiphilic environment. Each formulation is thoroughly characterized regarding their physical-chemical properties. Subsequently, the therapeutic performance of the lipid nanosystems is evaluated based on their protective roles against lipid peroxidation, as well as inhibition of cyclooxygenase (COX) and nitric oxide (NO) production in the RWA264.7 cell line. Finally, the lipid nanosystems are incorporated in hydrogel to allow their topical administration, then rheology, occlusion, and RSV release-diffusion assays are performed. Lipid nanoparticles provide occlusive effects at the skin surface. Liposomes provide sustained RSV release and their flexibility conferred by edge activator components enhances RSV diffusion, which is required to reach NO production cells and COX cell membrane enzymes. Overall, the inclusion of both lipid nanosystems in the same semisolid base constitutes a promising strategy for autoimmune, inflammatory, and cancerous skin diseases.

**42. Results of accelerated partial breast irradiation in patients not suitable for external beam irradiation stratified by GEC-ESTRO, ASTRO, and ABS guidelines.**

*Campos Magalhaes Garcia, LS and Garcia Trigo, ML. Brachytherapy. 2021;20(2):315-25 [IF: 2.362]*

**PURPOSE:** This study aims to review the outcome of an institution in multicatheter/interstitial accelerated partial breast irradiation (MC-APBI) for treatment of patients with breast cancer, either with strong criteria for APBI or unable to be treated with whole-breast irradiation. The outcomes were also stratified by the American Society for Radiation Oncology, American Brachytherapy Society, and Groupe Europeen de Curietherapie-European Society for Therapeutic Radiology and Oncology patient selection criteria. **METHODS:** The study includes 118 patients and 120 MC-APBI treatments, treated in a single tertiary center, between November 2003 and August 2016. The analysis is focused on the clinical baseline characteristics, local control, relapse-free survival, disease-specific survival (DSS), and overall survival. **RESULTS:** In accordance to the American Society for Radiation Oncology, American Brachytherapy Society, and Groupe Europeen de Curietherapie-European Society for Therapeutic Radiology and Oncology, 17.1% were "unsuitable," 19.2% were "unacceptable," and 19.5% were "high risk," respectively. The main reasons why high-risk patients were submitted to MC-APBI were as follows: cardiopathy (n = 7), social difficulties (n = 4), and mobility limitations (n = 4). At the median followup period of 86.5 months, ipsilateral breast tumor recurrence was observed in one (0.8%) patient. The 3-year and 5-year relapse-free survival were 100% and 99.1%, respectively. DSS was 100%. **CONCLUSIONS:** This study demonstrated excellent control rates, DFS, and DSS of MC-APBI, rendering APBI as an excellent treatment for patients with breast cancer, even those who are not necessarily eligible for this treatment approach. The selection criteria for APBI diverge according to different guidelines and are based on studies with discrepancies, making extremely possible that these recommendations could be changed.

**43. Single Nucleotide Polymorphism in Prolactin Gene Is Associated With Clinical Aggressiveness and Outcome of Canine Mammary Malignant Tumors.**

*Canadas-Sousa, A, Santos, M, Medeiros, R and Dias-Pereira, P. Vet Pathol. 2021;58(6):1051-7 [IF: 2.221]*

Prolactin (PRL) is a key hormone involved in canine mammary development and tumorigenesis. In this study, the influence of a single nucleotide polymorphism (SNP) in the PRL gene (rs23932236) on the clinicopathological parameters and survival of dogs with canine mammary tumors (CMTs) was investigated.

A total of 206 female dogs with spontaneous mammary tumors were enrolled in this study and circulating blood cells were genotyped. This specific SNP was associated with larger size (>3 cm diameter) for malignant tumors ( $P = .036$ ), tumors with infiltrative/invasive growth pattern ( $P = .010$ ), vascular invasion ( $P = .006$ ), and lymph node metastasis ( $P = .004$ ). Carriers of the variant allele had a shorter overall survival compared to the wild-type population with an overall survival of 18.7 months and 22.7 months, respectively ( $P = .004$ ). These findings suggest that SNP rs23932236 of canine PRL gene may be used as an indicator for the development of clinically aggressive forms of CMTs.

#### 44. Efficacy and safety of primary, early and late needle-knife fistulotomy for biliary access.

Canena, J, Lopes, L, Fernandes, J, Alexandrino, G, Figueiredo, L, Moreira, M, Araujo, T, Lourenco, L, Horta, D, Familiari, P and Dinis-Ribeiro, M. *Sci Rep*. 2021;11(1):16658 [IF: 4.379]

European Society of Gastrointestinal Endoscopy recommends needle-knife fistulotomy (NKF) as the preferred precut technique. However, there is little information on whether NKF performed at different times is associated with different success and adverse event rates. We compared the outcomes of 3 different timings of NKF. This was an observational study conducted at 4 institutions and this was a retrospective analysis of prospectively collected data. We included 330 consecutive patients submitted to NKF attempt for biliary access. Patients were divided into three groups: NKF as an initial procedure for biliary access (group A,  $n = 121$ ); early NKF defined as after 5 min, 5 attempts, or 2 pancreatic passages (group B,  $n = 99$ ); and late NKF: after at least 10 min of unsuccessful standard biliary cannulation (group C,  $n = 110$ ). We assessed the success rate of biliary cannulation at initial ERCP, time to perform NKF until biliary cannulation, overall biliary cannulation rate (second ERCP when initial failure), adverse event rate, and predictors of post-ERCP pancreatitis (PEP). The initial cannulation rate was 98%, 91% and 94% for groups A, B and C respectively,  $p = 0.08$ , whereas overall biliary cannulation rate was 100%, 95% and 98%,  $p = 0.115$ . The adverse event rate/PEP was 4.1%/2.5%, 7.1%/4% and 10.9%/8.2%, for groups A, B and C respectively, ( $p = 0.197$  and  $p = 0.190$ ). Median time for creating the fistula was A = 4.0 min, B = 3.2 min, and C = 5.6 min,  $p < 0.001$ . Each additional minute spent attempting cannulation increased the odds ratio (OR) for PEP by 1.072, and patients with 3 or more risk factors for pancreatitis had a higher chance of PEP. In conclusion, the timing of NKF does not appear to influence success rates but late NKF is associated with a higher time to create a fistula and an increased risk of pancreatitis. Primary NKF is associated with a high rate of success and a low rate of PEP and deserves additional investigation.

#### 45. Influence of a novel classification of the papilla of Vater on the outcome of needle-knife fistulotomy for biliary cannulation.

Canena, J, Lopes, L, Fernandes, J, Costa, P, Arvanitakis, M, Koch, AD, Poley, JW, Jimenez, J, Dominguez-Munoz, E, Familiari, P, Bruno, MJ and Dinis-Ribeiro, M. *BMC Gastroenterol*. 2021;21(1):147 [IF: 3.067]

BACKGROUND: Existing proposed classification systems for the Papilla of Vater (PV) suboptimally account for all relevant, encountered PV appearances, are too complex or have not been assessed for intra- or interobserver variability. We proposed a novel endoscopic classification system for PV, determined its inter- and intraobserver rates and used the classification system to assess whether the success and complications of needle-knife fistulotomy (NKF) are influenced by the morphology of the PV. METHODS: The classification system was developed by expert endoscopists. To evaluate the inter- and intraobserver agreement, an online questionnaire was sent to 20 endoscopists from several countries (10 experts and 10 nonexperts) that included 50 images of papillae of Vater divided among various categories. Four weeks later, a second survey, with the images from the first questionnaire randomly reordered, was sent to the same endoscopists. The inter- and intraobserver agreements among the experts and nonexperts was calculated. Using the proposed classification system, all 361 consecutive patients who underwent NKF for biliary access to a naive papilla were prospectively enrolled in the study. RESULTS: The novel classification system comprises 7 categories: type I, flat type, lacking an oral protrusion; type IIA, prominent tubular nonpleated type, with an oral protrusion and < 1 transverse fold over the oral protrusion; type IIB, prominent tubular pleated type, with an oral protrusion and > 2 transverse folds over the oral protrusion; type IIC: prominent bulging type, with an enlarged and bulging oral protrusion; type IIIA, diverticular-intradiverticular type, with a papillary orifice inside the diverticulum; type IIIB: diverticular-diverticular border type, with a papillary orifice less than 2 cm from the diverticular border; type IV: unclassified papilla,

with no morphology classified in the other categories. The interobserver agreement between experts was substantial (K = 0.611, 95% CI 0.498-0.709) and was higher than that between nonexperts (K = 0.516; 95% CI 0.410-0.636). The intraobserver agreement was substantial among both experts (K = 0,651; 95% CI 0.586-0.715) and nonexperts (K = 0.646, 95% CI 0.615-0.677). In a multivariate model, type IIIA and IIIB were the only independent risk factors for difficult rescue NKF biliary cannulation (P = 0.003 and P = 0.019, respectively), and type I and type IIB were the only independent risk factors for a prolonged cannulation time using NKF (P < 0.001 and P = 0.005, respectively). CONCLUSIONS: The novel endoscopic classification system for PV is highly reproducible among experienced ERCPists according to the substantial level of agreement between experts. However, nonexperts require further training in its use. Using the novel classification system, we identified different types of papillae significantly associated with a lower efficacy of NKF and a prolonged time to obtain successful biliary cannulation using NKF.

#### 46. Management of ibrutinib treatment in patients with B-cell malignancies: clinical practice in Portugal and multidisciplinary recommendations.

*Carda, JP, Santos, L, Mariz, JM, Monteiro, P, Goncalves, HM, Raposo, J and Gomes da Silva, M. Hematology. 2021;26(1):785-98 [IF: 2.269]*

OBJECTIVES: Ibrutinib, a potent inhibitor of the Bruton tyrosine kinase, has revolutionized the treatment of many B-cell malignancies. Ibrutinib has an established favorable toxicity profile with up to 8 years of experience in clinical trials; however, despite ibrutinib's favorable toxicity profile, dose reductions and treatment discontinuations are becoming more evident in clinical practice, particularly in the setting of specific clinical contexts and patient characteristics. This manuscript is set to provide practical recommendations on the management of patients treated with this agent in daily practice. METHODS: A group of multidisciplinary experts from Portugal met to discuss and highlight practical recommendations, supported on both literature and clinical insights, for the management of the treatment with ibrutinib. RESULTS/DISCUSSION: Handling of both toxicities and drug-drug interactions during ibrutinib treatment poses several challenges to healthcare providers and can benefit from a multidisciplinary approach. The involvement of specialties, such as cardiology, infectiology and pharmacology, can bring an added value to patient care, not only in anticipating/managing safety issues and dose adjustments but also in enhancing adherence to treatment, ultimately improving the risk/benefit balance. CONCLUSION: By involving a multidisciplinary group of experts, this work provides a set of key recommendations to optimize care and outcomes for ibrutinib-treated patients. Despite not being a fully comprehensive review on the topic, it is intended as a framework to hematologists and other healthcare professionals who manage these patients in their daily clinical practice.

#### 47. Epigenetic alterations as therapeutic targets in Testicular Germ Cell Tumours : current and future application of 'epidrugs'.

*Cardoso, AR, Lobo, J, Miranda-Goncalves, V, Henrique, R and Jeronimo, C. Epigenetics. 2021;16(4):353-72 [IF: 4.528]*

Testicular germ cell tumours (TGCTs) are heterogeneous neoplasms mostly affecting young-adult men. Despite high survival rates, some patients with disseminated disease acquire cisplatin resistance, entailing the need for less toxic therapies. Epigenetic alterations constitute an important feature of TGCTs, which are also implicated in resistance mechanism(s). These alterations might be used as potential targets to design epigenetic drugs. To date, several compounds have been explored and evaluated regarding therapeutic efficacy, making use of pre-clinical studies with in vitro and in vivo models, and some have already been explored in clinical trials. This review summarizes the several epigenetic mechanisms at play in these neoplasms, the current challenges in the field of TGCTs and critically reviews available data on 'epidrugs' in those tumours.

#### 48. DROSHA rs10719 and DICER1 rs3742330 polymorphisms in endometriosis and different diseases: Case-control and review studies.

*Cardoso, JV, Medeiros, R, Dias, F, Costa, IA, Ferrari, R, Berardo, PT and Perini, JA. Exp Mol Pathol. 2021;119:104616 [IF: 3.362]*

OBJECTIVE: DROSHA and DICER1 enzymes participate in the main stages of microRNA synthesis.

Polymorphisms can influence mRNAs stability and genes expression, and hence affect the binding of miRNAs. Thus, the present study evaluated the association of DROSHA and DICER1 polymorphisms in the development of endometriosis and other diseases. METHODS: A total of 240 endometriosis cases and 242 controls were genotyped for the DROSHA rs10719 G > A and DICER1 rs3742330 A > G polymorphisms using the TaqMan system. The association between polymorphisms and endometriosis was estimated by binary logistic regression. A literature review was also performed including all published articles (PubMed database) until December 2020, regarding the association of the studied polymorphisms and different diseases. RESULTS: DICER1 rs3742330GG was only found in endometriosis cases (2.1%) and deep infiltrative endometriosis (DIE) (2.5%). The DICER1 rs3742330GG genotype was significantly associated with endometriosis ( $P < 0.05$ ), suggesting a tendency to present an increased risk for disease. DROSHA rs10719A and DICER1 rs3742330G allele frequencies varied among populations (6%-79% and 10.2%-55.1%, respectively). In the Brazilian population, the frequencies of these alleles were 42.3% and 7.3%, respectively. Both polymorphisms were risk factors for nonsyndromic orofacial clefts, tuberculosis, stroke ischemia and mortality after stroke, recurrent idiopathic pregnancy loss, and some types of cancer. Moreover, the DICER1 rs3742330 polymorphism was a protective factor for precancerous cervical lesions, different types of cancer and tuberculosis. CONCLUSIONS: The results suggest that only the DICER1 rs3742330 A > G polymorphism may be associated with susceptibility to endometriosis. The frequencies of both polymorphisms were significantly different among populations, and there were discrepancies in the risk associations with the development of diseases.

#### 49. Colorectal cancer incidence, mortality, and stage distribution in European countries in the colorectal cancer screening era: an international population-based study.

Cardoso, R, Guo, F, Heisser, T, Hackl, M, Ihle, P, De Schutter, H, Van Damme, N, Valerianova, Z, Atanasov, T, Majek, O, Muzik, J, Nilbert, MC, Tybjerg, AJ, Innos, K, Magi, M, Malila, N, Bouvier, AM, Bouvier, V, Launoy, G, Woronoff, AS, Cariou, M, Robaszekiewicz, M, Delafosse, P, Poncet, F, Katalinic, A, Walsh, PM, Senore, C, Rosso, S, Vincerzevskiene, I, Lemmens, V, Elferink, MAG, Johannesen, TB, Korner, H, Pfeffer, F, Bento, MJ, Rodrigues, J, Alves da Costa, F, Miranda, A, Zadnik, V, Zagar, T, Lopez de Munain Marques, A, Marcos-Gragera, R, Puigdemont, M, Galceran, J, Carulla, M, Chirlaque, MD, Ballesta, M, Sundquist, K, Sundquist, J, Weber, M, Jordan, A, Herrmann, C, Mousavi, M, Ryzhov, A, Hoffmeister, M and Brenner, H. *Lancet Oncol.* 2021;22(7):1002-13 [IF: 41.316]

BACKGROUND: Colorectal cancer screening programmes and uptake vary substantially across Europe. We aimed to compare changes over time in colorectal cancer incidence, mortality, and stage distribution in relation to colorectal cancer screening implementation in European countries. METHODS: Data from nearly 3.1 million patients with colorectal cancer diagnosed from 2000 onwards (up to 2016 for most countries) were obtained from 21 European countries, and were used to analyse changes over time in age-standardised colorectal cancer incidence and stage distribution. The WHO mortality database was used to analyse changes over time in age-standardised colorectal cancer mortality over the same period for the 16 countries with nationwide data. Incidence rates were calculated for all sites of the colon and rectum combined, as well as the subsites proximal colon, distal colon, and rectum. Average annual percentage changes (AAPCs) in incidence and mortality were estimated and relevant patterns were descriptively analysed. FINDINGS: In countries with long-standing programmes of screening colonoscopy and faecal tests (ie, Austria, the Czech Republic, and Germany), colorectal cancer incidence decreased substantially over time, with AAPCs ranging from -2.5% (95% CI -2.8 to -2.2) to -1.6% (-2.0 to -1.2) in men and from -2.4% (-2.7 to -2.1) to -1.3% (-1.7 to -0.9) in women. In countries where screening programmes were implemented during the study period, age-standardised colorectal cancer incidence either remained stable or increased up to the year screening was implemented. AAPCs for these countries ranged from -0.2% (95% CI -1.4 to 1.0) to 1.5% (1.1 to 1.8) in men and from -0.5% (-1.7 to 0.6) to 1.2% (0.8 to 1.5) in women. Where high screening coverage and uptake were rapidly achieved (ie, Denmark, the Netherlands, and Slovenia), age-standardised incidence rates initially increased but then subsequently decreased. Conversely, colorectal cancer incidence increased in most countries where no large-scale screening programmes were available (eg, Bulgaria, Estonia, Norway, and Ukraine), with AAPCs ranging from 0.3% (95% CI 0.1 to 0.5) to 1.9% (1.2 to 2.6) in men and from 0.6% (0.4 to 0.8) to 1.1% (0.8 to 1.4) in women. The largest decreases in colorectal cancer mortality were seen in countries with long-standing screening programmes. INTERPRETATION: We

observed divergent trends in colorectal cancer incidence, mortality, and stage distribution across European countries, which appear to be largely explained by different levels of colorectal cancer screening implementation. FUNDING: German Cancer Aid (Deutsche Krebshilfe) and the German Federal Ministry of Education and Research.

#### 50. Enhanced Ultraviolet Spectroscopy by Optical Clearing for Biomedical Applications.

*Carneiro, J, Carvalho, S, Henrique, R, Selifonov, A, Oliveira, L and Tuchin, VV. IEEE Journal of Selected Topics in Quantum Electronics. 2021;27(4):1-8 [IF: 4.544]*

In this paper, we describe the combination of ultraviolet (UV) spectroscopy with the optical clearing technique to induce new tissue windows, evaluate their efficiency, study the diffusion properties of agents and discriminate cancer. The use of highly concentrated glycerol solutions has induced high efficiency clearing effects in the UV, both in human colorectal and gingival tissues. The protein dissociation rate obtained for colorectal tissues was approximately 3 times higher in pathological than in normal mucosa and the kinetics of diffuse reflectance in the UV allowed to estimate the diffusion coefficient for water in gingival mucosa at glycerol action as  $(1.78 \pm 0.26) \times 10^{-6} \text{ cm}^2/\text{s}$ .

#### 51. OmniSARS2: A Highly Sensitive and Specific RT-qPCR-Based COVID-19 Diagnostic Method Designed to Withstand SARS-CoV-2 Lineage Evolution.

*Carvalho-Correia, E, Calcada, C, Branca, F, Estevez-Gomez, N, De Chiara, L, Varela, N, Gallego-Garcia, P, Posada, D, Sousa, H, Sousa, J, Veiga, MI and Osorio, NS. Biomedicines. 2021;9(10) [IF: 6.081]*

Extensive transmission of SARS-CoV-2 during the COVID-19 pandemic allowed the generation of thousands of mutations within its genome. While several of these become rare, others largely increase in prevalence, potentially jeopardizing the sensitivity of PCR-based diagnostics. Taking advantage of SARS-CoV-2 genomic knowledge, we designed a one-step probe-based multiplex RT-qPCR (OmniSARS2) to simultaneously detect short fragments of the SARS-CoV-2 genome in ORF1ab, E gene and S gene. Comparative genomics of the most common SARS-CoV-2 lineages, other human betacoronavirus and alphacoronavirus, was the basis for this design, targeting both highly conserved regions across SARS-CoV-2 lineages and variable or absent in other Coronaviridae viruses. The highest analytical sensitivity of this method for SARS-CoV-2 detection was 94.2 copies/mL at 95% detection probability ( $\sim 1$  copy per total reaction volume) for the S gene assay, matching the most sensitive available methods. In vitro specificity tests, performed using reference strains, showed no cross-reactivity with other human coronavirus or common pathogens. The method was compared with commercially available methods and detected the virus in clinical samples encompassing different SARS-CoV-2 lineages, including B.1, B.1.1, B.1.177 or B.1.1.7 and rarer lineages. OmniSARS2 revealed a sensitive and specific viral detection method that is less likely to be affected by lineage evolution oligonucleotide-sample mismatch, of relevance to ensure the accuracy of COVID-19 molecular diagnostic methods.

#### 52. Emerging Lab-on-a-Chip Approaches for Liquid Biopsy in Lung Cancer: Status in CTCs and ctDNA Research and Clinical Validation.

*Carvalho, A, Ferreira, G, Seixas, D, Guimaraes-Teixeira, C, Henrique, R, Monteiro, FJ and Jeronimo, C. Cancers (Basel). 2021;13(9) [IF: 6.639]*

Despite the intensive efforts dedicated to cancer diagnosis and treatment, lung cancer (LCA) remains the leading cause of cancer-related mortality, worldwide. The poor survival rate among lung cancer patients commonly results from diagnosis at late-stage, limitations in characterizing tumor heterogeneity and the lack of non-invasive tools for detection of residual disease and early recurrence. Henceforth, research on liquid biopsies has been increasingly devoted to overcoming these major limitations and improving management of LCA patients. Liquid biopsy is an emerging field that has evolved significantly in recent years due its minimally invasive nature and potential to assess various disease biomarkers. Several strategies for characterization of circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA) have been developed. With the aim of standardizing diagnostic and follow-up practices, microfluidic devices have been introduced to improve biomarkers isolation efficiency and specificity. Nonetheless, implementation of lab-on-a-chip platforms in clinical practice may face some challenges, considering its recent application to liquid biopsies. In this review, recent advances and strategies for the use of liquid

biopsies in LCa management are discussed, focusing on high-throughput microfluidic devices applied for CTCs and ctDNA isolation and detection, current clinical validation studies and potential clinical utility.

### 53. Neuroendocrine Tumors of the Gastrointestinal Tract: A Focused Review and Practical Approach for Gastroenterologists.

*Carvalho, J, Dinis-Ribeiro, M, Pimentel-Nunes, P and Libanio, D. GE Port J Gastroenterol. 2021;28(5):336-48 [IF: NA]*

Neuroendocrine tumors (NETs) are rare tumors derived from the neuroendocrine cell system, and more commonly found in the gastrointestinal (GI) tract. Over the last decades, the incidence of GI-NETs has been steadily increasing, partly due to the expanding indications for endoscopy. Most patients with NETs are asymptomatic, and their NETs are noticed during screening examinations; thus, endoscopists are on the frontline of the diagnosis of GI-NETs. Since GI-NETs are less frequent than other malignancies, the natural history, diagnosis, and management of these tumors may not be fully understood. In this review, we aim to update the endoscopist on key clinical features and management of patients with gastric, duodenal, and rectal NETs.

### 54. Functional Genetic Variants in ATG10 Are Associated with Acute Myeloid Leukemia.

*Castro, I, Sampaio-Marques, B, A, CA, Sousa, H, Fernandes, A, Sanchez-Maldonado, JM, Cunha, C, Carvalho, A, Sainz, J and Ludovico, P. Cancers (Basel). 2021;13(6) [IF: 6.639]*

Acute myeloid leukemia (AML) is the most common acute leukemia, characterized by a heterogeneous genetic landscape contributing, among others, to the occurrence of metabolic reprogramming. Autophagy, a key player on metabolism, plays an essential role in AML. Here, we examined the association of three potentially functional genetic polymorphisms in the ATG10 gene, central for the autophagosome formation. We screened a multicenter cohort involving 309 AML patients and 356 healthy subjects for three ATG10 SNPs: rs1864182T>G, rs1864183C>T and rs3734114T>C. The functional consequences of the ATG10 SNPs in its canonical function were investigated in vitro using peripheral blood mononuclear cells from a cohort of 46 healthy individuals. Logistic regression analysis adjusted for age and gender revealed that patients carrying the ATG10rs1864182G allele showed a significantly decreased risk of developing AML (OR [odds ratio] = 0.58,  $p = 0.001$ ), whereas patients carrying the homozygous ATG10rs3734114C allele had a significantly increased risk of developing AML (OR = 2.70,  $p = 0.004$ ). Functional analysis showed that individuals carrying the ATG10rs1864182G allele had decreased autophagy when compared to homozygous major allele carriers. Our results uncover the potential of screening for ATG10 genetic variants in AML prevention strategies, in particular for subjects carrying other AML risk factors such as elderly individuals with clonal hematopoiesis of indeterminate potential.

### 55. Pharmacogenetics of advanced lung cancer: Predictive value of functional genetic polymorphism AGXT Pro11Leu in clinical outcome?

*Catarata, MJ, Lourenco, M, Martins, MF, Frade, J, Pego, A, Cordeiro, CR, Medeiros, R and Ribeiro, R. Pulmonology. 2021;27(2):116-23 [IF: 3.575]*

INTRODUCTION: AGXT gene codes for the enzyme alanine glyoxylate aminotransferase, which is involved in hepatic peroxisomal metabolism of platinum-based chemotherapeutic agents. The association of genetic variant AGXT rs34116584 on the clinical outcome and response to chemotherapy of patients with non-small cell lung cancer (NSCLC) remains to be established. Our aim was to evaluate the association of functional AGXT gene polymorphism in NSCLC progression, considering as primary and secondary endpoint, progression free survival (PFS) and overall survival (OS), respectively. METHODS: Genotyping of the AGXT rs34116584 genetic polymorphism was performed by mass spectrometry on 168 DNA samples from patients with NSCLC (stages IIIA-IVB). Univariate survival analysis included the study of Kaplan-Meier curves with the Log-Rank test, while Cox regression was used as a multivariate analysis. RESULTS: Multivariate analysis showed shorter PFS for T carriers [HR=2.0, 95% CI, 1.4-3.0,  $p < 0.0001$ ] and shorter OS [HR=1.8, 95% CI, 1.1-3.0,  $p = 0.017$ ] globally, as well as in a subgroup of patients ( $n = 144$ ) treated with first line platinum-based chemotherapy [HR=2.0, 95% CI, 1.3-3.1,  $p = 0.001$ ] and [HR=1.8, 95% CI, 1.1-3.1,  $p = 0.026$ ], respectively. CONCLUSION: This polymorphism seems to have an impact on NSCLC progression, opening new perspectives for its inclusion as a pharmacogenetic predictor of response to platinum-based

chemotherapy.

#### 56. Outcomes of Airway Stents in the Palliative Care of Patients With Cancer.

*Catarata, MJP, Saleiro, S and Araujo, VS. Am J Hosp Palliat Care. 2021;38(1):19-24 [IF: 2.500]*

**INTRODUCTION:** A significant proportion of patients with advanced primary or metastatic intrathoracic malignancy will eventually develop central airway obstruction. The morbidity associated with malignant airway obstruction (MAO) is considerable and the management is difficult. Our aim was to evaluate the outcomes of tracheobronchial stenting in patients with MAO and its role in palliative care. **MATERIAL AND METHODS:** This retrospective study involved a consecutive case series of patients with advanced cancer with MAO who underwent tracheobronchial stenting between August 2014 and August 2019. The European Cooperative Oncology Group (ECOG) scale was used to evaluate patient functional status before and after tracheobronchial stenting. Univariate survival analysis included Kaplan-Meier curves with Log-Rank test, while Cox regression was used as a multivariate analysis. **RESULTS:** We included 28 patients with median age of 55.0 years (interquartile range = 49.3-66.5) and 89.3% male. The most frequent primary tumour was the esophagus followed by lungs. The majority of the patients (75%) expressed immediate symptom relief after stenting and there was a significant improvement in the mean ECOG performance status (PS;  $P = .005$ ). There was no intraprocedure mortality and complications were observed in 6 patients. The median survival after airway stenting was 39.0 days (95% CI = 32.2-45.8) with poorer PS after stent insertion associated with lower overall survival (hazard ratio = 2.3 [95% CI = 1.1-4.9],  $P = .030$ ) on multivariate analysis. **CONCLUSION:** Airway stent is a safe and effective procedure that offers rapid palliation of symptoms with no major complications. Therefore, stent placement should be considered as part of the treatment of patients with terminal cancer.

#### 57. Mechanism of Antifungal Activity by 5-Aminoimidazole-4-Carbohydrazonamide Derivatives against *Candida albicans* and *Candida krusei*.

*Cerqueira, F, Maia, M, Gabriel, C, Medeiros, R, Cravo, S, Ribeiro, AI, Dantas, D, Dias, AM, Saraiva, L, Raimundo, L and Pinto, E. Antibiotics (Basel). 2021;10(2) [IF: 4.369]*

Systemic mycoses are one major cause of morbidity/mortality among immunocompromised/debilitated individuals. Studying the mechanism of action is a strategy to develop safer/potent antifungals, warning resistance emergence. The major goal of this study was to elucidate the mechanism of action of three (Z)-5-amino-N'-aryl-1-methyl-1H-imidazole-4-carbohydrazonamides (2h, 2k, 2l) that had previously demonstrated strong antifungal activity against *Candida krusei* and *C. albicans* ATCC strains. Activity was confirmed against clinical isolates, susceptible or resistant to fluconazole by broth microdilution assay. Ergosterol content (HPLC-DAD), mitochondrial dehydrogenase activity (MTT), reactive oxygen species (ROS) generation (flow cytometry), germ tube inhibition and drug interaction were evaluated. None of the compounds inhibited ergosterol synthesis. Ascorbic acid reduced the antifungal effect of compounds and significantly decreased ROS production. The metabolic viability of *C. krusei* was significantly reduced for values of 2MIC. Compounds 2h and 2k caused a significant increase in ROS production for MIC values while for 2l a significant increase was only observed for concentrations above MIC. ROS production seems to be involved in antifungal activity and the higher activity against *C. krusei* versus *C. albicans* may be related to their unequal sensitivity to different ROS. No synergism with fluconazole or amphotericin was observed, but the association of 2h with fluconazole might be valuable due to the significant inhibition of the dimorphic transition, a *C. albicans* virulence mechanism.

#### 58. When to Stop TKIs in Patients with Chronic Myeloid Leukemia and How to Follow Them Subsequently.

*Cerveira, N, Bizarro, S, Teixeira, MR and Mariz, JM. Curr Treat Options Oncol. 2021;22(6):49 [IF: 5.036]*

**OPINION STATEMENT:** ABL1 tyrosine kinase inhibitors (TKI) have dramatically improved the outcome for CML (chronic myeloid leukemia) patients. When TKI therapy is addressed appropriately, it can lead to an optimal molecular response in the majority of CML patients and a life expectancy that approaches that of the general population. However, lifelong TKI therapy may have consequences, including chronic, mostly low-grade, adverse events that can substantially impact patients' quality of life, adherence to therapy and, consequently, success of treatment. In the last few years, several groups have demonstrated that

approximately 50% of chronic phase CML patients (CP-CML) who have achieved a stable deep molecular response (DMR) can stop therapy without suffering molecular relapse. Nowadays, treatment-free remission (TFR) has a significant role in the management of CML and should be considered in selected motivated patients that fulfill well-defined requirements to maximize the probability of successful discontinuation of TKI therapy.

**59. Delayed surgery for localised and metastatic renal cell carcinoma: a systematic review and meta-analysis for the COVID-19 pandemic.**

*Chan, VW, Tan, WS, Leow, JJ, Tan, WP, Ong, WLK, Chiu, PK, Gurung, P, Pirola, GM, Orecchia, L, Liew, MPC, Lee, HY, Wang, Y, Chen, IA, Castellani, D, Wroclawski, ML, Mayor, N, Sathianathan, NJ, Braga, J, Liu, Z, Moon, D, Tikkinen, K, Kamat, A, Meng, M, Ficarra, V, Giannarini, G and Teoh, JY. World J Urol. 2021;39(12):4295-303 [IF: 4.226]*

**PURPOSE:** The COVID-19 pandemic has led to the cancellation or deferment of many elective cancer surgeries. We performed a systematic review on the oncological effects of delayed surgery for patients with localised or metastatic renal cell carcinoma (RCC) in the targeted therapy (TT) era. **METHOD:** The protocol of this review is registered on PROSPERO(CRD4202190882). A comprehensive literature search was performed on Medline, Embase and Cochrane CENTRAL using MeSH terms and keywords for randomised controlled trials and observational studies on the topic. Risks of biases were assessed using the Cochrane RoB tool and the Newcastle-Ottawa Scale. For localised RCC, immediate surgery [including partial nephrectomy (PN) and radical nephrectomy (RN)] and delayed surgery [including active surveillance (AS) and delayed intervention (DI)] were compared. For metastatic RCC, upfront versus deferred cytoreductive nephrectomy (CN) were compared. **RESULTS:** Eleven studies were included for quantitative analysis. Delayed surgery was significantly associated with worse cancer-specific survival (HR 1.67, 95% CI 1.23-2.27,  $p < 0.01$ ) in T1a RCC, but no significant difference was noted for overall survival. For localised  $\geq$  T1b RCC, there were insufficient data for meta-analysis and the results from the individual reports were contradictory. For metastatic RCC, upfront TT followed by deferred CN was associated with better overall survival when compared to upfront CN followed by deferred TT (HR 0.61, 95% CI 0.43-0.86,  $p < 0.001$ ). **CONCLUSION:** Noting potential selection bias, there is insufficient evidence to support the notion that delayed surgery is safe in localised RCC. For metastatic RCC, upfront TT followed by deferred CN should be considered.

**60. Re: Lucia Nappi, Marisa Thi, Nabil Adra, et al. Integrated Expression of Circulating miR375 and miR371 to Identify Teratoma and Active Germ Cell Malignancy Components in Malignant Germ Cell Tumors. Eur Urol 2021;79:16-9.**

*Christiansen, A, Lobo, J and Fankhauser, CD. Eur Urol. 2021;80(1):e35-e6 [IF: 20.096]*

**61. Lower-Limb Lymphedema after Sentinel Lymph Node Biopsy in Cervical Cancer Patients.**

*Cibula, D, Borcinova, M, Marnitz, S, Jarkovsky, J, Klat, J, Pilka, R, Torne, A, Zapardiel, I, Petiz, A, Lay, L, Sehnal, B, Ponce, J, Felsinger, M, Arencibia-Sanchez, O, Kascak, P, Zalewski, K, Presl, J, Palop-Moscardo, A, Tingulstad, S, Vergote, I, Redecha, M, Fruhauf, F, Kohler, C and Kocian, R. Cancers (Basel). 2021;13(10) [IF: 6.639]*

**BACKGROUND:** To prospectively assess LLL incidence among cervical cancer patients treated by uterine surgery complemented by SLN biopsy, without PLND. **METHODS:** A prospective study in 150 patients with stage IA1-IB2 cervical cancer treated by uterine surgery with bilateral SLN biopsy. Objective LLL assessments, based on limb volume increase (LVI) between pre- and postoperative measurements, and subjective patient-perceived swelling were conducted in six-month periods over 24-months post-surgery. **RESULTS:** The cumulative incidence of LLL at 24 months was 17.3% for mild LLL (LVI 10-19%), 9.2% for moderate LLL (LVI 20-39%), while only one patient (0.7%) developed severe LLL (LVI  $>$  40%). The median interval to LLL onset was nine months. Transient edema resolving without intervention within six months was reported in an additional 22% of patients. Subjective LLL was reported by 10.7% of patients, though only a weak and partial correlation between subjective-report and objective-LVI was found. No risk factor directly related to LLL development was identified. **CONCLUSIONS:** The replacement of standard PLND by bilateral SLN biopsy in the surgical treatment of cervical cancer does not eliminate the risk of mild to

moderate LLL, which develops irrespective of the number of SLN removed.

#### 62. Exploring the roles of HPV16 variants in head and neck squamous cell carcinoma: current challenges and opportunities.

*Cochicho, D, Gil da Costa, R and Felix, A. Virol J. 2021;18(1):217 [IF: 4.099]*

The incidence of squamous cell carcinomas of the head and neck (HNSCC) is consistently increasing, in association with human papillomavirus (HPV) infection, especially HPV16. HPV variants show heterogeneity in the pathogenicity of cervical cancer, but little has been established about their relevance on HNSCC. This review addresses the distribution of HPV16 variants in HNSCC and their potential contribution to clinical practice. A search was performed in PubMed using the keywords HNSCC HPV16 variants. Sixty articles were identified between 2000 and 2020 and 9 articles were selected for a systematic analysis. Clinical cohorts comprised 4 to 253 patients aged between 17 and 91 years with confirmed HPV16-positive HNSCC. Samples were collected from fresh biopsies of the tumour, oral rinse or formal fixed/paraffin embedded tissue, from the oral cavity, oropharynx, hypopharynx, larynx and Waldeyer's tonsillar ring. HPV16 variants were identified using Sanger sequencing techniques. Seven studies addressed the HPV16 E6 gene, one studied E6 and E7, another studied L1 and one focused on the long control region. European variants represent 25-95%, Asian-American 5-57% and African 2-4% of the total isolates, suggesting a marked predominance of European strains. No correlations could be drawn with patient prognosis, partly because many studies relied on small patient cohorts. Additional studies are needed, particularly those employing next generation sequencing techniques (NGS), which will allow faster and accurate analysis of large numbers of samples.

#### 63. The Upper Digestive Tract Microbiome and Oesophageal Squamous Cell Carcinoma: Epidemiology, Pathogenesis, and Clinical Implications in Africa.

*Come, J, Pereira, JB, Pinto, R, Carrilho, C, Pereira, L and Lara Santos, L. Pathobiology. 2021;88(2):141-55 [IF: 4.342]*

The study of the microbiome has significantly contributed to our understanding of complex diseases including cancer, with a profound influence of the microbiota on clinical prognosis and the efficacy of cancer treatments. Oesophageal cancer is positioned amongst the most aggressive malignant diseases, resulting from a complex interaction between anthropometric, genetic, immune response, and environmental factors. Oesophageal squamous cell carcinoma (OSCC) is the most common type of oesophageal cancer and is a serious burden in Eastern Africa, in the area known as the African oesophageal cancer corridor (AOCC). OSCC is often diagnosed at a late stage, with patients already suffering from severe malnutrition and dehydration due to swallowing difficulties, leading to high mortality rates. So far, aetiological factors have been individually analysed with an inappropriate contextualisation. The upper digestive tract microbiome has been proposed to contribute to the onset and progression of OSCC but with limited understanding of the mechanisms behind this interaction. Data on African populations are limited, and the aetiology of AOCC is still poorly understood. This review discusses the current knowledge of the aetiology of OSCC in Africa, with special focus on the probable influence of the upper digestive tract microbiota.

#### 64. Trans-ancestry genome-wide association meta-analysis of prostate cancer identifies new susceptibility loci and informs genetic risk prediction.

*Conti, DV, Darst, BF, Moss, LC, Saunders, EJ, Sheng, X, Chou, A, Schumacher, FR, Olama, AAA, Benlloch, S, Dadaev, T, Brook, MN, Sahimi, A, Hoffmann, TJ, Takahashi, A, Matsuda, K, Momozawa, Y, Fujita, M, Muir, K, Lophatananon, A, Wan, P, Le Marchand, L, Wilkens, LR, Stevens, VL, Gapstur, SM, Carter, BD, Schleutker, J, Tammela, TLJ, Sipeky, C, Auvinen, A, Giles, GG, Southey, MC, MacInnis, RJ, Cybulski, C, Wokolorczyk, D, Lubinski, J, Neal, DE, Donovan, JL, Hamdy, FC, Martin, RM, Nordestgaard, BG, Nielsen, SF, Weischer, M, Bojesen, SE, Roder, MA, Iversen, P, Batra, J, Chambers, S, Moya, L, Horvath, L, Clements, JA, Tilley, W, Risbridger, GP, Gronberg, H, Aly, M, Szulkin, R, Eklund, M, Nordstrom, T, Pashayan, N, Dunning, AM, Ghousaini, M, Travis, RC, Key, TJ, Riboli, E, Park, JY, Sellers, TA, Lin, HY, Albanes, D, Weinstein, SJ, Mucci, LA, Giovannucci, E, Lindstrom, S, Kraft, P, Hunter, DJ, Penney, KL, Turman, C, Tangen, CM, Goodman, PJ, Thompson, IM, Jr., Hamilton, RJ, Fleshner, NE, Finelli, A, Parent, ME, Stanford, JL, Ostrander, EA, Geybels, MS, Koutros, S, Freeman, LEB, Stampfer, M, Wolk, A, Hakansson, N, Andriole, GL, Hoover, RN, Machiela, MJ,*

Sorensen, KD, Borre, M, Blot, WJ, Zheng, W, Yeboah, ED, Mensah, JE, Lu, YJ, Zhang, HW, Feng, N, Mao, X, Wu, Y, Zhao, SC, Sun, Z, Thibodeau, SN, McDonnell, SK, Schaid, DJ, West, CML, Burnet, N, Barnett, G, Maier, C, Schnoeller, T, Luedeke, M, Kibel, AS, Drake, BF, Cussenot, O, Cancel-Tassin, G, Menegaux, F, Truong, T, Koudou, YA, John, EM, Grindedal, EM, Maehle, L, Khaw, KT, Ingles, SA, Stern, MC, Vega, A, Gomez-Caamano, A, Fachal, L, Rosenstein, BS, Kerns, SL, Ostrer, H, Teixeira, MR, Paulo, P, Brandao, A, Watya, S, Lubwama, A, Bensen, JT, Fontham, ETH, Mohler, J, Taylor, JA, Kogevinas, M, Llorca, J, Castano-Vinyals, G, Cannon-Albright, L, Teerlink, CC, Huff, CD, Strom, SS, Multigner, L, Blanchet, P, Brureau, L, Kaneva, R, Slavov, C, Mitev, V, Leach, RJ, Weaver, B, Brenner, H, Cuk, K, Holleczeck, B, Saum, KU, Klein, EA, Hsing, AW, Kittles, RA, Murphy, AB, Logothetis, CJ, Kim, J, Neuhausen, SL, Steele, L, Ding, YC, Isaacs, WB, Nemesure, B, Hennis, AJM, Carpten, J, Pandha, H, Michael, A, De Ruyck, K, De Meerleer, G, Ost, P, Xu, J, Razack, A, Lim, J, Teo, SH, Newcomb, LF, Lin, DW, Fowke, JH, Neslund-Dudas, C, Rybicki, BA, Gamulin, M, Lessel, D, Kulis, T, Usmani, N, Singhal, S, Parliament, M, Claessens, F, Joniau, S, Van den Broeck, T, Gago-Dominguez, M, Castelao, JE, Martinez, ME, Larkin, S, Townsend, PA, Aukim-Hastie, C, Bush, WS, Aldrich, MC, Crawford, DC, Srivastava, S, Cullen, JC, Petrovics, G, Casey, G, Roobol, MJ, Jenster, G, van Schaik, RHN, Hu, JJ, Sanderson, M, Varma, R, McKean-Cowdin, R, Torres, M, Mancuso, N, Berndt, SI, Van Den Eeden, SK, Easton, DF, Chanock, SJ, Cook, MB, Wiklund, F, Nakagawa, H, Witte, JS, Eeles, RA, Kote-Jarai, Z and Haiman, CA. *Nat Genet.* 2021;53(1):65-75 [IF: 38.330]

Prostate cancer is a highly heritable disease with large disparities in incidence rates across ancestry populations. We conducted a multi-ancestry meta-analysis of prostate cancer genome-wide association studies (107,247 cases and 127,006 controls) and identified 86 new genetic risk variants independently associated with prostate cancer risk, bringing the total to 269 known risk variants. The top genetic risk score (GRS) decile was associated with odds ratios that ranged from 5.06 (95% confidence interval (CI), 4.84-5.29) for men of European ancestry to 3.74 (95% CI, 3.36-4.17) for men of African ancestry. Men of African ancestry were estimated to have a mean GRS that was 2.18-times higher (95% CI, 2.14-2.22), and men of East Asian ancestry 0.73-times lower (95% CI, 0.71-0.76), than men of European ancestry. These findings support the role of germline variation contributing to population differences in prostate cancer risk, with the GRS offering an approach for personalized risk prediction.

#### 65. Innate-like NKp30(+)/CD8(+) T cells armed with TCR/CAR target tumor heterogeneity.

Correia, MP, Stojanovic, A, Wels, WS and Cerwenka, A. *Oncoimmunology.* 2021;10(1):1973783 [IF: 8.110]

Intratumoral heterogeneity is frequently associated with tumor immune escape, with MHC-class I and antigen expression loss rendering tumor cells invisible to T cell killing, representing a major challenge for the design of successful adoptive transfer protocols for cancer immunotherapy. While CD8(+) T cell recognition of tumor cells is based on the detection of MHC-peptide complexes via specific T cell receptors (TCRs), Natural Killer (NK) cells detect tumor-associated NK ligands by an array of NK receptors. We have recently identified a population of innate-like CD8(+) T cells marked by the expression of NKp30, a potent natural cytotoxicity activating NK receptor, whose tumor ligand, B7H6, is frequently upregulated on several cancer types. Here, we harnessed the dual-recognition potential of NKp30(+)/CD8(+) T cells, by arming these cells with TCRs or chimeric antigen receptors (CARs) targeting Epidermal Growth Factor Receptor 2 (ErbB2, or HER2), a tumor-associated target overexpressed in several malignancies. HER2-specific NKp30(+)/CD8(+) T cells killed not only HER2-expressing target cell lines, but also eliminated tumor cells in the absence of MHC-class I or antigen expression, making them especially effective in eliminating heterogeneous tumor cell populations. Our results show that NKp30(+)/CD8(+) T cells equipped with a specific TCR or CAR display a dual capacity to recognize and kill target cells, combining the anti-tumor activity of both CD8(+) T and NK cells. This dual-recognition capacity allows these effector cells to target tumor heterogeneity, thus improving therapeutic strategies against tumor escape.

#### 66. Impact of immune cells on the hallmarks of cancer: A literature review.

Costa, AC, Santos, JMO, Gil da Costa, RM and Medeiros, R. *Crit Rev Oncol Hematol.* 2021;168:103541 [IF: 6.312]

Tumor-infiltrating immune cells (TIICs) are critical players in the tumor microenvironment, modulating cancer cell functions. TIICs are highly heterogenic and plastic and may either suppress cancers or provide support for tumor growth. A wide range of studies have shed light on how tumor-associated macrophages,

dendritic cells, neutrophils, mast cells, natural killer cells and lymphocytes contribute for the establishment of several hallmarks of cancer and became the basis for successful immunotherapies. Many of those TIICs play pivotal roles in several hallmarks of cancer. This review contributes to elucidate the multifaceted roles of immune cells in cancer development, highlighting molecular components that constitute promising therapeutic targets. Additional studies are needed to clarify the relation between TIICs and hallmarks such as enabling replicative immortality, evading growth suppressors, sustaining proliferative signaling, resisting cell death and genome instability and mutation, to further explore their therapeutic potential and improve the outcomes of cancer patients.

#### **67. Characterization of Oral Enterobacteriaceae Prevalence and Resistance Profile in Chronic Kidney Disease Patients Undergoing Peritoneal Dialysis.**

*Costa, C, Merino-Ribas, A, Ferreira, C, Campos, C, Silva, N, Pereira, L, Garcia, A, Azevedo, A, Mesquita, RBR, Rangel, A, Manaia, CM and Sampaio-Maia, B. Front Microbiol. 2021;12:736685 [IF: 5.640]*

Chronic Kidney Disease (CKD) is a growing public-health concern worldwide. Patients exhibit compromised immunity and are more prone to infection than other populations. Therefore, oral colonization by clinically relevant members of the Enterobacteriaceae family, major agents of both nosocomial and dialysis-associated infections with frequent prevalence of antibiotic resistances, may constitute a serious risk. Thus, this study aimed to assess the occurrence of clinically relevant enterobacteria and their antibiotic resistance profiles in the oral cavity of CKD patients undergoing peritoneal dialysis (CKD-PD) and compare it to healthy controls. Saliva samples from all the participants were cultured on MacConkey Agar and evaluated regarding the levels of urea, ammonia, and pH. Bacterial isolates were identified and characterized for antibiotic resistance phenotype and genotype. The results showed that CKD-PD patients exhibited significantly higher salivary pH, urea, and ammonia levels than controls, that was accompanied by higher prevalence and diversity of oral enterobacteria. Out of all the species isolated, only the prevalence of *Raoultella ornithinolytica* varied significantly between groups, colonizing the oral cavity of approximately 30% of CKD-PD patients while absent from controls. Antibiotic resistance phenotyping revealed mostly putative intrinsic resistance phenotypes (to amoxicillin, ticarcillin, and cephalothin), and resistance to sulfamethoxazole (~43% of isolates) and streptomycin (~17%). However, all isolates were resistant to at least one of the antibiotics tested and multidrug resistance isolates were only found in CKD-PD group (31,6%). Mobile genetic elements and resistance genes were detected in isolates of the species *Raoultella ornithinolytica*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Escherichia coli*, and *Enterobacter asburiae*, mostly originated from CKD-PD patients. PD-related infection history revealed that Enterobacteriaceae were responsible for ~8% of peritonitis and ~16% of exit-site infections episodes in CKD-PD patients, although no association was found to oral enterobacteria colonization at the time of sampling. The results suggest that the CKD-induced alterations of the oral milieu might promote a dysbiosis of the commensal oral microbiome, namely the proliferation of clinically relevant Enterobacteriaceae potentially harboring acquired antibiotic resistance genes. This study highlights the importance of the oral cavity as a reservoir for pathobionts and antibiotic resistances in CKD patients undergoing peritoneal dialysis.

#### **68. Aggressive Neuroblastoma in a Pediatric Patient with Severe Hemophilia A.**

*Costa, L, Couto, ME, Moutinho, J, Ferreira, AM, Costa, E, Roncon, S, Santos, LL, Cruz, E and Morais, S. Pediatr Rep. 2021;13(1):125-30 [IF: NA]*

Despite the extensive information regarding hemophilia's hemorrhagic complications, the literature on cancer in hemophilia is scarce, especially in pediatric patients. Many uncertainties remain concerning diagnosis and workup. We report a rare case of two severe diseases (neuroblastoma and hemophilia A (HA)) concomitantly present in the same pediatric patient. We highlight that the diagnosis of severe HA did not have a negative impact on the patient's oncologic course. This case also illustrates the significance of the cooperation among different specialties and hospitals when caring for the same patient.

#### **69. Retroperitoneal Ewing Sarcoma: a challenging diagnosis.**

*Costa, PC, C. Radiología. 2021 [IF: NA]*

#### **70. Target Score-A Proteomics Data Selection Tool Applied to Esophageal Cancer Identifies GLUT1-Sialyl**

**Tn Glycoforms as Biomarkers of Cancer Aggressiveness.**

*Cotton, S, Ferreira, D, Soares, J, Peixoto, A, Relvas-Santos, M, Azevedo, R, Piairo, P, Dieguez, L, Palmeira, C, Lima, L, Silva, AMN, Lara Santos, L and Ferreira, JA. Int J Mol Sci. 2021;22(4) [IF: 5.923]*

Esophageal cancer (EC) is a life-threatening disease, demanding the discovery of new biomarkers and molecular targets for precision oncology. Aberrantly glycosylated proteins hold tremendous potential towards this objective. In the current study, a series of esophageal squamous cell carcinomas (ESCC) and EC-derived circulating tumor cells (CTCs) were screened by immunoassays for the sialyl-Tn (STn) antigen, a glycan rarely expressed in healthy tissues and widely observed in aggressive gastrointestinal cancers. An ESCC cell model was glycoengineered to express STn and characterized in relation to cell proliferation and invasion in vitro. STn was found to be widely present in ESCC (70% of tumors) and in CTCs in 20% of patients, being associated with general recurrence and reduced survival. Furthermore, STn expression in ESCC cells increased invasion in vitro, while reducing cancer cells proliferation. In parallel, an ESCC mass spectrometry-based proteomics dataset, obtained from the PRIDE database, was comprehensively interrogated for abnormally glycosylated proteins. Data integration with the Target Score, an algorithm developed in-house, pinpointed the glucose transporter type 1 (GLUT1) as a biomarker of poor prognosis. GLUT1-STn glycoproteoforms were latter identified in tumor tissues in patients facing worst prognosis. Furthermore, healthy human tissues analysis suggested that STn glycosylation provided cancer specificity to GLUT1. In conclusion, STn is a biomarker of worst prognosis in EC and GLUT1-STn glycoforms may be used to increase its specificity on the stratification and targeting of aggressive ESCC forms.

**71. Palliative care in onco-hematology: a perspective.**

*Couto, ME and Ferraz-Goncalves, J. Support Care Cancer. 2021;29(5):2251-3 [IF: 3.603]*

Palliative care (PC) is focused on individualized symptomatic control, psychological help, and support in the context of severe disease. Oncologic patients are still the most referred to PC and hematologic patients are only 7%. This is a commentary about PC applied to hematologic patients. There is evidence supporting that these patients behave as a special group in PC when compared with other tumors: there is a smaller number of referrals, with more advanced disease status, more symptomatology expressed, and less time between the last treatment date and the referral date or death. This article also expresses the experience of an oncologic palliative care unit. More health education programs in PC are needed for specialized professionals in hematology, as well as a change of nowadays health politics, in order to increase the participation of this specialized care in hematology.

**72. Gastric Diffuse Large B-Cell Lymphoma: A Single-Center 9-Year Experience.**

*Couto, ME, Oliveira, I, Domingues, N, Viterbo, L, Martins, A, Moreira, I, Espirito-Santo, A, Chacim, S, Moreira, C, Pereira, D, Henrique, R and Mariz, J. Indian J Hematol Blood Transfus. 2021:1-5 [IF: 0.900]*

Gastric diffuse large B cell lymphoma (DLBCL) represents the majority of all gastric lymphomas. We report a series of gastric DLBCL diagnosed and treated in a single center, between 2010 and 2018 (included). We retrospectively analyzed the population demographic features, treatment outcomes and survival. One-hundred-and-one patients were studied, 50.5% males and median age of 64 years [23-94]. Lugano staging was I in 16.8%, II1 in 20.8%, II2 in 10.9%, IIE in 13.9% and IV in 34.7% of cases. Twenty percent had *Helicobacter pylori* infection. R-CHOP-like therapy was used as first line in 96.9% of the patients. A complete response was achieved in 80% after first line therapy. At 3-years of follow-up (FU), 54% were in complete remission. The mean FU time was 73.6 months. Median overall survival and median progression free survival were not reached. We identified seven factors with negative impact in survival: age above 65 years-old ( $p < 0.01$ ), ECOG 2-3 ( $p < 0.01$ ), B symptoms ( $p = 0.001$ ), bulky disease ( $p = 0.003$ ), IPI 3-4 ( $p = 0.001$ ), more than 3 treatment lines ( $p < 0.01$ ), absence of response to first line treatment ( $p < 0.01$ ). This study demonstrates that gastric DLBCL is a potentially curable disease with R-CHOP-like therapy, entailing long term survival and comparing well with other published series.

**73. IgA nephropathy in IgG kappa multiple myeloma.**

*Couto, ME, Sousa, D, Ferreira, H, Tavares, A, Oliveira, I, Domingues, N, Paiva, A, Chuva, T, Maximino, J, Henrique, RMF and Mariz, JM. Porto Biomed J. 2021;6(5):e142 [IF: NA]*

Multiple myeloma (MM) frequently affects kidney function through multiple mechanisms. Nonetheless,

some patients develop kidney injury due to other causes. A 54-year-old woman was diagnosed with IgG kappa MM developed IgA nephropathy without cast nephropathy. Further studies did not show criteria for MM progression or other causes. This case highlights the need for further investigation of kidney injury in MM patients (such as toxicity of previous drugs, infectious events, or immune-mediated disorders).

#### **74. Is There a Role for Sex Hormone Receptors in Head-and-neck Cancer? Links with HPV Infection and Prognosis.**

*CP, DEON, Brito, HO, RMG, DAC and Brito, LMO. Anticancer Res. 2021;41(8):3707-16 [IF: 2.480]*

**BACKGROUND/AIM:** Head-and-neck squamous cell carcinoma (HNSCC) is the fifth most common cancer in the world and human papillomavirus (HPV) is an important risk factor for this neoplasm. Recent studies showed an association between sex hormone receptors and pathogenesis and/or prognosis in patients with HNSCC. The aim of this study was to clarify the expression patterns of sex hormone receptors in HPV-positive and HPV-negative HNSCC and their associations with tumour biopathology and biological behaviour. **MATERIALS AND METHODS:** Scientific literature indexed in PubMed about sex hormone receptors in HNSCC was retrieved and critically analyzed, to obtain an overview of expression patterns and their possible implications for tumour biopathology and prognosis. **RESULTS:** Sex hormone receptors were more frequently detected in oropharyngeal tumours compared with HNSCC from other locations. ERalpha was associated with HPV-positive tumours. The androgen and progesterone receptors were associated with poor patient prognosis. Estrogen receptor alpha (ERalpha) is implicated in the biopathology of HNSCC in different ways, by promoting DNA hypermutation and facilitating HPV integration thus contributing to an immunogenic phenotype, but also by cooperating with the epithelial growth factor receptor (EGFR) to promote resistance to therapy. **CONCLUSION:** The expression of sex hormone receptors may be of prognostic value in specific tumour subgroups, but the use of hormonal therapies for HNSCC is still not in close sight.

#### **75. Pancoast Tumor as the Initial Presentation of a Metastatic Colon Adenocarcinoma.**

*Cunha, A, Quintela, M, Costa, C, Quispe-Cornejo, AA and Freitas-Silva, M. Cureus. 2021;13(2):e13371 [IF: NA]*

A Pancoast tumor is a rare condition, representing 3% to 5% of all lung cancers. The particular location of these lesions leads to the invasion of structures in the thoracic inlet, causing a constellation of symptoms known as Pancoast-Tobias syndrome. Diagnosis can be challenging due to their low prevalence and the possibility of being asymptomatic. Most of these tumors are non-small cell lung cancers. However, rare conditions might arise at the same location, and histologic confirmation is relevant. We report the case of a 45-year-old man admitted to the internal medicine department with a one-month history of night sweats. A full-body computed tomography (CT) scan revealed a mass on the upper lobe of the left lung, with soft tissue invasion. Histopathologic examination revealed an adenocarcinoma pattern originating from the colon. Colonoscopy showed two synchronous lesions. Hitherto, this is the second case ever described of a Pancoast tumor as metastasis of colon adenocarcinoma.

#### **76. Control Strategies for Carcinogenic-Associated Helminthiases: An Integrated Overview.**

*da Costa, JMC, Gouveia, MJ, Rinaldi, G, Brindley, PJ, Santos, J and Santos, LL. Front Cell Infect Microbiol. 2021;11:626672 [IF: 5.293]*

Helminthiases are extremely prevalent in the developing world. In addition, the chronic infection with some parasitic worms are classified as carcinogenic. Therefore, it is utmost importance to understand the parasite-host interactions, the mechanisms underlay carcinogenesis and how they could be counteracted. This knowledge may ultimately guide novel control strategies that include chemotherapy-based approaches targeting these pathogens and associated pathologies caused by their infections. Little is known on how some helminthiases are associated with cancer; however, it has been hypothesized that chemical carcinogenesis may be involved in the process. Here, we summarize the current knowledge on chemical carcinogenesis associated with helminthiases, along with available therapeutic options and potential therapeutic alternatives including chemotherapy and/or immunotherapy. Ideally, the treatment of the carcinogenic helminthiases should target both the parasite and associated pathologies. The success of any chemotherapeutic regimen often depends on the host immune response during the infection and

nutritional status among other factors. The close association between chemotherapy and cell-mediated immunity suggests that a dual therapeutic approach would be advantageous. In addition, there is a pressing need for complementary drugs that antagonize the carcinogenesis process associated with the helminth infections.

**77. Meta-analyses of machine learning in endoscopy: stacking apples and oranges.**

*de Groof, J, Antonelli, G, Dinis-Ribeiro, MJ and Bergman, JJ. *Gastrointest Endosc.* 2021;93(5):1016-8 [IF: 9.427]*

**78. Differential Incidence of Tongue Base Cancer in Male and Female HPV16-Transgenic Mice: Role of Female Sex Hormone Receptors.**

*de Oliveira Neto, CP, Medeiros-Fonseca, B, Estevao, D, Mestre, VF, Costa, NR, de Andrade, FE, Oliveira, PA, Bastos, M, Medeiros, R, Assis, D, Felix, A, Ferreira Lopes, F, Gil da Costa, RM, Brito, HO and Brito, LMO. *Pathogens.* 2021;10(10) [IF: 3.492]*

A growing proportion of oropharyngeal squamous cell carcinomas (OPSCC) are associated with infection by high-risk human papillomavirus (HPV). For reasons that remain largely unknown, HPV+OPSCC is significantly more common in men than in women. This study aims to determine the incidence of OPSCC in male and female HPV16-transgenic mice and to explore the role of female sex hormone receptors in the sexual predisposition for HPV+ OPSCC. The tongues of 30-weeks-old HPV16-transgenic male (n = 80) and female (n = 90) and matched wild-type male (n = 10) and female (n = 10) FVB/n mice were screened histologically for intraepithelial and invasive lesions in 2017 at the Centre for the Research and Technology of Agro-Environmental and Biological Sciences (CITAB), Portugal. Expression of estrogen receptors alpha (ERalpha) and beta (ERbeta), progesterone receptors (PR) and matrix metalloproteinase 2 (MMP2) was studied immunohistochemically. Collagen remodeling was studied using picrosirius red. Female mice showed robust ERalpha and ERbeta expression in intraepithelial and invasive lesions, which was accompanied by strong MMP2 expression and marked collagen remodeling. Male mice showed minimal ERalpha, ERbeta and MMP2 expression and unaltered collagen patterns. These results confirm the association of HPV16 with tongue base cancer in both sexes. The higher cancer incidence in female versus male mice contrasts with data from OPSCC patients and is associated with enhanced ER expression via MMP2 upregulation.

**79. Self-Care in Heart Failure Inpatients: What Is the Role of Gender and Pathophysiological Characteristics? A Cross-Sectional Multicentre Study.**

*Delgado, B, Lopes, I, Mendes, T, Lopes, P, Sousa, L, López-Espuela, F, Preto, L, Mendes, E, Gomes, B and Novo, A. *Healthcare.* 2021;9(4):434 [IF: 2.645]*

Heart failure is often characterised by low exercise capacity and a great impairment of performance in the activities of daily living. The correct management of the disease can prevent the worsening of symptoms and promote a better quality of life. The aims of this study are to understand the relationship of gender and pathophysiological characteristics with self-care behaviour and to evaluate the self-care behaviour in a sample of Portuguese heart failure inpatients, using the Self-Care of Heart Failure Index (SCHFI). A cross-sectional multicentre study enrolling 225 heart failure inpatients from eight hospitals from Portugal was performed. At admission, each patient's functional capacity was evaluated as well as their self-care behaviour, using the SCHFI Portuguese v6.2. A comparison between self-care behaviour with gender was performed. The patients' mean age was 68.4 ± 10.7 years old, 68% were male and 82.3% had reduced ejection fraction. A mean value of 47.9, 35.6 and 38.8 points was found in the SCHFI score of the sections self-care maintenance, self-care management and self-care confidence, respectively. Heart failure inpatients present inadequate levels of self-care behaviour. The results do not suggest a relationship between gender and pathophysiological characteristics with self-care behaviour.

**80. Phase III randomized study of tasisib or placebo with fulvestrant in estrogen receptor-positive, PIK3CA-mutant, HER2-negative, advanced breast cancer: the SANDPIPER trial.**

*Dent, S, Cortes, J, Im, YH, Dieras, V, Harbeck, N, Krop, IE, Wilson, TR, Cui, N, Schimmoller, F, Hsu, JY, He, J, De Laurentiis, M, Sousa, S, Drullinsky, P and Jacot, W. *Ann Oncol.* 2021;32(2):197-207 [IF: 32.976]*

BACKGROUND: The phase III SANDPIPER study assessed tasisib (GDC-0032), a potent, selective PI3K

inhibitor, plus fulvestrant in estrogen receptor-positive, HER2-negative, PIK3CA-mutant locally advanced or metastatic breast cancer. PATIENTS AND METHODS: Postmenopausal women with disease recurrence/progression during/after an aromatase inhibitor were randomized 2 : 1 to receive tasisib (4 mg; tasisib arm) or placebo (placebo arm) plus fulvestrant (500 mg). Stratification factors were visceral disease, endocrine sensitivity, and geographic region. Patients with PIK3CA-mutant tumors (central cobas(R) PIK3CA Mutation Test) were randomized separately from those without detectable mutations. The primary endpoint was investigator-assessed progression-free survival (INV-PFS) in patients with PIK3CA-mutant tumors. Secondary endpoints included objective response rate, overall survival, clinical benefit rate, duration of objective response, PFS by blinded independent central review (BICR-PFS), safety, and time to deterioration in health-related quality of life. RESULTS: The PIK3CA-mutant intention-to-treat population comprised 516 patients (placebo arm: n = 176; tasisib arm: n = 340). INV-PFS was significantly improved in the tasisib {7.4 months [95% confidence interval (CI), 7.26-9.07]} versus placebo arm (5.4 months [95% CI, 3.68-7.29]) (stratified hazard ratio [HR] 0.70; 95% CI, 0.56-0.89; P = 0.0037) and confirmed by BICR-PFS (HR 0.66). Secondary endpoints, including objective response rate, clinical benefit rate, and duration of objective response, showed consistent improvements in the tasisib arm. Safety was assessed in all randomized patients who received at least one dose of tasisib/placebo or fulvestrant regardless of PIK3CA-mutation status (n = 629). Serious adverse events were lower in the placebo versus tasisib arm (8.9% versus 32.0%). There were more discontinuations (placebo arm: 2.3%; tasisib arm: 16.8%) and dose reductions (placebo arm: 2.3%; tasisib arm: 36.5%) in the tasisib arm. CONCLUSION: SANDPIPER met its primary endpoint; however, the combination of tasisib plus fulvestrant has no clinical utility given its safety profile and modest clinical benefit.

#### **81. Narrow band imaging for detection of gastric intestinal metaplasia and dysplasia: A systematic review and meta-analysis.**

*Desai, M, Boregowda, U, Srinivasan, S, Kohli, DR, Al Awadhi, S, Murino, A, Yu, LHK, Dinis-Ribeiro, DM and Sharma, P. J Gastroenterol Hepatol. 2021;36(8):2038-46 [IF: 4.029]*

BACKGROUND AND AIMS: Gastric intestinal metaplasia (GIM), a precursor of gastric adenocarcinoma, is challenging to diagnose with white light endoscopy (WLE) and can be missed by random gastric biopsies. Narrowband imaging (NBI) may potentially improve the detection of GIM. However, pooled estimates from prospective studies are lacking. METHODS: Electronic databases were searched for studies comparing NBI and WLE alone for detection of GIM and synchronous dysplasia. Primary outcome was pooled detection rate of GIM by NBI compared with WLE in prospective studies. The secondary outcome was concurrent dysplasia detection. RESULTS: Ten studies were found eligible from 306 articles screened. Eight prospective studies were found eligible for primary endpoint of GIM detection. Two other retrospective studies were included for dysplasia detection. A total of 1366 subjects (694 males, 54.4 +/- 5.08 years) underwent upper endoscopy. GIM was detected in 482 (35.3%) subjects. NBI detected GIM in 32% additional subjects (70% vs 38%, RR 1.79; 95% CI 1.34-2.37; P < 0.01). Subgroup analysis revealed newer NBI scopes (GIF260) detected significantly more GIM than WLE (RR 2.47; 95% CI 1.63-3.76; P < 0.01) but not the older (H180) NBI endoscopes (RR 1.33; 95% CI 0.93-1.88; P = 0.11). There was moderate heterogeneity between the studies (I(2) = 63%). In five studies (n = 628) that reported dysplasia, there was no significant difference between NBI and WLE in dysplasia detection (RR 1.09; 95% CI 0.81-1.47; P = 0.58). CONCLUSION: Narrowband imaging can significantly increase the detection of GIM when used in addition to standard white light exam during an upper endoscopy.

#### **82. LAT1 and ASCT2 Related microRNAs as Potential New Therapeutic Agents against Colorectal Cancer Progression.**

*Dias, F, Almeida, C, Teixeira, AL, Morais, M and Medeiros, R. Biomedicines. 2021;9(2) [IF: 6.081]*

The development and progression of colorectal cancer (CRC) have been associated with genetic and epigenetic alterations and more recently with changes in cell metabolism. Amino acid transporters are key players in tumor development, and it is described that tumor cells upregulate some AA transporters in order to support the increased amino acid (AA) intake to sustain the tumor additional needs for tumor growth and proliferation through the activation of several signaling pathways. LAT1 and ASCT2 are two AA transporters involved in the regulation of the mTOR pathway that has been reported as upregulated in CRC.

Some attempts have been made in order to develop therapeutic approaches to target these AA transporters, however none have reached the clinical setting so far. MiRNA-based therapies have been gaining increasing attention from pharmaceutical companies and now several miRNA-based drugs are currently in clinical trials with promising results. In this review we combine a bioinformatic approach with a literature review in order to identify a miRNA profile with the potential to target both LAT1 and ASCT2 with potential to be used as a therapeutic approach against CRC.

### 83. Long non-coding RNAs regulate the hallmarks of cancer in HPV-induced malignancies.

*Dias, TR, Santos, JMO, Gil da Costa, RM and Medeiros, R. Crit Rev Oncol Hematol. 2021;161:103310 [IF: 6.312]*

High-risk human papillomavirus (HPV) is the most frequent sexually transmitted agent worldwide and is responsible for approximately 5% of human cancers. Identifying novel biomarkers and therapeutic targets for these malignancies requires a deeper understanding of the mechanisms involved in the progression of HPV-induced cancers. Long non-coding RNAs (lncRNAs) are crucial in the regulation of biological processes. Importantly, these molecules are key players in the progression of multiple malignancies and are able to regulate the development of the different hallmarks of cancer. This review highlights the action of lncRNAs in the regulation of cellular processes leading to the typical hallmarks of cancer. The regulation of lncRNAs by HPV oncogenes, their targets and also their mechanisms of action are also discussed, in the context of HPV-induced malignancies. Overall, accumulating data indicates that lncRNAs may have a significant potential to become useful tools for clinical practice as disease biomarkers or therapy targets.

### 84. Diabetes: a silent player in musculoskeletal interventional radiology response.

*Dimitri-Pinheiro, S, Pimenta, M, Cardoso-Marinho, B, Torrao, H, Soares, R and Karantanas, A. Porto Biomed J. 2021;6(1):e112 [IF: NA]*

Diabetes has an important role in the development of several musculoskeletal disorders, such as adhesive capsulitis of the shoulder (ACs) and stenosing flexor tenosynovitis of the finger (SfTf). The etiopathophysiology of ACs and SfTf in diabetic patients is associated with both chronic hyperglycemia, increased amounts of visceral adiposity and chronic inflammation. Chronic hyperglycemia stimulates the creation of cross-links between collagen molecules, impairing degradation and resulting in the build-up of excessive collagen deposits in the cartilage, ligaments, tendon sheaths and tendons. Increased adipocytes in diabetic patients secrete proteins and cytokines such as TNF-alpha, IL-6 and IL-13 which result in overproduction of pro-inflammatory factors, destruction of normal tissue architecture and fibrosis. Both hyperglycemia and adipocytes inhibit efferocytosis, limiting natural resolution. Recently, multiple image-guided interventional radiology musculoskeletal treatment options have been developed, such as ultrasound-guided glenohumeral capsule hydrodistension for ACs and ultrasound-guided percutaneous pulley release for trigger finger. Diabetes can negatively influence outcomes in patients with ACs and SfTf and may impact the decision of which specific procedure technique should be employed. Further studies are necessary to define how diabetes influences response to interventional radiology treatments of these disorders, as well as the extent to which control of blood sugar levels can contribute towards the personalization and optimization of patient follow up.

### 85. Protein Aggregation Patterns Inform about Breast Cancer Response to Antiestrogens and Reveal the RNA Ligase RTCB as Mediator of Acquired Tamoxifen Resistance.

*Direito, I, Monteiro, L, Melo, T, Figueira, D, Lobo, J, Enes, V, Moura, G, Henrique, R, Santos, MAS, Jeronimo, C, Amado, F, Fardilha, M and Helguero, LA. Cancers (Basel). 2021;13(13) [IF: 6.639]*

The protein quality control network, including autophagy, the proteasome and the unfolded protein response (UPR), is triggered by stress and is overactive in acquired antiestrogen therapy resistance. We show for the first time that the aggresome load correlates with apoptosis and is increased in antiestrogen-sensitive cells compared to endocrine-resistant variants. LC-MS/MS analysis of the aggregated proteins obtained after 4OH-tamoxifen and Fulvestrant treatment identified proteins with essential function in protein quality control in antiestrogen-sensitive cells, but not in resistant variants. These include the UPR modulators RTCB and PDIA6, as well as many proteasome proteins such as PSMC2 and PSMD11. RTCB is a tRNA and XBP1 ligase and its aggregation induced by antiestrogens correlated with impaired XBP1s

expression in sensitive cells. Knock down of RTCB was sufficient to restore sensitivity to tamoxifen in endocrine-resistant cells and increased the formation of aggresomes, leading to apoptotic cell death. Analysis of primary human breast cancer samples and their metastases appearing after endocrine treatment showed that RTCB is only localized to aggresomes in the primary tumors, while total aggresomes, including aggregated RTCB, were significantly reduced in the metastases. Therefore, different protein aggregation patterns may indicate loss of function of essential proteins resulting in enhanced protein aggregation that can be used to identify antiestrogen-resistant breast cancer cells and improve the response to antiestrogenic therapy.

**86. Serum amyloid P component is an essential element of resistance against *Aspergillus fumigatus*.**

*Doni, A, Parente, R, Laface, I, Magrini, E, Cunha, C, Colombo, FS, Lacerda, JF, Campos, A, Jr., Mapelli, SN, Petroni, F, Porte, R, Schorn, T, Inforzato, A, Mercier, T, Lagrou, K, Maertens, J, Lambris, JD, Bottazzi, B, Garlanda, C, Botto, M, Carvalho, A and Mantovani, A. Nat Commun. 2021;12(1):3739 [IF: 14.919]*

Serum amyloid P component (SAP, also known as Pentraxin 2; APCS gene) is a component of the humoral arm of innate immunity involved in resistance to bacterial infection and regulation of tissue remodeling. Here we investigate the role of SAP in antifungal resistance. *Apcs*(-/-) mice show enhanced susceptibility to *A. fumigatus* infection. Murine and human SAP bound conidia, activate the complement cascade and enhance phagocytosis by neutrophils. *Apcs*(-/-) mice are defective in vivo in terms of recruitment of neutrophils and phagocytosis in the lungs. Opsonic activity of SAP is dependent on the classical pathway of complement activation. In immunosuppressed mice, SAP administration protects hosts against *A. fumigatus* infection and death. In the context of a study of hematopoietic stem-cell transplantation, genetic variation in the human APCS gene is associated with susceptibility to invasive pulmonary aspergillosis. Thus, SAP is a fluid phase pattern recognition molecule essential for resistance against *A. fumigatus*.

**87. The role of ultrasound guided serratus plane block on chronic neuropathic pain after breast surgery in cancer patient.**

*Dos Santos Rodrigues da Silva, MJ, Lousame, AA, Ferreira, MLN, Fernandez Gacio, M and Miranda, MLC. Rev Esp Anesthesiol Reanim (Engl Ed). 2021;68(6):338-45 [IF: NA]*

BACKGROUND: Breast cancer is the most commonly occurring cancer among women. Among its treatment sequelae is chronic neuropathic pain after breast surgery (CNPBS). Pain management is difficult and classically consists in a pharmacological approach, however recent studies have advocated the use of locoregional techniques as adjuvants. Serratus plane block (SPB) has recently emerged as a potential tool for the control of CNPBS. This study aims to evaluate the efficacy and potential role of the ultrasound-guided SPB on CNPBS. METHODS: A retrospective analysis was performed on 30 patients with CNPBS refractory to drug therapy, who underwent SPB between 2017-2019. The following parameters were analyzed: basal pain, pain at 24 hours, 1 week and at 1 month. The Mann-Whitney test was applied. Statistical significance was considered at the level of  $p < 0.05$ . All statistical analysis was performed with SPSS 20. RESULTS: 3 patients were excluded. At 24 hours, we report pain improvement (at least 30% reduction on basal pain score) on 20 patients and after 1 week on 12. At 1 month after, 22 patients had improved, from these: 11 improved with no therapeutic adjustment; 11 patients improved with therapeutic adjustment (8 in gabapentinoid monotherapy, 3 with introduction of polytherapy). 5 patients didn't improve. CONCLUSION: Our study demonstrated SPB as a valid alternative for CNPBS management when pharmacologic therapy has been proven insufficient, with no side effects reported. Randomized studies are needed to assess the magnitude of SPB on CNPBS and to identify the patients who benefit the most from SPB.

**88. Disseminated *Saprochaete capitata* fungal infection in a patient with acute myeloid leukemia.**

*Duarte, D, Morais, CI, Azevedo, R, Coelho, F, Martins, A, Pereira, B, Coelho, S, Domingues, N, Lebre, A, Trigo, F, Romero, I, Guimaraes, MA, Mariz, JM and Faria, F. Clin Case Rep. 2021;9(4):2489-91 [IF: NA]*

The case highlights the importance of actively obtaining informative samples at an early stage and of prompt initiation of combination therapy with antifungal drugs.

**89. Case Report: Pheochromocytoma and Synchronous Neuroblastoma in a Family With Hereditary**

**Pheochromocytoma Associated With a MAX Deleterious Variant.**

*Duarte, DB, Ferreira, L, Santos, AP, Costa, C, Lima, J, Santos, C, Afonso, M, Teixeira, MR, Carvalho, R and Cardoso, MH. Front Endocrinol (Lausanne). 2021;12:609263 [IF: 5.555]*

Introduction: Pheochromocytomas are rare catecholamine-producing neuroendocrine tumours arising from chromaffin cells of the adrenal medulla or extra-adrenal sympathetic paraganglia. Recent studies have indicated that up to 40% of pheochromocytomas could be attributable to an inherited germline variant in an increasing list of susceptibility genes. Germline variants of the MYC-associated factor (MAX) gene have been associated with familial pheochromocytomas and paragangliomas with an autosomal dominant pattern of inheritance, a median age at onset of 33 years and an overall frequency estimated at 1.9%. We describe a deleterious MAX variant associated with hereditary pheochromocytoma in a family with four affected individuals. Case presentation: The first patient presented with bilateral pheochromocytoma in 1995; genetic testing was proposed to his oldest son, when he was diagnosed with a bilateral pheochromocytoma with a synchronous neuroblastoma. Upon the identification of the MAX variant c.97C>T, p.(Arg33Ter), in the latter individual, his two siblings and their father were tested and the same variant was identified in all of them. Both siblings were subsequently diagnosed with pheochromocytoma (one of them bilateral) and choose to remain on active surveillance before they were submitted to adrenalectomy. All the tumours secreted predominantly norepinephrine, accordingly to the typical biochemical phenotype ascribed to variants in the MAX gene. Conclusion: This case series is, to our knowledge, the one with the largest number of individuals with hereditary pheochromocytoma with a deleterious MAX variant in the same family. It is also the first case with a synchronous pheochromocytoma and neuroblastoma in carriers of a MAX deleterious variant. This report draws attention to some ill-defined features of pheochromocytoma and other malignancies associated with a MAX variant and highlights the importance of understanding the genotype-phenotype correlation in hereditary pheochromocytoma and the impact of oriented genetic testing to detect, survey and treat patients and kindreds at risk.

**90. ST6Gal1 targets the ectodomain of ErbB2 in a site-specific manner and regulates gastric cancer cell sensitivity to trastuzumab.**

*Duarte, HO, Rodrigues, JG, Gomes, C, Hensbergen, PJ, Ederveen, ALH, de Ru, AH, Mereiter, S, Polonia, A, Fernandes, E, Ferreira, JA, van Veelen, PA, Santos, LL, Wuhrer, M, Gomes, J and Reis, CA. Oncogene. 2021;40(21):3719-33 [IF: 9.867]*

The clinical performance of the therapeutic monoclonal antibody trastuzumab in the treatment of ErbB2-positive unresectable gastric cancer (GC) is severely hampered by the emergence of molecular resistance. Trastuzumab's target epitope is localized within the extracellular domain of the oncogenic cell surface receptor tyrosine kinase (RTK) ErbB2, which is known to undergo extensive N-linked glycosylation. However, the site-specific glycan repertoire of ErbB2, as well as the detailed molecular mechanisms through which specific aberrant glycan signatures functionally impact the malignant features of ErbB2-addicted GC cells, including the acquisition of trastuzumab resistance, remain elusive. Here, we demonstrate that ErbB2 is modified with both alpha2,6- and alpha2,3-sialylated glycan structures in GC clinical specimens. In-depth mass spectrometry-based glycomic and glycoproteomic analysis of ErbB2's ectodomain disclosed a site-specific glycosylation profile in GC cells, in which the ST6Gal1 sialyltransferase specifically targets ErbB2 N-glycosylation sites occurring within the receptor's trastuzumab-binding domain. Abrogation of ST6Gal1 expression reshaped the cellular and ErbB2-specific glycomes, expanded the cellular half-life of the ErbB2 receptor, and sensitized ErbB2-dependent GC cells to trastuzumab-induced cytotoxicity through the stabilization of ErbB dimers at the cell membrane, and the decreased activation of both ErbB2 and EGFR RTKs. Overall, our data demonstrates that ST6Gal1-mediated aberrant alpha2,6-sialylation actively tunes the resistance of ErbB2-driven GC cells to trastuzumab.

**91. Seroprevalence of Anti-SARS-CoV-2 Antibodies Three Months Post Infection in Healthcare Professionals at an Oncology Hospital in Northern Portugal.**

*e Silva, DF, Silva, PD, Torral, A, Braaga, S, Rocha, D, Ochoa, C, Oliveira, Á, Rocha, L, Dias, JM and Baldaque, I. Acta Médica Portuguesa; Vol 34, No 6 (2021): JuneDO - 10.20344/amp.16336. 2021N/a. [IF: 1.141]*

**92. Gastric perforation by fish bone with hepatic abscess formation presenting as prolonged fever.**

*Enes Silva, J, Pinelas, S, Pacheco, M, Patacho, M and Almeida, J. IDCases. 2021;24:e01159 [IF: NA]*

A 70-year-old woman presented to the emergency department with a 3-week history of prolonged fever, asthenia and anorexia, denying other symptoms. Physical examination was unremarkable and the patient admitted for further investigation. Initial laboratory testing showed leucocytosis, elevated C-reactive protein and cholestasis, without hyperbilirubinemia or cytolysis. Abdominal ultrasonography found no abnormalities. Viral serologies, autoimmune tests and blood cultures were collected for further investigation of causes of prolonged fever with hepatic involvement. After two days, *Citrobacter koseri* was isolated in blood cultures and intravenous (IV) piperacillin-tazobactam initiated. Computed tomography (CT) scan of the abdomen showed a left lobe hepatic abscess with gas and a linear hyperdense image, possibly a foreign body, piercing through the gastric antrum into the abscess. Surgical exploration was done for source control. The abscess was drained and the foreign body, a 3.5cm long fishbone, was removed. The patient's condition rapidly improved. Gastrointestinal perforation due to the ingestion of sharp and elongated foreign bodies usually occur in ileal loops, where the intestinal wall is thinner, causing extravasation of fluids and air into the peritoneum and typically presents with an acute abdomen. The uncommon location of perforation masked these symptoms leading to the unusual presentation with prolonged fever.

### 93. The role of TP53 pathogenic variants in early-onset HER2-positive breast cancer.

*Escudeiro, C, Pinto, C, Vieira, J, Peixoto, A, Pinto, P, Pinheiro, M, Santos, C, Guerra, J, Lisboa, S, Santos, R, Silva, J, Leal, C, Coimbra, N, Lopes, P, Ferreira, M, Sousa, AB and Teixeira, MR. Fam Cancer. 2021;20(3):173-80 [IF: 2.375]*

Breast cancer is the most frequent event in Li-Fraumeni syndrome associated with germline TP53 variants. Some studies have shown that breast cancers in women with Li-Fraumeni syndrome are commonly HER2-positive, suggesting that HER2 amplification or over-expression in a young woman may be a useful criterion to test for germline variants in the TP53 gene. We assessed the prevalence of germline TP53 variants by Sanger sequencing or next-generation sequencing in 149 women with HER2-positive breast cancer diagnosed until age 40. The pattern of HER2 amplification was evaluated with dual-probe FISH in a subset of breast carcinomas from patients with germline TP53 variants as compared with those of noncarriers. Among 149 women tested, three presented a deleterious TP53 germline variant (2%), with one patient diagnosed at age 31 and the other two with bilateral breast cancer at ages 29/33 and 28/32, respectively. Three of the 36 patients (8.3%) with the first breast cancer diagnosed at age 31 or younger presented a pathogenic TP53 variant. Additionally, all TP53 deleterious variant carriers had a first degree relative diagnosed with different early-onset cancers (frequently not belonging to the Li-Fraumeni syndrome tumor spectrum) diagnosed at age 45 or younger. Higher levels of HER2 amplification were found in breast carcinomas of TP53 pathogenic variant carriers than in those of noncarriers. Deleterious germline TP53 variants account for a small proportion of early-onset HER2-positive breast cancers, but these seem to have higher HER2 amplification ratios. All TP53 pathogenic variant carriers found in this study had the first breast carcinoma diagnosed at age 31 or younger and a first-degree relative with early-onset cancer. Further studies are needed to clarify if HER2 status in early-onset breast cancer patients, in combination with other personal and/or familial cancer history, is useful to update the TP53 testing criteria.

### 94. Neurosurgical anatomy of the floor of the third ventricle and related vascular structures.

*Fernandes-Silva, J, Silva, SM, Alves, H, Andrade, JP and Arantes, M. Surg Radiol Anat. 2021;43(12):1915-25 [IF: 1.246]*

**PURPOSE:** Anatomical knowledge of the floor of the third ventricle (FTV) is essential in avoiding surgical complications during endoscopic third ventriculostomy. The purpose of this study was to characterize the morphometry of FTV and related arteries, particularly the basilar artery (BA), as well as the factors that influence it. **METHODS:** Twenty-six formalin-fixed adult brains and two hundred adult brain MRIs were studied focusing on FTV and related arteries. Dimensions of interest were measured using image analysis software. Morphometric data obtained were statistically analysed. **RESULTS:** Distances between FTV, intermammillary sulcus (IMS), infundibulum, BA bifurcation, and posterior communicating arteries (PCoAs) were described on the cadavers and the MRIs. Distance between right and left PCoAs was greater at their anterior extremity ( $p < 0.001$ ). Right PCoA was longer ( $p = 0.016$ ). BA was lateralized in 58.4% of cases and

its calibre was larger in males ( $p < 0.001$ ). The distance from BA apex to FTV was inversely correlated with BA diameter ( $p < 0.001$ ) and age ( $p = 0.004$ ). Distance from IMS to infundibulum and the distance between both PCoAs were greater in MRI series when compared to cadaver series ( $p < 0.001$ ). CONCLUSIONS: A quantitative description of the morphometry of the region of the FTV and related vessels was obtained, helping neurosurgeons in planning their surgical approach. The distance from BA apex to FTV was shorter in individuals with larger BA calibre and in older subjects. MRI studies were qualitatively superior to cadaveric studies in evaluating the anatomy of this region.

#### 95. Outcomes of single-endoscopist-performed needle-knife fistulotomy for selective biliary access in 842 consecutive patients: learning curve and changes over a 14-year period in a retrospective study.

Fernandes, J, Canena, J, Alexandrino, G, Figueiredo, L, Rafael, M, Moreira, M, Araujo, T, Lourenco, L, Horta, D, Familiari, P, Dinis-Ribeiro, M and Lopes, L. *Scand J Gastroenterol.* 2021;56(11):1363-70 [IF: 2.423]

BACKGROUND AND AIMS: Needle-knife fistulotomy (NKF) has emerged as the preferred precut technique. From a late strategy, NKF has shifted to an early rescue technique and has been used recently as a primary method for biliary access. It is unknown how these changes have affected NKF outcomes. We analyzed the outcomes of NKF over time in a large cohort of patients. METHODS: Multicenter retrospective cohort study of 842 patients who underwent NKF for biliary access between 2006 and 2019. Patients were divided into four study periods according to a late or early cannulation strategy and to the use of post-ERCP pancreatitis prophylaxis (Period 1-Period 4). We assessed outcomes of NKF, learning curves and shifts over time.

RESULTS: Bile duct access was obtained in 88.0% of the patients. The initial cannulation rate increased significantly from 77.5% in P1 to 92.0% in P4 ( $p < .001$ ). An endoscopist can obtain 80% success rate after performing 100 NKF procedures (95% CI: 0.79-0.86) and a 95% success rate after 830 procedures (95% CI: 0.92-0.98). Adverse events and pancreatitis were observed in 6.5% and 4.9% of patients respectively. The rate of pancreatitis was not significantly different during the 4 periods ( $p = .190$ ). A decline in the pancreatitis rate was observed from 2006 until 2016 (no trainees) and then an increase until 2019 (trainees involved). The presence of trainees increased the rate of pancreatitis in the last period by 9.9%.

CONCLUSIONS: The success of NKF has increased significantly over the years, initially in a rapid manner and then more slowly. It is associated with a low rate of complications, which tend to decrease with experience. The involvement of trainees is associated with an increased rate of pancreatitis.

#### 96. Diffuse reflectance and machine learning techniques to differentiate colorectal cancer ex vivo.

Fernandes, L, Carvalho, S, Carneiro, I, Henrique, R, Tuchin, VV, Oliveira, HP and Oliveira, LM. *Chaos.* 2021;31(5):053118 [IF: 3.642]

In this study, we used machine learning techniques to reconstruct the wavelength dependence of the absorption coefficient of human normal and pathological colorectal mucosa tissues. Using only diffuse reflectance spectra from the ex vivo mucosa tissues as input to algorithms, several approaches were tried before obtaining good matching between the generated absorption coefficients and the ones previously calculated for the mucosa tissues from invasive experimental spectral measurements. Considering the optimized match for the results generated with the multilayer perceptron regression method, we were able to identify differentiated accumulation of lipofuscin in the absorption coefficient spectra of both mucosa tissues as we have done before with the corresponding results calculated directly from invasive measurements. Considering the random forest regressor algorithm, the estimated absorption coefficient spectra almost matched the ones previously calculated. By subtracting the absorption of lipofuscin from these spectra, we obtained similar hemoglobin ratios at 410/550 nm: 18.9-fold/9.3-fold for the healthy mucosa and 46.6-fold/24.2-fold for the pathological mucosa, while from direct calculations, those ratios were 19.7-fold/10.1-fold for the healthy mucosa and 33.1-fold/17.3-fold for the pathological mucosa. The higher values obtained in this study indicate a higher blood content in the pathological samples used to measure the diffuse reflectance spectra. In light of such accuracy and sensibility to the presence of hidden absorbers, with a different accumulation between healthy and pathological tissues, good perspectives become available to develop minimally invasive spectroscopy methods for in vivo early detection and monitoring of colorectal cancer.

#### 97. Tissue Spectroscopy and Optical Clearing of Colorectal Mucosa in the Pursuit of New Cancer

**Diagnostic Approaches.**

*Fernandes, L, Silva, H, Martins, I, Carvalho, S, Carneiro, I, Henrique, R, Tuchin, VV and Oliveira, LM. Journal of Biomedical Photonics & Engineering. 2021;7(4) [IF: NA]*

In this paper we present three studies that demonstrate the applicability of spectroscopy methods and optical clearing treatments in pathology identification and monitoring. In the first study, by obtaining the absorption spectra of human healthy and pathological (adenocarcinoma) colorectal mucosa tissues, it was possible to identify a higher content of a pigment in the diseased tissues. This study also shows that machine learning methods can be used to reach the same differentiated results in vivo through diffuse reflectance spectroscopy. In the second study, the combination of collimated transmittance spectroscopy with optical clearing treatments allowed to obtain the diffusion coefficients of glucose in healthy and pathological colorectal mucosa as:  $D_{\text{glucose}} \times 10^7 = 5.8-7 \text{ cm}^2/\text{s}$  and  $D_{\text{glucose}} \times 10^7 = 4.4-7 \text{ cm}^2/\text{s}$ , respectively. This study also demonstrated that the diseased tissues contains about 5% more mobile water than the healthy tissues. The third study was performed to evaluate the protein dissociation mechanism of optical clearing. By treating both healthy and pathological colorectal mucosa tissues with 93%-glycerol, a protein dissociation rate of about 3 times higher was obtained for the pathological mucosa. All the discriminating parameters that result from these studies can be obtained in the in vivo situation through diffuse reflectance spectroscopy and further studies to evaluate their values in different stages of cancer progression are of great importance to develop disease monitoring protocols.

**98. Competitive Endogenous RNA Network Involving miRNA and lncRNA in Non-Hodgkin Lymphoma: Current Advances and Clinical Perspectives.**

*Fernandes, M, Marques, H, Teixeira, AL and Medeiros, R. Biomedicines. 2021;9(12) [IF: 6.081]*

Non-Hodgkin lymphoma (NHL) is a heterogeneous malignancy with variable patient outcomes. There is still a lack of understanding about the different players involved in lymphomagenesis, and the identification of new diagnostic and prognostic biomarkers is urgent. MicroRNAs and long non-coding RNAs emerged as master regulators of B-cell development, and their deregulation has been associated with the initiation and progression of lymphomagenesis. They can function by acting alone or, as recently proposed, by creating competing endogenous RNA (ceRNA) networks. Most studies have focused on individual miRNAs/lncRNAs function in lymphoma, and there is still limited data regarding their interactions in lymphoma progression. The study of miRNAs' and lncRNAs' deregulation in NHL, either alone or as ceRNAs networks, offers new insights into the molecular mechanisms underlying lymphoma pathogenesis and opens a window of opportunity to identify potential diagnostic and prognostic biomarkers. In this review, we summarized the current knowledge regarding the role of miRNAs and lncRNAs in B-cell lymphoma, including their interactions and regulatory networks. Finally, we summarized the studies investigating the potential of miRNAs and lncRNAs as clinical biomarkers, with a special focus on the circulating profiles, to be applied as a non-invasive, easy-to-obtain, and reproducible liquid biopsy for dynamic management of NHL patients.

**99. miRNA- and lncRNA-Based Therapeutics for Non-Hodgkin's Lymphoma: Moving towards an RNA-Guided Precision Medicine.**

*Fernandes, M, Marques, H, Teixeira, AL and Medeiros, R. Cancers (Basel). 2021;13(24) [IF: 6.639]*

Increasing evidence has demonstrated the functional roles of miRNAs and lncRNAs in lymphoma onset and progression, either by acting as tumor-promoting ncRNAs or as tumor suppressors, emphasizing their appeal as lymphoma therapeutics. In fact, their intrinsic ability to modulate multiple dysregulated genes and/or signaling pathways makes them an attractive therapeutic approach for a multifactorial pathology like lymphoma. Currently, the clinical application of miRNA- and lncRNA-based therapies still faces obstacles regarding effective delivery systems, off-target effects, and safety, which can be minimized with the appropriate chemical modifications and the development of tumor site-specific delivery approaches. Moreover, miRNA- and lncRNA-based therapeutics are being studied not only as monotherapies but also as complements of standard treatment regimens to provide a synergic effect, improving the overall treatment efficacy and reducing the therapeutic resistance. In this review, we summarize the fundamentals of miRNA- and lncRNA-based therapeutics by discussing the different types of delivery systems, with a focus on those that have been investigated in lymphoma in vitro and in vivo. Moreover, we described the ongoing clinical

trials of novel miRNA- and lncRNA-based therapeutics in lymphoma.

#### 100. Cushing Syndrome as a Manifestation of Neuroendocrine Prostate Cancer: A Rare Presentation Within a Rare Tumor.

*Fernandes, R, Dos Santos, J, Reis, F and Monteiro, S. Cureus. 2021;13(9):e18160 [IF: NA]*

Neuroendocrine prostate cancer (NEPC) is a rare entity representing 1% of all prostate malignancies, associated with poor prognosis and often concomitant with paraneoplastic syndromes such as Cushing's syndrome (CS) with ectopic adrenocorticotrophic hormone (ACTH) production. We present a case of a 56-year-old man with recent lower urinary tract symptoms hospitalized for pelvic pain, rectal tenesmus, and fatigue. A CT scan documented a large prostatic mass, adenomegalies, and hepatic lesions. Bone scintigraphy showed dispersed osteoblastic metastazation. The patient had uncontrolled hypertension and hypokalemia that lead to the diagnosis of paraneoplastic ACTH-dependent CS. Prostate biopsy confirmed small cell NEPC. Potassium supplementation, anti-hypertensive medication, and metyrapone were initiated. The patient was proposed for palliative chemotherapy but died within a few days from a urinary tract infection. The authors aim to draw attention to a case of paraneoplastic CS, a rare manifestation, within the rarity that is NEPC.

#### 101. Complications of Biliary Drainage in Patients with Malignant Biliary Obstruction.

*Ferraz Goncalves, JA, Rosendo, E, Sousa, L, Lopes, AR, Leao, I, Queiros, R, Marote, S and Sousa, MJ. J Gastrointest Cancer. 2021;52(3):1067-72 [IF: NA]*

PURPOSE: Biliary tract obstruction in cancer patients is usually associated with a poor prognosis. The obstruction may cause distressing symptoms, such as pruritus. As this situation occurs mostly in advanced cancer, the primary objective of the treatment is in many cases symptom control and not prolonging life. However, some patients can be candidates for chemotherapy. To see the outcomes of stenting insertion in patients of our oncology center. METHODS: A retrospective study of patients who have undergone this procedure between 1 October 2011 and 31 December 2018 was carried out. RESULTS: Insertion of a biliary stent was performed in 171 patients. The most common diagnoses were gastric and colorectal cancers, each with 42 (24%), followed by pancreatic (34 (20%)) and biliary tract cancer (25 (14%)). Most stents (155 (91%)) were placed percutaneously. Complications were seen in 91 (53%) patients and the most common was cholangitis in 48 (53%) patients, and the median survival was 75.5 days (3-1246). A total of 168 (98%) patients were referred to palliative care. In a multivariable analysis, the ECOG performance status was associated with survival, with the ECOG 0, 1, and 2 associated with better survival and peritoneal metastases associated with lower survival. CONCLUSIONS: For many patients with advanced cancers, it may not be clear if the benefits of palliative biliary stents outweigh the risks. Therefore, the problem should be discussed with the patients and their families, making clear the goals of care and the potential benefits and risks that can be expected.

#### 102. Breastfeeding and childhood obesity in the Azores.

*Ferreira, A, Rosendo, I, Santiago, LM and Simões, J. Family Medicine & Primary Care Review. 2021;23(1):81-6 [IF: NA]*

Background. The hypothesis that breastfeeding has a protective effect in childhood obesity is not new; however, controversial results have been published. Since the Azores reported the lowest rate of breastfeeding in Portugal and a high prevalence of childhood obesity, it becomes important to understand whether these facts are related or not. Objectives. To investigate the relationship between breastfeeding and childhood obesity in a population of Azorean children. Material and methods. A cross-sectional study was carried out on 183 Azorean children between 5–10 years of age between September and December 2016. The weight and height of the children were measured at the consultation and other variables were investigated through a questionnaire. The association between breastfeeding and childhood obesity was tested using logistic regression models. Results. 18.6% of the children were obese and 74.3% were breastfed. The exclusive breastfeeding rate at 6 months was 3.3%. Complementary breastfeeding was present in 39.3% at 6 months and 7.1% at 2 years. Obese children were breastfed less time than non-obese children, suggesting a dose-effect relationship ( $p = 0.025$ ). We found a significant and independent relationship between infant obesity and total time of breastfeeding (RR = 0.906; 95% CI [0.842, 0.974];  $p =$

0.008), physical activity (RR = 0.883; 95% CI [0.801, 0.972]; p = 0.012) and maternal nutritional status (RR = 3.452; 95% CI [1.361, 8.755]; p = 0.009). Conclusions. Breastfeeding and physical activity behaved as protective factors for childhood obesity, while the nutritional status of the mother acted as a risk factor. Childhood obesity is a current problem in the Azores, and breastfeeding can be an effective, simple and affordable tool to reduce this.

#### 103. Participation in clinical trials increases the detection of pre-malignant lesions during colonoscopy.

*Ferreira, AO, Costa-Santos, MP, Gomes, C, Morao, B, Gloria, L, Cravo, M, Dinis-Ribeiro, M and Canena, J. Rev Esp Enferm Dig. 2021 [IF: 2.086]*

BACKGROUND: Colorectal adenoma detection has been associated with cancer prevention effectiveness. Clinical trials have been conceived to determine the role of several interventions to increase the detection of pre-malignant lesions. We hypothesized that colonoscopy in the setting of such trials have higher pre-malignant lesion detection rates. METHODS: We performed a cross-sectional study comparing the detection of pre-malignant lesions in 147 randomly sampled non-research colonoscopies and 294 from the control groups of two prospective trials. We included outpatients aged 40-79 who had no personal history of CRC. RESULTS: Baseline characteristics were similar between the two groups. The pre-malignant lesion detection rate in the trial vs control group was 65.6% vs 44.2% (OR 2.411; 95% CI 1.608-3.614; p<0.001), the polyp detection rate was 73.8% vs 59.9% (OR 1.889; 95% CI 1.242-2.876; p=0.003), the adenoma detection rate was 62.6% vs 44.2% (OR 2.110; 95% CI 1.411-3.155; p<0.001) and the sessile serrated lesion detection rate was 17% vs 4.1% (OR 4.816; 95% CI 2.014-11.515; p<0.001). The mean number of pre-malignant and sessile serrated lesions was 1.70 vs 1.06 (p=0.002) and 0.32 vs 0.06 (p=0.001) lesions per colonoscopy. In a multivariate analysis with each single potential confounder, there was no significant change in any of the study outcomes. CONCLUSIONS: Patients involved in colonoscopy trials may benefit from higher quality examinations, as shown by the higher detection rates. Institutions should consider supporting clinical research in colonoscopy as a simple means to improve colonoscopy quality and colorectal cancer prevention.

#### 104. Polyphasic characterization of carbapenem-resistant *Klebsiella pneumoniae* clinical isolates suggests vertical transmission of the blaKPC-3 gene.

*Ferreira, C, Bikkarolla, SK, Frykholm, K, Pohjanen, S, Brito, M, Lameiras, C, Nunes, OC, Westerlund, F and Manaia, CM. PLoS One. 2021;16(2):e0247058 [IF: 3.240]*

Carbapenem-resistant *Klebsiella pneumoniae* are a major global threat in healthcare facilities. The propagation of carbapenem resistance determinants can occur through vertical transmission, with genetic elements being transmitted by the host bacterium, or by horizontal transmission, with the same genetic elements being transferred among distinct bacterial hosts. This work aimed to track carbapenem resistance transmission by *K. pneumoniae* in a healthcare facility. The study involved a polyphasic approach based on conjugation assays, resistance phenotype and genotype analyses, whole genome sequencing, and plasmid characterization by pulsed field gel electrophoresis and optical DNA mapping. Out of 40 *K. pneumoniae* clinical isolates recovered over two years, five were carbapenem- and multidrug-resistant and belonged to multilocus sequence type ST147. These isolates harboured the carbapenemase encoding blaKPC-3 gene, integrated in conjugative plasmids of 140 kbp or 55 kbp, belonging to replicon types incFIA/incFIIK or incN/incFIIK, respectively. The two distinct plasmids encoding the blaKPC-3 gene were associated with distinct genetic lineages, as confirmed by optical DNA mapping and whole genome sequence analyses. These results suggested vertical (bacterial strain-based) transmission of the carbapenem-resistance genetic elements. Determination of the mode of transmission of antibiotic resistance in healthcare facilities, only possible based on polyphasic approaches as described here, is essential to control resistance propagation.

#### 105. Glycoproteogenomics: Setting the Course for Next-generation Cancer Neoantigen Discovery for Cancer Vaccines.

*Ferreira, JA, Relvas-Santos, M, Peixoto, A, A, MNS and Lara Santos, L. Genomics Proteomics Bioinformatics. 2021;19(1):25-43 [IF: 7.691]*

Molecular-assisted precision oncology gained tremendous ground with high-throughput next-generation sequencing (NGS), supported by robust bioinformatics. The quest for genomics-based cancer medicine set

the foundations for improved patient stratification, while unveiling a wide array of neoantigens for immunotherapy. Upfront pre-clinical and clinical studies have successfully used tumor-specific peptides in vaccines with minimal off-target effects. However, the low mutational burden presented by many lesions challenges the generalization of these solutions, requiring the diversification of neoantigen sources. Oncoproteogenomics utilizing customized databases for protein annotation by mass spectrometry (MS) is a powerful tool toward this end. Expanding the concept toward exploring proteoforms originated from post-translational modifications (PTMs) will be decisive to improve molecular subtyping and provide potentially targetable functional nodes with increased cancer specificity. Walking through the path of systems biology, we highlight that alterations in protein glycosylation at the cell surface not only have functional impact on cancer progression and dissemination but also originate unique molecular fingerprints for targeted therapeutics. Moreover, we discuss the outstanding challenges required to accommodate glycoproteomics in oncoproteogenomics platforms. We envisage that such rationale may flag a rather neglected research field, generating novel paradigms for precision oncology and immunotherapy.

#### 106. Toxicological and anti-tumor effects of a linden extract (*Tilia platyphyllos* Scop.) in a HPV16-transgenic mouse model.

*Ferreira, T, Nascimento-Goncalves, E, Macedo, S, Borges, I, Gama, A, R, MGdC, Neuparth, MJ, Lanzarin, G, Venancio, C, Felix, L, Gaivao, I, Alvarado, A, Pires, MJ, Bastos, M, Medeiros, R, Nogueira, A, Barros, L, Ferreira, I, Rosa, E and Oliveira, PA. Food Funct. 2021;12(9):4005-14 [IF: 5.396]*

*Tilia platyphyllos* Scop. is a popular broad-leaved tree, native to Central and Southern Europe. Hydroethanolic extracts rich in phenolic compounds obtained from *T. platyphyllos* Scop. have shown in vitro antioxidant, anti-inflammatory and antitumor properties. The aim of this work was to evaluate the therapeutic properties of a hydroethanolic extract obtained from *T. platyphyllos* in HPV16-transgenic mice. The animals were divided into eight groups according to their sex and phenotype. Four groups of female: HPV+ exposed to linden (HPV linden; n = 6), HPV+ (HPV water; n = 4), HPV- exposed to linden (WT linden; n = 5) and HPV- (WT water; n = 4) and four groups of male: HPV+ exposed to linden (HPV linden; n = 5), HPV+ (HPV water; n = 5), HPV- exposed to linden (WT linden; n = 5) and HPV- (WT water; n = 7). The linden (*Tilia platyphyllos* Scop.) extract was orally administered at a dose of 4.5 mg/10 mL per animal (dissolved in water) and changed daily for 33 days. The hydroethanolic extract of *T. platyphyllos* consisted of protocatechuic acid and (-)-epicatechin as the most abundant phenolic acid and flavonoid, respectively, and was found to be stable during the studied period. In two male groups a significant positive weight gain was observed but without association with the linden extract. Histological, biochemical, and oxidative stress analyses for the evaluation of kidney and liver damage support the hypothesis that the linden extract is safe and well-tolerated under the present experimental conditions. Skin histopathology does not demonstrate the chemopreventive effect of the linden extract against HPV16-induced lesions. The linden extract has revealed a favourable toxicological profile; however, additional studies are required to determine the chemopreventive potential of the linden extract.

#### 107. Bridging the Gaps between Circulating Tumor Cells and DNA Methylation in Prostate Cancer.

*Flores, BCT, Correia, MP, Rodriguez, JG, Henrique, R and Jeronimo, C. Cancers (Basel). 2021;13(16) [IF: 6.639]*

Prostate cancer is the second most common male malignancy, with a highly variable clinical presentation and outcome. Therefore, diagnosis, prognostication, and management remain a challenge, as available clinical, imaging, and pathological parameters provide limited risk assessment. Thus, many biomarkers are under study to fill this critical gap, some of them based on epigenetic aberrations that might be detected in liquid biopsies. Herein, we provide a critical review of published data on the usefulness of DNA methylation and circulating tumor cells in diagnosis and treatment decisions in cases of prostate cancer, underlining key aspects and discussing the importance of these advances to the improvement of the management of prostate cancer patients. Using minimally invasive blood tests, the detection of highly specific biomarkers might be crucial for making therapeutic decisions, determining response to specific treatments, and allowing early diagnosis.

#### 108. Reverse Transcription Polymerase Chain Reaction Pattern of SARS-CoV-2 Beta Variant.

*Fonseca, ESD, Silva, PD and Baldaque, I. Acta Med Port. 2021 [IF: 1.141]*

**109. Systematic review with meta-analysis: the appropriateness of colonoscopy increases the probability of relevant findings and cancer while reducing unnecessary exams.**

*Frazzoni, L, La Marca, M, Radaelli, F, Spada, C, Laterza, L, Zagari, RM, Bazzoli, F, Hassan, C, Frazzoni, M, Dinis-Ribeiro, M and Fuccio, L. Aliment Pharmacol Ther. 2021;53(1):22-32 [IF: 8.171]*

**BACKGROUND:** Colonoscopy is frequently performed in industrialised countries. Inappropriate colonoscopies might lead to unnecessary exams, increasing risks and costs. **AIM:** To estimate the impact of colonoscopy appropriateness in terms of gain in additional diagnoses and sparing of unnecessary exams. **METHODS:** Systematic review including studies reporting the prevalence of relevant findings, colorectal cancer (CRC) and inflammatory bowel disease (IBD) according to colonoscopy appropriateness as defined by the American Society for Gastrointestinal Endoscopy and European Panel on Appropriateness of Gastrointestinal Endoscopy. **RESULTS:** Twenty-one studies with 19,822 patients were included. Colonoscopy was appropriate in 15,162 (71%, CI 64%-78%). Appropriateness significantly increased the probability of relevant findings (34% vs. 18%; RR 1.81, CI 1.53-2.14), CRC (7% vs. 2%; RR 3.62, CI 2.44-5.37) and IBD (6% vs. 4%; RR 1.86, CI 1.09-3.19). Appropriateness had sensitivity 88% (CI 85%-91%), 97% (CI 93%-98%) and 89% (CI 80%-94%), and specificity 24% (CI 20%-29%), 22% (CI 18%-26%) and 24% (CI 20%-28%) for relevant findings, CRC and IBD, respectively. On average, performing colonoscopy with appropriate indication would find 15 (CI 10-21) more relevant findings, five (CI 3-9) more CRCs and three (CI 1-9) more diagnoses of IBD per 100 patients, and save 24 (CI 20-29), 22 (CI 18-26) and 24 (CI 20-28) examinations per 100 patients for relevant findings, CRC and IBD, respectively. **CONCLUSIONS:** Appropriateness affects the diagnostic yield of colonoscopy for CRC, IBD and relevant findings. Appropriateness criteria are useful, although integrated with clinical evaluation of the patient.

**110. Risk factors among stroke subtypes and its impact on the clinical outcome of patients of Northern Portugal under previous aspirin therapy.**

*Freitas-Silva, M, Medeiros, R and Nunes, JPL. Clin Neurol Neurosurg. 2021;203:106564 [IF: 1.876]*

**BACKGROUND:** In Western European countries, acute ischemic stroke (AIS) remains the third leading cause of death. Among the risk factors for cerebrovascular disease, some have more influence than others in certain stroke subtypes. The aim of this study was to evaluate the impact of risk factors among Stroke Subtypes on the clinical outcome of Portuguese patients under previous aspirin therapy. **MATERIALS AND METHODS:** We studied a cohort of 371 patients diagnosed with AIS and a clinical follow-up protocol was set up. The patients were admitted in a Department of Internal Medicine of a major hospital. Standardized data assessment and stroke subtype classification (Oxfordshire Community Stroke Project) were used. **RESULTS:** Arterial hypertension (80.4 %), overweight (72.6 %) and dyslipidemia (62.0 %) were the most prevalent risk factors with no statistical differences among the group's subtypes. Current smoking was more prevalent in POCI (62.9 %) with differences among subtypes ( $p = 0.002$ ). Atrial fibrillation was more commonly reported in TACI (39.3 %) and less common in POCI (8.1 %) ( $p < 0.001$ ). Comparing TACI vs Non TACI Stroke Subtypes demonstrated major differences in cumulative survival, among the cases with no previous aspirin treatment, after 3 years (51.9 % vs 88.8 %). The increased risk of mortality at 12 months is consistently observed for the presence of a previous atrial fibrillation (OR 3.01 95 % CI 1.69-5.39), TACI subtype (OR 10.4 95 % CI 4.83-22.6) and NIHSS over 10 (OR 9.33 95 % CI 4.49-19.4). When we analyze the impact of previous aspirin treatment in the risk for a new stroke event, it seems to have a protective effect in a time frame of 12 months, but this protection is lost extending at 24 months ( $p = 0.094$  vs  $p = 0.005$ ). **DISCUSSION:** Our results indicate that smoking, atrial fibrillation and age have different relevance in their distribution among ischemic stroke subtypes at the time of diagnosis. Concerning the influence of the main stroke risk factors on the clinical outcome, our results present a strong influence of atrial fibrillation and of age. Severity of disease at diagnosis, represented by TACI subtype is clearly associated to decreased survival among patients with no record of previous aspirin therapy. Our results reinforce the relevance cohort studies of different populations, to achieve a more comprehensive knowledge of the impact of risk factors on stroke subtypes and on its clinical outcome.

**111. Single-pot enzymatic synthesis of cancer-associated MUC16 O-glycopeptide libraries and multivalent protein glycoconjugates: a step towards cancer glycovaccines.**

*Freitas, R, Relvas-Santos, M, Azevedo, R, Soares, J, Fernandes, E, Teixeira, B, Santos, LL, Silva, AMN and Ferreira, JA. New Journal of Chemistry. 2021;45(20):9197-211 [IF: 3.591]*

Cancer cells often overexpress and/or express de novo glycoproteins modified with short-chain sialylated O-glycans, sialyl-Tn (STn), sialyl-3-T (S3T) and sialyl-6-T (S6T) antigens, that hold potential for carbohydrate-based vaccines. However, the generation of glycopeptide libraries composed by structurally defined standards remains a critical step for carbohydrate metrology and vaccine development. A simple and fast multi-enzymatic single-pot method was applied for generating a wide array of STn, S3T and S6T glycopeptides. A 20-mer tandem repeat peptide from the cancer-associated glycoprotein MUC16 was used as a scaffold towards this end. Different glycosyltransferases and nucleotide sugars were combined in a stepwise manner to generate the glycopeptide libraries. TiO<sub>2</sub> enrichment was further used to isolate sialoglycopeptides, and the glycopeptide libraries were characterized by nanoLC-MS. Multiple glycopeptides were conjugated with protein immunogens, bovine serum albumin (BSA) and keyhole limpet hemocyanin (KLH), foreseeing multivalent glycoepitopes that may pave the way for immunotherapy. We have synthesized MUC16-Tn antigens containing up to 5 glycosites and mapped the main occupied glycosites. We have also successfully synthesized MUC16-STn, S3T and S6T glycopeptides and hybrid MUC16-Tn/STn, MUC16-Tn/S3T, MUC16-T/S6T and MUC16-Tn/T/S6T glycoproteoforms. As proof-of-concept, we have coupled MUC16-Tn/STn glycopeptides to immunogenic proteins. This sets the molecular background for the future development of multivalent glycan-based vaccines exploiting MUC16 glycoepitopes.

**112. Merkel cell carcinoma metastatic to the testis: report of a rare diagnosis and review of the literature.**

*Gigliano, D, Lobo, J, Lopes, P, Juliao, I, Lobo, F, Azevedo, R, Henrique, R and Rodrigues, A. Autops Case Rep. 2021;11:e2020198 [IF: NA]*

Merkel cell carcinoma is an aggressive malignancy that frequently recurs/disseminates, but metastases to the genitourinary tract are rare. Only eight cases of Merkel cell carcinoma metastatic to the testis are reported. We describe the ninth case of this event and provide a review of the literature. A 58-year-old man diagnosed with Merkel cell carcinoma of the wrist, presented, 37 months later, a recurrence in the form of a testicular metastasis. The tumor consisted of a monotonous proliferation of small, blue, round cells, with immunoreexpression of neuroendocrine markers and the typical dot-like paranuclear immunostaining for cytokeratin 20, in the absence of immunostaining for cytokeratin 7. The patient is alive with no evidence of disease. Clinicians should be aware of the possibility of metastatic dissemination to the testis since genital examination/imaging is not part of routine follow-up for these patients, but timely orchiectomy may be curative.

**113. Editorial: Biology and Pathology of Tumor Viruses in Animals.**

*Gil da Costa, RM and Abreu-Silva, AL. Front Vet Sci. 2021;8:797596 [IF: 3.412]*

**114. The histology of brain tumors for 67 331 children and 671 085 adults diagnosed in 60 countries during 2000-2014: a global, population-based study (CONCORD-3).**

*Girardi, F, Rous, B, Stiller, CA, Gatta, G, Fersht, N, Storm, HH, Rodrigues, JR, Herrmann, C, Marcos-Gragera, R, Peris-Bonet, R, Valkov, M, Weir, HK, Woods, RR, You, H, Cueva, PA, De, P, Di Carlo, V, Johannesen, TB, Lima, CA, Lynch, CF, Coleman, MP, Allemani, C and Group, CW. Neuro Oncol. 2021;23(10):1765-76 [IF: 12.300]*

BACKGROUND: Global variations in survival for brain tumors are very wide when all histological types are considered together. Appraisal of international differences should be informed by the distribution of histology, but little is known beyond Europe and North America. METHODS: The source for the analysis was the CONCORD database, a program of global surveillance of cancer survival trends, which includes the tumor records of individual patients from more than 300 population-based cancer registries. We considered all patients aged 0-99 years who were diagnosed with a primary brain tumor during 2000-2014,

whether malignant or nonmalignant. We presented the histology distribution of these tumors, for patients diagnosed during 2000-2004, 2005-2009, and 2010-2014. RESULTS: Records were submitted from 60 countries on 5 continents, 67 331 for children and 671 085 for adults. After exclusion of irrelevant morphology codes, the final study population comprised 60 783 children and 602 112 adults. Only 59 of 60 countries covered in CONCORD-3 were included because none of the Mexican records were eligible. We defined 12 histology groups for children, and 11 for adults. In children (0-14 years), the proportion of low-grade astrocytomas ranged between 6% and 50%. Medulloblastoma was the most common subtype in countries where low-grade astrocytoma was less commonly reported. In adults (15-99 years), the proportion of glioblastomas varied between 9% and 69%. International comparisons were made difficult by wide differences in the proportion of tumors with unspecified histology, which accounted for up to 52% of diagnoses in children and up to 65% in adults. CONCLUSIONS: To our knowledge, this is the first account of the global histology distribution of brain tumors, in children and adults. Our findings provide insights into the practices and the quality of cancer registration worldwide.

#### 115. Elective Cancer Surgery in COVID-19-Free Surgical Pathways During the SARS-CoV-2 Pandemic: An International, Multicenter, Comparative Cohort Study.

Glasbey, JC, Nepogodiev, D, Simoes, JFF, Omar, O, Li, E, Venn, ML, Pgdme, Abou Char, MK, Capizzi, V, Chaudhry, D, Desai, A, Edwards, JG, Evans, JP, Fiore, M, Videria, JF, Ford, SJ, Ganly, I, Griffiths, EA, Gujjuri, RR, Koliass, AG, Kaafarani, HMA, Minaya-Bravo, A, McKay, SC, Mohan, HM, Roberts, KJ, San Miguel-Mendez, C, Pockney, P, Shaw, R, Smart, NJ, Stewart, GD, Sundar Mrcog, S, Vidya, R, Bhangu, AA and Collaborative, CO. *J Clin Oncol.* 2021;39(1):66-78 [IF: 44.544]

PURPOSE: As cancer surgery restarts after the first COVID-19 wave, health care providers urgently require data to determine where elective surgery is best performed. This study aimed to determine whether COVID-19-free surgical pathways were associated with lower postoperative pulmonary complication rates compared with hospitals with no defined pathway. PATIENTS AND METHODS: This international, multicenter cohort study included patients who underwent elective surgery for 10 solid cancer types without preoperative suspicion of SARS-CoV-2. Participating hospitals included patients from local emergence of SARS-CoV-2 until April 19, 2020. At the time of surgery, hospitals were defined as having a COVID-19-free surgical pathway (complete segregation of the operating theater, critical care, and inpatient ward areas) or no defined pathway (incomplete or no segregation, areas shared with patients with COVID-19). The primary outcome was 30-day postoperative pulmonary complications (pneumonia, acute respiratory distress syndrome, unexpected ventilation). RESULTS: Of 9,171 patients from 447 hospitals in 55 countries, 2,481 were operated on in COVID-19-free surgical pathways. Patients who underwent surgery within COVID-19-free surgical pathways were younger with fewer comorbidities than those in hospitals with no defined pathway but with similar proportions of major surgery. After adjustment, pulmonary complication rates were lower with COVID-19-free surgical pathways (2.2% v 4.9%; adjusted odds ratio [aOR], 0.62; 95% CI, 0.44 to 0.86). This was consistent in sensitivity analyses for low-risk patients (American Society of Anesthesiologists grade 1/2), propensity score-matched models, and patients with negative SARS-CoV-2 preoperative tests. The postoperative SARS-CoV-2 infection rate was also lower in COVID-19-free surgical pathways (2.1% v 3.6%; aOR, 0.53; 95% CI, 0.36 to 0.76). CONCLUSION: Within available resources, dedicated COVID-19-free surgical pathways should be established to provide safe elective cancer surgery during current and before future SARS-CoV-2 outbreaks.

#### 116. Langerhans Cell Histiocytosis-A Benign Presentation Heralding a Serious Disease.

Gomes, N, Costa-Silva, M, Nogueira, A, Lopes, JM, Marques, A, Brito, I, Trigo, F, Couto, C, Azevedo, F and Mota, A. *Skinmed.* 2021;19(3):233-6 [IF: NA]

A 3-year old White boy was referred to our dermatology department with a papular disseminated eruption, evolving for 7 months. Several topical antibiotics and corticosteroids were used without improvement. The dermatosis was locally asymptomatic, and systemic symptoms were absent. Examination revealed multiple, skin-colored to pinkish monomorphic papules with a generalized distribution involving the face, trunk, and limbs (Figure 1). The lesions spared the scalp, palms, and soles. Cervical, axillary, and inguinal lymphatic nodes were not palpable. Cutaneous biopsy of one of the abdominal lesions revealed an unremarkable epidermis but a reticular dermis with clusters of histiocytic, lymphocytic, and rare eosinophil cells. In the

immunohistochemical study, expression of CD1a was observed in the histiocytic cells and S100 in the antigen-presenting cells of the dermal infiltrate (Figures 2 and 3). Taking into account the clinical presentation and the histopathologic result, a diagnosis of Langerhans cell histiocytosis (LCH) was established.

**117. On the predictability of postoperative complications for cancer patients: a Portuguese cohort study.**  
Goncalves, D, Henriques, R, Santos, LL and Costa, RS. *BMC Med Inform Decis Mak.* 2021;21(1):200 [IF: 2.796]

Postoperative complications are still hard to predict despite the efforts towards the creation of clinical risk scores. The published scores contribute for the creation of specialized tools, but with limited predictive performance and reusability for implementation in the oncological context. This work aims to predict postoperative complications risk for cancer patients, offering two major contributions. First, to develop and evaluate a machine learning-based risk score, specific for the Portuguese population using a retrospective cohort of 847 cancer patients undergoing surgery between 2016 and 2018, for 4 outcomes of interest: (1) existence of postoperative complications, (2) severity level of complications, (3) number of days in the Intermediate Care Unit (ICU), and (4) postoperative mortality within 1 year. An additional cohort of 137 cancer patients from the same center was used for validation. Second, to improve the interpretability of the predictive models. In order to achieve these objectives, we propose an approach for the learning of risk predictors, offering new perspectives and insights into the clinical decision process. For postoperative complications the Receiver Operating Characteristic Curve (AUC) was 0.69, for complications' severity AUC was 0.65, for the days in the ICU the mean absolute error was 1.07 days, and for 1-year postoperative mortality the AUC was 0.74, calculated on the development cohort. In this study, predictive models which could help to guide physicians at organizational and clinical decision making were developed. Additionally, a web-based decision support tool is further provided to this end.

**118. Attitudes toward assisted death amongst doctors in Northern Portugal.**

Gonçalves, F. *Clinical Ethics.* 2020;16(2):88-97 [IF: NA]

**Introduction**Context: In Portugal assisted death was approved in February 2020 by the Parliament, although the law is not yet in force.**Objectives**To find out what doctors think about those practices.**Methods**A link to a questionnaire was sent by email three times, at intervals of one week, to the doctors registered in the Northern Section of the Portuguese Medical Association, before the Parliamentary approval.**Results**The questionnaire was returned by 1148 (9%) physicians. A minority of doctors would practice a form of assisted death under the present law or if it was legalized, but a higher percentage think that euthanasia should be legalized, and more would like to have that option if they themselves were in a terminal phase of a disease. Religion has a strong influence on the attitudes of doctors, so too does their contact with patients in a terminal phase, as doctors who deal with more patients with far advanced diseases are more likely to be unfavorable to assisted death. On the other hand, younger doctors are more in favor of these practices.**Conclusion**The small percentage of questionnaires sent back is a weakness in this study and casts doubts on the generalizability of the conclusions. However, this is, so far, the best approximation to the opinions of Portuguese doctors on assisted death.

**119. The prevalence and risk-factors of oral HPV DNA detection among HIV-infected men between men who have sex with men and heterosexual men.**

Goncalves, HM, Silva, J, Pintado Maury, I, Tavares, A, Campos, C, Sousa, H, Jacinto, A, Aguiar, P, Caldeira, L and Medeiros, R. *Infect Dis (Lond).* 2021;53(1):19-30 [IF: 3.404]

**BACKGROUND:** Human papillomavirus (HPV)-associated oropharyngeal carcinomas are becoming more common with epidemiological impact on human immunodeficiency virus (HIV)- positive individuals.  
**Objective:** We evaluated prevalence and risk factors for oral HPV DNA among HIV-infected men who have sex with men (MSM) or heterosexual men. **Methods:** This cross-sectional hospital-based study included 255 HIV-infected men with different sexual orientation 142 MSM and 113 heterosexual men, who answered a self-administered questionnaire on sociodemographic, clinical and behavioural data. Oral swab and mouthwash samples were analysed by polymerase chain reaction and genotyped by Anyplex(TM) II 28 (Seegene((R))). **Results:** Oral HPV was detected in 17.6% (95% Confidence Interval (CI) 13.5-22.8%), 17.6% in

MSM and 17.7% in heterosexual men ( $p = .984$ ). Multiple HPV infections were detected in 86.7% of HPV-positive men. HPV 56 (13.7%) was the most prevalent high-risk genotype, HPV 66 (7.8%) and HPV 70 (12.3%) were the most prevalent probable HR and low-risk HPV genotypes (12.3% and 7.1%, respectively). At multivariable analysis models, oral HPV was associated with >100 lifetime sexual partners (Odds Ratio (OR) 3.73; 95% CI 1.42-9.77) or lifetime tongue-kissing partners (OR 3.20; 95% CI 1.22-8.39) and lower education level (OR 2.90; 95% CI 1.08-7.78 and 2.74; 95% CI 1.04-7.27, respectively). Conclusions: Oral HPV prevalence was similar between HIV-infected MSM and heterosexual men. Oral HPV was associated with lifetime sexual partners, lifetime tongue-kissing partners and being undergraduate, independently of sexual orientation.

#### 120. Genetic Variation in PFKFB3 Impairs Antifungal Immunometabolic Responses and Predisposes to Invasive Pulmonary Aspergillosis.

*Goncalves, SM, Antunes, D, Leite, L, Mercier, T, Horst, RT, Vieira, J, Espada, E, Pinho Vaz, C, Branca, R, Campilho, F, Freitas, F, Ligeiro, D, Marques, A, van de Veerdonk, FL, Joosten, LAB, Lagrou, K, Maertens, J, Netea, MG, Lacerda, JF, Campos, A, Jr., Cunha, C and Carvalho, A. mBio. 2021;12(3):e0036921 [IF: 7.867]*

Activation of immune cells in response to fungal infection involves the reprogramming of their cellular metabolism to support antimicrobial effector functions. Although metabolic pathways such as glycolysis are known to represent critical regulatory nodes in antifungal immunity, it remains undetermined whether these are differentially regulated at the interindividual level. In this study, we identify a key role for 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) in the immunometabolic responses to *Aspergillus fumigatus*. A genetic association study performed in 439 recipients of allogeneic hematopoietic stem cell transplantation (HSCT) and corresponding donors revealed that the donor, but not recipient, rs646564 variant in the PFKFB3 gene increased the risk of invasive pulmonary aspergillosis (IPA) after transplantation. The risk genotype impaired the expression of PFKFB3 by human macrophages in response to fungal infection, which was correlated with a defective activation of glycolysis and the ensuing antifungal effector functions. In patients with IPA, the risk genotype was associated with lower concentrations of cytokines in the bronchoalveolar lavage fluid samples. Collectively, these findings demonstrate the important contribution of genetic variation in PFKFB3 to the risk of IPA in patients undergoing HSCT and support its inclusion in prognostic tools to predict the risk of fungal infection in this clinical setting. **IMPORTANCE** The fungal pathogen *Aspergillus fumigatus* can cause severe and life-threatening forms of infection in immunocompromised patients. Activation of glycolysis is essential for innate immune cells to mount effective antifungal responses. In this study, we report the contribution of genetic variation in the key glycolytic activator 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) to the risk of invasive pulmonary aspergillosis (IPA) after allogeneic hematopoietic stem cell transplantation. The PFKFB3 genotype associated with increased risk of infection was correlated with an impairment of the antifungal effector functions of macrophages *in vitro* and in patients with IPA. This work highlights the clinical relevance of genetic variation in PFKFB3 to the risk of IPA and supports its integration in risk stratification and preemptive measures for patients at high risk of IPA.

#### 121. 18F-FDG PET/CT in Patients with Vulvar and Vaginal Cancer: A Preliminary Study of 20 Cases.

*Gouveia, P, Sa Pinto, A, Violante, L, Nunes, S, Teixeira, R, Petiz, A and Duarte, LH. Acta Med Port. 2021 [IF: 1.141]*

**INTRODUCTION:** Despite the growing evidence supporting the use of 2-[F-18]-fluor-2-desoxy-D-glucose positron emission tomography/computed tomography in cervical and ovarian malignant tumours, data on vulvar and vaginal cancer is sparse. Our aim was to assess the role of 2-[F-18]-fluor-2-desoxy-D-glucose positron emission tomography/computed tomography in patients with vulvar and vaginal cancer.

**MATERIAL AND METHODS:** A retrospective study was conducted on a cohort of 20 patients with biopsy-proven vulvar ( $n = 17$ ) and vaginal ( $n = 3$ ) cancer who performed 2-[F-18]-fluor-2-desoxy-D-glucose positron emission tomography/computed tomography, between January 2013 and April 2018. We collected the clinical data of all patients, as well as the indication for 2-[F-18]-fluor-2-desoxy-D-glucose positron emission tomography/computed tomography, its results, and the main lesion maximum standard uptake value (SUV<sub>max</sub>). In addition, we correlated the results of 2-[F-18]-fluor-2-desoxy-D-glucose positron emission

tomography/computed tomography with other diagnostic modalities, namely histological findings, computed tomography and magnetic resonance imaging. Patients were divided into two groups, one with newly diagnosed disease and another with recurrent disease. RESULTS: Six patients had newly diagnosed disease and 14 had recurrent disease. The main lesion was detected by 2-[F-18]-fluor-2-desoxy-D-glucose positron emission tomography/computed tomography in five out of six patients with newly diagnosed disease and in all 14 patients with recurrent disease. Additional sites of 2-[F-18]-fluor-2-desoxy-D-glucose uptake were identified in inguinal and iliac lymph nodes and in distant lesions. Magnetic resonance imaging and computed tomography were performed in 12 cases. In four patients with recurrent disease, abnormalities (main lesion/ metastatic lymph nodes) identified by 2-[F-18]-fluor-2-desoxy-D-glucose positron emission tomography/computed tomography were not detected as suspicious by computed tomography. DISCUSSION: In our study, 2-[F-18]-fluor-2-desoxy-D-glucose positron emission tomography/computed tomography identified abnormalities more often than conventional computed tomography scans in recurrent disease. In comparison with histology, 2-[F-18]-fluor-2-desoxy-D-glucose positron emission tomography/computed tomography had a sensitivity of 95% and a positive predictive value of 100% in identifying the primary tumour and the recurrent main lesion. Little data is available regarding the usefulness of 2-[F-18]-fluor-2-desoxy-D-glucose positron emission tomography/computed tomography in the management of vulvar and vaginal cancers. The existing evidence supports a high accuracy in detecting lymph node metastases and a change of 36.0% - 61.5% in patient management. Our findings reinforce the usefulness of this technique in vulvar and vaginal cancer. Limitations of our study include its retrospective nature and the rareness of both vulvar and vaginal cancer, which leads to a small sample size and few comparative imaging tests. CONCLUSION: In this preliminary study, 2-[F-18]-fluor-2-desoxy-D-glucose positron emission tomography/computed tomography demonstrated it can be a useful method in patients with vulvar and vaginal cancers, namely in defining the extent of disease and contributing to accurate staging and restaging.

#### **122. Endoscopic diagnosis and management of nonvariceal upper gastrointestinal hemorrhage (NVUGIH): European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Update 2021.**

*Gralnek, IM, Stanley, AJ, Morris, AJ, Camus, M, Lau, J, Lanas, A, Laursen, SB, Radaelli, F, Papanikolaou, IS, Curdia Goncalves, T, Dinis-Ribeiro, M, Awadie, H, Braun, G, de Groot, N, Udd, M, Sanchez-Yague, A, Neeman, Z and van Hooft, JE. Endoscopy. 2021;53(3):300-32 [IF: 10.093]*

1: ESGE recommends in patients with acute upper gastrointestinal hemorrhage (UGIH) the use of the Glasgow-Blatchford Score (GBS) for pre-endoscopy risk stratification. Patients with GBS  $\leq$  1 are at very low risk of rebleeding, mortality within 30 days, or needing hospital-based intervention and can be safely managed as outpatients with outpatient endoscopy. Strong recommendation, moderate quality evidence. 2: ESGE recommends that in patients with acute UGIH who are taking low-dose aspirin as monotherapy for secondary cardiovascular prophylaxis, aspirin should not be interrupted. If for any reason it is interrupted, aspirin should be re-started as soon as possible, preferably within 3-5 days. Strong recommendation, moderate quality evidence. 3: ESGE recommends that following hemodynamic resuscitation, early ( $\leq$  24 hours) upper gastrointestinal (GI) endoscopy should be performed. Strong recommendation, high quality evidence. 4: ESGE does not recommend urgent ( $\leq$  12 hours) upper GI endoscopy since as compared to early endoscopy, patient outcomes are not improved. Strong recommendation, high quality evidence. 5: ESGE recommends for patients with actively bleeding ulcers (Fla, Flb), combination therapy using epinephrine injection plus a second hemostasis modality (contact thermal or mechanical therapy). Strong recommendation, high quality evidence. 6: ESGE recommends for patients with an ulcer with a nonbleeding visible vessel (FlIa), contact or noncontact thermal therapy, mechanical therapy, or injection of a sclerosing agent, each as monotherapy or in combination with epinephrine injection. Strong recommendation, high quality evidence. 7 : ESGE suggests that in patients with persistent bleeding refractory to standard hemostasis modalities, the use of a topical hemostatic spray/powder or cap-mounted clip should be considered. Weak recommendation, low quality evidence. 8: ESGE recommends that for patients with clinical evidence of recurrent peptic ulcer hemorrhage, use of a cap-mounted clip should be considered. In the case of failure of this second attempt at endoscopic hemostasis, transcatheter angiographic embolization (TAE) should be considered. Surgery is indicated when TAE is not locally available or after failed TAE. Strong recommendation, moderate quality evidence. 9: ESGE recommends high dose proton

pump inhibitor (PPI) therapy for patients who receive endoscopic hemostasis and for patients with FIIb ulcer stigmata (adherent clot) not treated endoscopically. (A): PPI therapy should be administered as an intravenous bolus followed by continuous infusion (e. g., 80 mg then 8 mg/hour) for 72 hours post endoscopy. (B): High dose PPI therapies given as intravenous bolus dosing (twice-daily) or in oral formulation (twice-daily) can be considered as alternative regimens. Strong recommendation, high quality evidence. 10: ESGE recommends that in patients who require ongoing anticoagulation therapy following acute NVUGIH (e. g., peptic ulcer hemorrhage), anticoagulation should be resumed as soon as the bleeding has been controlled, preferably within or soon after 7 days of the bleeding event, based on thromboembolic risk. The rapid onset of action of direct oral anticoagulants (DOACS), as compared to vitamin K antagonists (VKAs), must be considered in this context. Strong recommendation, low quality evidence.

### 123. Mixed medullary-papillary thyroid carcinoma with mixed lymph node metastases: A case report.

*Guerreiro, V, Costa, C, Oliveira, J, Santos, AP, Farinha, M, Jacome, M, Freitas, P, Carvalho, D and Torres, I. Clin Case Rep. 2021;9(5):e04165 [IF: NA]*

Mixed medullary-follicular-derived carcinoma is a very rare event. It is extremely important to make the correct diagnosis, due to prognostic and treatment implications. A genetic study of these patients is advisable to exclude the presence of MEN 2.

### 124. Adequate magnesium level as an associated factor of pre-diabetes and diabetes mellitus remission in patients with obesity submitted to bariatric surgery.

*Guerreiro, V, Maia, I, Neves, JS, Salazar, D, Ferreira, MJ, Mendonca, F, Silva, MM, Viana, S, Costa, C, Pedro, J, Varela, A, Lau, E, Freitas, P and Carvalho, D. Sci Rep. 2021;11(1):21223 [IF: 4.379]*

Bariatric surgery (BS) can lead to remission of type 2 diabetes mellitus (T2DM), however, the evidence on the influence of preoperative serum magnesium levels on this reversal is scarce. To study the influence of preoperative serum magnesium levels on the pre-T2DM and T2DM remission one year after BS. Retrospective study carried out among 1656 patients with obesity who underwent BS in the Centro Hospitalar Universitario Sao Joao. T2DM and pre-T2DM remission were defined as being normal glycaemic measures of at least one year's after BS and without pharmacological therapy. To assess the association between preoperative serum magnesium levels and pre- and T2DM remission, logistic regression models, crude and adjusted for sex, age and body mass index were computed. Patients with normoglycaemia presented hypomagnesaemia less often than those patients with pre-T2DM and T2DM (17.0% vs. 21.3% vs. 39.9%) ( $p < 0.001$ ). One year after BS, 62.9% of patients with pre-T2DM or T2DM before BS showed remission. Adequate magnesium levels were positively associated with T2DM and pre-T2DM remission, one year after BS (OR 1.79; 95% CI 1.34-2.38), independently of sex, age, and body mass index. Adequate preoperative serum magnesium levels showed to be an important clinical parameter for pre-T2DM and T2DM remission.

### 125. Deregulation of N6-Methyladenosine RNA Modification and Its Erasers FTO/ALKBH5 among the Main Renal Cell Tumor Subtypes.

*Guimaraes-Teixeira, C, Barros-Silva, D, Lobo, J, Soares-Fernandes, D, Constancio, V, Leite-Silva, P, Silva-Santos, R, Braga, I, Henrique, R, Miranda-Goncalves, V and Jeronimo, C. J Pers Med. 2021;11(10)(1) [IF: 4.945]*

Background: Methylation of N(6)-adenosine (m(6)A) is the most abundant messenger RNA (mRNA) modification in eukaryotes. We assessed the expression profiles of m(6)A regulatory proteins in renal cell carcinoma (RCC) and their clinical relevance, namely, as potential biomarkers. (2) Methods: In silico analysis of The Cancer Genome Atlas (TCGA) dataset was used for evaluating the expression of the m(6)A regulatory proteins among RCC subtypes and select the most promising candidates for further validation. ALKBH5 and FTO transcript and protein expression were evaluated in a series of primary RCC (n = 120) and 40 oncocytomas selected at IPO Porto. (3) Results: In silico analysis of TCGA dataset disclosed altered expression of the major m(6)A demethylases among RCC subtypes, particularly FTO and ALKBH5. Furthermore, decreased FTO mRNA levels associated with poor prognosis in ccRCC and pRCC. In IPO Porto's cohort, FTO and ALKBH5 transcript levels discriminated ccRCC from oncocytomas. Furthermore, FTO and

ALKBH5 immunoexpression differed among RCC subtypes, with higher expression levels found in ccRCC comparatively to the other RCC subtypes and oncocytomas. (4) Conclusion: We conclude that altered expression of m(6)A RNA demethylases is common in RCC and seems to be subtype specific. Specifically, FTO and ALKBH5 might constitute new candidate biomarkers for RCC patient management, aiding in differential diagnosis of renal masses and prognostication.

#### 126. Cancer Mechanisms and Emerging Therapies.

*Gulei, D, Indini, A, Jeronimo, C, Iuga, CA and Grossi, F. Pharmaceuticals. 2021;13(7) [IF: 6.321]*

Over the last decades, cancer has become one of the most relevant health issues at a worldwide level [...].

#### 127. Quality of Life With Pembrolizumab for Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinoma: KEYNOTE-040.

*Harrington, KJ, Soulieres, D, Le Tourneau, C, Dinis, J, Licitra, LF, Ahn, MJ, Soria, A, Machiels, JH, Mach, N, Mehra, R, Burtness, B, Ellison, MC, Cheng, JD, Chirovsky, DR, Swaby, RF and Cohen, EEW. J Natl Cancer Inst. 2021;113(2):171-81 [IF: 13.506]*

BACKGROUND: Head and neck squamous cell carcinoma (HNSCC) affects health-related quality of life (HRQoL); few treatments have demonstrated clinically meaningful HRQoL benefit. KEYNOTE-040 evaluated pembrolizumab vs standard of care (SOC) in patients with recurrent and/or metastatic HNSCC whose disease recurred or progressed after platinum-containing regimen. METHODS: Patients received pembrolizumab 200 mg or SOC (methotrexate, docetaxel, or cetuximab). Exploratory HRQoL analyses used European Organisation for Research and Treatment of Cancer (EORTC) 30 quality-of-life, EORTC 35-question quality-of-life head and neck cancer-specific module, and EuroQoL 5-dimensions questionnaires. RESULTS: The HRQoL population comprised 469 patients (pembrolizumab = 241, SOC = 228). HRQoL compliance for patients in the study at week 15 was 75.3% (116 of 154) for pembrolizumab and 74.6% (85 of 114) for SOC. The median time to deterioration in global health status (GHS) and QoL scores were 4.8 months with pembrolizumab and 2.8 months with SOC (hazard ratio = 0.79, 95% confidence interval [CI] = 0.59 to 1.05). At week 15, GHS / QoL scores were stable for pembrolizumab (least squares mean [LSM] = 0.39, 95% CI = -3.00 to 3.78) but worsened for SOC (LSM = -5.86, 95% CI = -9.68 to -2.04); the LSM between-group difference was 6.25 points (95% CI = 1.32 to 11.18; nominal 2-sided P = .01). A greater difference in the LSM for GHS / QoL score occurred with pembrolizumab vs docetaxel (10.23, 95% CI = 3.15 to 17.30) compared with pembrolizumab vs methotrexate (6.21, 95% CI = -4.57 to 16.99) or pembrolizumab vs cetuximab (-1.44, 95% CI = -11.43 to 8.56). Pembrolizumab-treated patients had stable functioning and symptoms at week 15, with no notable differences from SOC. CONCLUSIONS: GHS / QoL scores were stable with pembrolizumab but declined with SOC in patients at week 15, supporting the clinically meaningful benefit of pembrolizumab in recurrent and/or metastatic HNSCC.

#### 128. Bone sarcoma: success through interdisciplinary collaboration.

*Hecker-Nolting, S, Maia Ferreira, A and Bielack, SS. J Child Orthop. 2021;15(4):331-6 [IF: 1.548]*

Purpose: Osteosarcoma and Ewing sarcoma are the most frequent malignant bone tumours of childhood and adolescence. This review summarizes the oncologist's view of these diseases and their treatment. Methods: A non-systematic literature review was performed, the personal impressions and experience of the authors is described. Results: Local therapy and chemotherapy, each on their own, will not cure patients with malignant bone sarcomas. Together, they present a highly efficacious combination. While the most effective drugs were defined decades ago, progress since then has been limited. It is hoped that substances shown to be active in relapsed disease will be forwarded into even more efficacious frontline treatments. Good palliative therapy is necessary when cure is no longer an option. Conclusion: Close interdisciplinary collaboration is the key to successful treatment of bone sarcomas in paediatric patients.

#### 129. Avapritinib in unresectable or metastatic gastrointestinal stromal tumor with PDGFRA exon 18 mutation: safety and efficacy.

*Henriques-Abreu, M and Serrano, C. Expert Rev Anticancer Ther. 2021;21(10):1081-8 [IF: 4.512]*

INTRODUCTION: Avapritinib (formerly known as BLU-285) is an orally available type I tyrosine kinase inhibitor that, in 2020, obtained regulatory approval for the treatment of patients with gastrointestinal

stromal tumors (GISTs) harboring a primary mutation in PDGFRA exon 18, including the PDGFRA D842V mutation. AREAS COVERED: Herein, we comprehensively review the available efficacy and safety data on avapritinib, with the final goal of providing practical knowledge to both sarcoma and community-based oncologists for the correct management of this rare GIST subpopulation with this novel therapy. EXPERT OPINION: The approval of avapritinib in GIST is a milestone in precision oncology, as this is the first agent ever demonstrating unequivocal antitumoral activity in GIST driven by the multi-resistant PDGFRA D842V mutation. The safety profile is manageable and tolerability-guided dose adjustment is recommended to manage treatment-related adverse events without compromising efficacy. Based on its unprecedented activity, avapritinib should be considered as first-line therapy for GIST patients harboring this mutation. We strongly recommend to determine KIT/PDGFRA genotype in order to identify the different GIST molecular subtypes and guide treatment decision.

### 130. Polygenic hazard score is associated with prostate cancer in multi-ethnic populations.

Huynh-Le, MP, Fan, CC, Karunamuni, R, Thompson, WK, Martinez, ME, Eeles, RA, Kote-Jarai, Z, Muir, K, Schleutker, J, Pashayan, N, Batra, J, Gronberg, H, Neal, DE, Donovan, JL, Hamdy, FC, Martin, RM, Nielsen, SF, Nordestgaard, BG, Wiklund, F, Tangen, CM, Giles, GG, Wolk, A, Albanes, D, Travis, RC, Blot, WJ, Zheng, W, Sanderson, M, Stanford, JL, Mucci, LA, West, CML, Kibel, AS, Cussenot, O, Berndt, SI, Koutros, S, Sorensen, KD, Cybulski, C, Grindedal, EM, Menegaux, F, Khaw, KT, Park, JY, Ingles, SA, Maier, C, Hamilton, RJ, Thibodeau, SN, Rosenstein, BS, Lu, YJ, Watya, S, Vega, A, Kogevinas, M, Penney, KL, Huff, C, Teixeira, MR, Multigner, L, Leach, RJ, Cannon-Albright, L, Brenner, H, John, EM, Kaneva, R, Logothetis, CJ, Neuhausen, SL, De Ruyck, K, Pandha, H, Razack, A, Newcomb, LF, Fowke, JH, Gamulin, M, Usmani, N, Claessens, F, Gago-Dominguez, M, Townsend, PA, Bush, WS, Roobol, MJ, Parent, ME, Hu, JJ, Mills, IG, Andreassen, OA, Dale, AM, Seibert, TM, collaborators, U, Apcb, Investigators, N-LP, Committee, ISS, Collaborators, Canary, PI, Profile Study Steering, C and Consortium, P. *Nat Commun.* 2021;12(1):1236 [IF: 14.919]

Genetic models for cancer have been evaluated using almost exclusively European data, which could exacerbate health disparities. A polygenic hazard score (PHS1) is associated with age at prostate cancer diagnosis and improves screening accuracy in Europeans. Here, we evaluate performance of PHS2 (PHS1, adapted for OncoArray) in a multi-ethnic dataset of 80,491 men (49,916 cases, 30,575 controls). PHS2 is associated with age at diagnosis of any and aggressive (Gleason score  $\geq 7$ , stage T3-T4, PSA  $\geq 10$  ng/mL, or nodal/distant metastasis) cancer and prostate-cancer-specific death. Associations with cancer are significant within European ( $n = 71,856$ ), Asian ( $n = 2,382$ ), and African ( $n = 6,253$ ) genetic ancestries ( $p < 10^{-180}$ ). Comparing the 80(th)/20(th) PHS2 percentiles, hazard ratios for prostate cancer, aggressive cancer, and prostate-cancer-specific death are 5.32, 5.88, and 5.68, respectively. Within European, Asian, and African ancestries, hazard ratios for prostate cancer are: 5.54, 4.49, and 2.54, respectively. PHS2 risk-stratifies men for any, aggressive, and fatal prostate cancer in a multi-ethnic dataset.

### 131. Curriculum for ERCP and endoscopic ultrasound training in Europe: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement.

Johnson, G, Webster, G, Boskoski, I, Campos, S, Golder, SK, Schlag, C, Anderloni, A, Arnelo, U, Badaoui, A, Bekkali, N, Christodoulou, D, Czako, L, Fernandez, YVM, Hritz, I, Hucl, T, Kalaitzakis, E, Kylanpaa, L, Nedoluzhko, I, Petrone, MC, Poley, JW, Seicean, A, Vila, J, Arvanitakis, M, Dinis-Ribeiro, M, Ponchon, T and Bisschops, R. *Endoscopy.* 2021;53(10):1071-87 [IF: 10.093]

The European Society of Gastrointestinal Endoscopy (ESGE) has recognized the need to formalize and enhance training in endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS). This manuscript represents the outcome of a formal Delphi process resulting in an official Position Statement of the ESGE and provides a framework to develop and maintain skills in ERCP and EUS. This curriculum is set out in terms of the prerequisites prior to training; recommended steps of training to a defined syllabus; the quality of training; and how competence should be defined and evidenced before independent practice. 1: Trainees should be competent in gastroscopy prior to commencing training. Formal training courses and the use of simulation in training are recommended. 2: Trainees should keep a contemporaneous logbook of their procedures, including key performance indicators and the degree of independence. Structured formative assessment is encouraged to enhance feedback. There should be a summative assessment process prior to commencing independent practice to ensure there is robust

evidence of competence. This evidence should include a review of a trainee's procedure volume and current performance measures. A period of mentoring is strongly recommended in the early stages of independent practice. 3: Specifically for ERCP, all trainees should be competent up to Schutz level 2 complexity (management of distal biliary strictures and stones > 10 mm), with advanced ERCP requiring a further period of training. Prior to independent practice, ESGE recommends that a trainee can evidence a procedure volume of > 300 cases, a native papilla cannulation rate of  $\geq 80\%$  (90% after a period of mentored independent practice), complete stones clearance of  $\geq 85\%$ , and successful stenting of distal biliary strictures of  $\geq 90\%$  (90% and 95% respectively after a mentored period of independent practice). 4: The progression of EUS training and competence attainment should start from diagnostic EUS and then proceed to basic therapeutic EUS, and finally to advanced therapeutic EUS. Before independent practice, ESGE recommends that a trainee can evidence a procedure volume of > 250 cases (75 fine-needle aspirations/biopsies [FNA/FNBs]), satisfactory visualization of key anatomical landmarks in  $\geq 90\%$  of cases, and an FNA/FNB accuracy rate of  $\geq 85\%$ . ESGE recognizes the often inadequate quality of the evidence and the need for further studies pertaining to training in advanced endoscopy, particularly in relation to therapeutic EUS.

### 132. [Consensus on HPV of the Portuguese Society of Andrology, Sexual Medicine and Reproduction: Treatment].

*Jorge Pereira, B, Graca, B, Palmas, A, Eufrazio, P, Lebre, A, Andrade, P, Louro, N, Azinhais, P, Cardoso, P, Tomada, N and Vendeira, P. Rev Int Androl. 2021;19(3):150-9 [IF: 1.063]*

The treatment of condyloma is generally a challenge in clinical practice. Although the spontaneous resolution rate is high, a significant proportion of patients seek treatment, not because of symptomatology, but mainly for aesthetic issues and concerns related to the transmission or worsening of existing lesions. The available treatments should be applied only for clinically evident macroscopic lesions. Ideally, available therapies should have rapid action onset and clearance, resolve symptoms, reduce recurrence rate and viral load, be effective in treating small lesions, and be well tolerated. However, none of the currently available treatments is clearly more effective than the others and there is no ideal treatment for all patients or for all condyloma. Therefore, the therapeutic decision should be based on the clinician's experience, available resources, lesion morphology, size, number and location, primary or recurrent lesions, disease severity, patient preference and expectations, patient's immune competence, convenience, tolerance, cost of treatment and results of previous therapies. The available treatments are divided into three groups: applied by the patient himself (imiquimod 3.75 or 5%, podophyllotoxin .5%, synecatekines 10% or 15%), applied by the health care provider (bi- and tricloacetic acids 80%-90%, intralesional interferon alpha, cryotherapy, surgical removal, electrofulguration, laser ablation) and experimental or alternative therapies (topical cidofovir, intralesional bleomycin, photodynamic therapy). Treatment methodologies can be further divided into their action - ablative or destructive treatment (cryotherapy, electrofulguration, laser ablation, surgical excision), cytotoxic or proapoptotic treatments (podophyllotoxin .5%, 5-fluoruracil, bleomycin) and immunomodulatory treatments (imiquimod 3.75% or 5%, synecatekines 10% or 15%, intralesional interferon alpha). The overall success rate of the various treatments available ranges from 23% to 94%. Only treatments that include cryotherapy or surgical excision are suitable in condyloma with any anatomical location and that have the highest success rate in monotherapy. Recurrences are common regardless of the treatment received. In contrast, immunomodulatory therapies despite having lower initial clearance rates appear to have higher probabilities of cure in the medium term, with low recurrence rates. Some treatments may be combined with each other and the effectiveness of combined therapies appears to be superior to monotherapy (proactive sequential treatment). The consensus for the treatment of HPV also consider special situations: immunocompromised patients, meatus and intraurethral lesions and treatment of the partner.

### 133. Rare Germline Variants in ATM Predispose to Prostate Cancer: A PRACTICAL Consortium Study.

*Karlsson, Q, Brook, MN, Dadaev, T, Wakerell, S, Saunders, EJ, Muir, K, Neal, DE, Giles, GG, MacInnis, RJ, Thibodeau, SN, McDonnell, SK, Cannon-Albright, L, Teixeira, MR, Paulo, P, Cardoso, M, Huff, C, Li, D, Yao, Y, Scheet, P, Permuth, JB, Stanford, JL, Dai, JY, Ostrander, EA, Cussenot, O, Cancel-Tassin, G, Hoegel, J, Herkommer, K, Schleutker, J, Tammela, TLJ, Rathinakannan, V, Sipeky, C, Wiklund, F, Gronberg, H, Aly, M,*

Isaacs, WB, Dickinson, JL, FitzGerald, LM, Chua, MLK, Nguyen-Dumont, T, Consortium, P, Schaid, DJ, Southey, MC, Eeles, RA and Kote-Jarai, Z. *Eur Urol Oncol.* 2021;4(4):570-9 [IF: 7.479]

BACKGROUND: Germline ATM mutations are suggested to contribute to predisposition to prostate cancer (PrCa). Previous studies have had inadequate power to estimate variant effect sizes. OBJECTIVE: To precisely estimate the contribution of germline ATM mutations to PrCa risk. DESIGN, SETTING, AND PARTICIPANTS: We analysed next-generation sequencing data from 13 PRACTICAL study groups comprising 5560 cases and 3353 controls of European ancestry. OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS: Variant Call Format files were harmonised, annotated for rare ATM variants, and classified as tier 1 (likely pathogenic) or tier 2 (potentially deleterious). Associations with overall PrCa risk and clinical subtypes were estimated. RESULTS AND LIMITATIONS: PrCa risk was higher in carriers of a tier 1 germline ATM variant, with an overall odds ratio (OR) of 4.4 (95% confidence interval [CI]: 2.0-9.5). There was also evidence that PrCa cases with younger age at diagnosis (<65 yr) had elevated tier 1 variant frequencies (p-difference = 0.04). Tier 2 variants were also associated with PrCa risk, with an OR of 1.4 (95% CI: 1.1-1.7). CONCLUSIONS: Carriers of pathogenic ATM variants have an elevated risk of developing PrCa and are at an increased risk for earlier-onset disease presentation. These results provide information for counselling of men and their families. PATIENT SUMMARY: In this study, we estimated that men who inherit a likely pathogenic mutation in the ATM gene had an approximately a fourfold risk of developing prostate cancer. In addition, they are likely to develop the disease earlier.

#### 134. Additional SNPs improve risk stratification of a polygenic hazard score for prostate cancer.

Karunamuni, RA, Huynh-Le, MP, Fan, CC, Thompson, W, Eeles, RA, Kote-Jarai, Z, Muir, K, Lophatananon, A, collaborators, U, Schleutker, J, Pashayan, N, Batra, J, BioResource, A, Gronberg, H, Walsh, EI, Turner, EL, Lane, A, Martin, RM, Neal, DE, Donovan, JL, Hamdy, FC, Nordestgaard, BG, Tangen, CM, MacInnis, RJ, Wolk, A, Albanes, D, Haiman, CA, Travis, RC, Stanford, JL, Mucci, LA, West, CML, Nielsen, SF, Kibel, AS, Wiklund, F, Cussenot, O, Berndt, SI, Koutros, S, Sorensen, KD, Cybulski, C, Grindedal, EM, Park, JY, Ingles, SA, Maier, C, Hamilton, RJ, Rosenstein, BS, Vega, A, Committee, ISS, Collaborators, Kogevinas, M, Penney, KL, Teixeira, MR, Brenner, H, John, EM, Kaneva, R, Logothetis, CJ, Neuhausen, SL, Razack, A, Newcomb, LF, Canary, PI, Gamulin, M, Usmani, N, Claessens, F, Gago-Dominguez, M, Townsend, PA, Roobol, MJ, Zheng, W, Profile Study Steering, C, Mills, IG, Andreassen, OA, Dale, AM, Seibert, TM and Consortium, P. *Prostate Cancer Prostatic Dis.* 2021;24(2):532-41 [IF: 5.554]

BACKGROUND: Polygenic hazard scores (PHS) can identify individuals with increased risk of prostate cancer. We estimated the benefit of additional SNPs on performance of a previously validated PHS (PHS46). MATERIALS AND METHOD: 180 SNPs, shown to be previously associated with prostate cancer, were used to develop a PHS model in men with European ancestry. A machine-learning approach, LASSO-regularized Cox regression, was used to select SNPs and to estimate their coefficients in the training set (75,596 men). Performance of the resulting model was evaluated in the testing/validation set (6,411 men) with two metrics: (1) hazard ratios (HRs) and (2) positive predictive value (PPV) of prostate-specific antigen (PSA) testing. HRs were estimated between individuals with PHS in the top 5% to those in the middle 40% (HR95/50), top 20% to bottom 20% (HR80/20), and bottom 20% to middle 40% (HR20/50). PPV was calculated for the top 20% (PPV80) and top 5% (PPV95) of PHS as the fraction of individuals with elevated PSA that were diagnosed with clinically significant prostate cancer on biopsy. RESULTS: 166 SNPs had non-zero coefficients in the Cox model (PHS166). All HR metrics showed significant improvements for PHS166 compared to PHS46: HR95/50 increased from 3.72 to 5.09, HR80/20 increased from 6.12 to 9.45, and HR20/50 decreased from 0.41 to 0.34. By contrast, no significant differences were observed in PPV of PSA testing for clinically significant prostate cancer. CONCLUSIONS: Incorporating 120 additional SNPs (PHS166 vs PHS46) significantly improved HRs for prostate cancer, while PPV of PSA testing remained the same.

#### 135. Endoscopic submucosal dissection (ESD): how do Western endoscopists value animal models?

Kuttner-Magalhaes, R, Pimentel-Nunes, P, Araujo-Martins, M, Libanio, D, Borges-Canha, M, Marcos-Pinto, R, Koch, AD and Dinis-Ribeiro, M. *Scand J Gastroenterol.* 2021;56(4):492-7 [IF: 2.423]

INTRODUCTION: Endoscopic Submucosal Dissection (ESD) was introduced in the West later than in the East. Our aim was to assess how Western endoscopists performing ESD have been trained and how they value animal models for training. MATERIAL AND METHODS: An online survey regarding training in ESD was sent

to Western endoscopists who published articles on advanced resection techniques. RESULTS: From 279 endoscopists, 58 (21%) completed the questionnaire, of which 50 confirmed performance of clinical ESD. Endoscopists had a median of 15 years of endoscopic experience (IQR 9.75-20.25) and all of them were performing conventional EMR, before starting ESD. Prior to clinical ESD, 74% (n = 37) underwent training with ex vivo models, 84% (n = 42) with live animal models and 92% (n = 46) with at least, one of the two models. After starting clinical ESD, as trainers, 52% (n = 26) were involved with ex vivo and 60% (n = 30) with live animal models. Personal usefulness of ex vivo and live animal models was rated with a median of 9 (IQR 8-10) and 10 (IQR 8-10), out of 10, respectively. Courses with ex vivo and live animal models were considered a prerequisite before clinical practice by 84% (n = 42) and 78% (n = 39), respectively. CONCLUSIONS: Western endoscopists have extensive endoscopic experience before starting ESD. The majority had pre-clinical training with ex vivo and live animal models and more than half are acting as trainers of other endoscopists with these models. Animal models are considered very useful and deemed a prerequisite before clinical practice by the majority of the endoscopists.

**136. The predictive ability of the 313 variant-based polygenic risk score for contralateral breast cancer risk prediction in women of European ancestry with a heterozygous BRCA1 or BRCA2 pathogenic variant.**

Lakeman, IMM, van den Broek, AJ, Vos, JAM, Barnes, DR, Adlard, J, Andrulis, IL, Arason, A, Arnold, N, Arun, BK, Balmana, J, Barrowdale, D, Benitez, J, Borg, A, Caldes, T, Caligo, MA, Chung, WK, Claes, KBM, Collaborators, GS, Collaborators, E, Collee, JM, Couch, FJ, Daly, MB, Dennis, J, Dhawan, M, Domchek, SM, Eeles, R, Engel, C, Evans, DG, Feliubadalo, L, Foretova, L, Friedman, E, Frost, D, Ganz, PA, Garber, J, Gayther, SA, Gerdes, AM, Godwin, AK, Goldgar, DE, Hahnen, E, Hake, CR, Hamann, U, Hogervorst, FBL, Hooning, MJ, Hopper, JL, Hulick, PJ, Imyanitov, EN, Investigators, O, Investigators, H, KconFab, I, Isaacs, C, Izatt, L, Jakubowska, A, James, PA, Janavicius, R, Jensen, UB, Jiao, Y, John, EM, Joseph, V, Karlan, BY, Kets, CM, Konstantopoulou, I, Kwong, A, Legrand, C, Leslie, G, Lesueur, F, Loud, JT, Lubinski, J, Manoukian, S, McGuffog, L, Miller, A, Gomes, DM, Montagna, M, Mouret-Fourme, E, Nathanson, KL, Neuhausen, SL, Nevanlinna, H, Yie, JNY, Olah, E, Olopade, OI, Park, SK, Parsons, MT, Peterlongo, P, Piedmonte, M, Radice, P, Rantala, J, Rennert, G, Risch, HA, Schmutzler, RK, Sharma, P, Simard, J, Singer, CF, Stadler, Z, Stoppa-Lyonnet, D, Sutter, C, Tan, YY, Teixeira, MR, Teo, SH, Teule, A, Thomassen, M, Thull, DL, Tischkowitz, M, Toland, AE, Tung, N, van Rensburg, EJ, Vega, A, Wappenschmidt, B, Devilee, P, van Asperen, CJ, Bernstein, JL, Offit, K, Easton, DF, Rookus, MA, Chenevix-Trench, G, Antoniou, AC, Robson, M and Schmidt, MK. *Genet Med.* 2021;23(9):1726-37 [IF: 8.822]

PURPOSE: To evaluate the association between a previously published 313 variant-based breast cancer (BC) polygenic risk score (PRS313) and contralateral breast cancer (CBC) risk, in BRCA1 and BRCA2 pathogenic variant heterozygotes. METHODS: We included women of European ancestry with a prevalent first primary invasive BC (BRCA1 = 6,591 with 1,402 prevalent CBC cases; BRCA2 = 4,208 with 647 prevalent CBC cases) from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA), a large international retrospective series. Cox regression analysis was performed to assess the association between overall and ER-specific PRS313 and CBC risk. RESULTS: For BRCA1 heterozygotes the estrogen receptor (ER)-negative PRS313 showed the largest association with CBC risk, hazard ratio (HR) per SD = 1.12, 95% confidence interval (CI) (1.06-1.18), C-index = 0.53; for BRCA2 heterozygotes, this was the ER-positive PRS313, HR = 1.15, 95% CI (1.07-1.25), C-index = 0.57. Adjusting for family history, age at diagnosis, treatment, or pathological characteristics for the first BC did not change association effect sizes. For women developing first BC < age 40 years, the cumulative PRS313 5th and 95th percentile 10-year CBC risks were 22% and 32% for BRCA1 and 13% and 23% for BRCA2 heterozygotes, respectively. CONCLUSION: The PRS313 can be used to refine individual CBC risks for BRCA1/2 heterozygotes of European ancestry, however the PRS313 needs to be considered in the context of a multifactorial risk model to evaluate whether it might influence clinical decision-making.

**137. Trimodality approach, using modern radiation techniques, for management of locally advanced adrenocortical carcinoma – case report.**

Laranja, A and Ferreira, C. *Journal of Radiotherapy in Practice.* 2021:1-4 [IF:NA]

Background: Adrenocortical carcinoma (ACC) is a rare and aggressive malignancy. Surgery is the mainstay of treatment, still even after a R0 surgical margins, there is a high risk of recurrence. Case Presentation: A 26-

year-old female diagnosed with a large functioning ACC treated with a trimodality approach (surgery, radiotherapy and chemotherapy). Postoperative radiotherapy was proposed regarding the high risk of recurrence. A dose of 50.4 Gy in 28 fractions was delivered to the patient using a volumetric-modulated arc therapy plan. Radiotherapy was safe and well tolerated, and no local recurrence was observed so far (13 months after radiotherapy). Conclusions: Due to the rarity of ACC and the lack of evidence regarding this entity, therapeutic approach can be challenging. Recent evidence suggests that radiotherapy could have an important role in the therapeutic arsenal.

**138. Efficacy and safety of oral panobinostat plus subcutaneous bortezomib and oral dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma (PANORAMA 3): an open-label, randomised, phase 2 study.**

*Laubach, JP, Schjesvold, F, Mariz, M, Dimopoulos, MA, Lech-Maranda, E, Spicka, I, Hungria, VTM, Shelekhova, T, Abdo, A, Jacobasch, L, Polprasert, C, Hajek, R, Illes, A, Wrobel, T, Sureda, A, Beksac, M, Goncalves, IZ, Blade, J, Rajkumar, SV, Chari, A, Lonial, S, Spencer, A, Maison-Blanche, P, Moreau, P, San-Miguel, JF and Richardson, PG. Lancet Oncol. 2021;22(1):142-54 [IF: 41.316]*

**BACKGROUND:** Improved therapeutic options are needed for patients with relapsed or relapsed and refractory multiple myeloma. Subcutaneous bortezomib has replaced intravenous bortezomib as it is associated with a more favourable toxicity profile. We investigated the activity and safety of three different dosing regimens of oral panobinostat in combination with subcutaneous bortezomib and oral dexamethasone for this indication. **METHODS:** PANORAMA 3 is an open-label, randomised, phase 2 study being done at 71 sites (hospitals and medical centres) across 21 countries. Patients aged 18 years or older with relapsed or relapsed and refractory multiple myeloma (as per International Myeloma Working Group 2014 criteria), who had received one to four previous lines of therapy (including an immunomodulatory agent), and had an Eastern Cooperative Oncology Group performance status of 2 or lower, were randomly assigned (1:1:1) to receive oral panobinostat 20 mg three times weekly, 20 mg twice weekly, or 10 mg three times weekly, plus subcutaneous bortezomib and oral dexamethasone. All study drugs were administered in 21-day cycles. Randomisation was done by an interactive response technology provider, and stratified by number of previous treatment lines and age. The primary endpoint was overall response rate after up to eight treatment cycles (analysed in all randomly assigned patients by intention to treat). Safety analyses included all patients who received at least one dose of any study drug. No statistical comparisons between groups were planned. This trial is ongoing and registered with ClinicalTrials.gov, NCT02654990. **FINDINGS:** Between April 27, 2016, and Jan 17, 2019, 248 patients were randomly assigned (82 to panobinostat 20 mg three times weekly, 83 to panobinostat 20 mg twice weekly, and 83 to 10 mg panobinostat three times weekly). Median duration of follow-up across all treatment groups was 14.7 months (IQR 7.8-24.1). The overall response rate after up to eight treatment cycles was 62.2% (95% CI 50.8-72.7; 51 of 82 patients) for the 20 mg three times weekly group, 65.1% (53.8-75.2; 54 of 83 patients) for the 20 mg twice weekly group, and 50.6% (39.4-61.8; 42 of 83 patients) for the 10 mg three times weekly group. Grade 3-4 adverse events occurred in 71 (91%) of 78 patients in the 20 mg three times weekly group, 69 (83%) of 83 patients in the 20 mg twice weekly group, and 60 (75%) of 80 patients in the 10 mg three times weekly group; the most common ( $\geq 20\%$  patients in any group) grade 3-4 adverse events were thrombocytopenia (33 [42%] of 78, 26 [31%] of 83, and 19 [24%] of 83 patients) and neutropenia (18 [23%], 13 [16%], and six [8%]). Serious adverse events occurred in 42 (54%) of 78 patients in the 20 mg three times weekly group, 40 (48%) of 83 patients in the 20 mg twice weekly group, and 35 (44%) of 83 patients in the 10 mg three times weekly group; the most common serious adverse event ( $\geq 10\%$  patients in any group) was pneumonia (nine [12%] of 78, ten [12%] of 83, and nine [11%] of 80 patients). There were 14 deaths during the study (five [6%] of 78 patients in the 20 mg three times weekly group, three [4%] of 83 in the 20 mg twice weekly group, and six [8%] of 80 in the 10 mg three times weekly group); none of these deaths was deemed treatment related. **INTERPRETATION:** The safety profile of panobinostat 20 mg three times weekly was more favourable than in previous trials of this regimen with intravenous bortezomib, suggesting that subcutaneous bortezomib improves the tolerability of the panobinostat plus bortezomib plus dexamethasone regimen. The overall response rate was highest in the 20 mg three times weekly and 20 mg twice weekly groups, with 10 mg three times weekly best tolerated. **FUNDING:** Novartis Pharmaceuticals and Secura Bio.

### 139. Breast Cancer Metastasis in a Renal Carcinoma Pulmonary Metastasis: A Rare Example of Tumor-to-Tumor Metastasis.

*Lima, A, Peixoto, I, Sarandao, S, Melo, D, Rodrigues, A and Pereira, H. Case Rep Oncol Med. 2021;2021:3054232 [IF: NA]*

The tumor-to-tumor metastasis phenomenon remains fairly uncommon, with fewer than 100 cases described to present time. Virtually any tumor can be a donor or a recipient neoplasm. Nevertheless, renal carcinomas have been implicated as the most common malignant tumors to harbor metastasis, while lung and breast tumors are the most frequent donors. This article reports an extremely rare case of a breast cancer metastasis in a lung metastasis of clear cell type renal cell carcinoma that met all Campbell and coworkers' tumor-to-tumor metastasis criteria. Additionally, we present the literature case reports of breast cancer metastasis in renal cell carcinomas and try to discuss the mechanisms underlying its occurrence. Since this phenomenon identification will impact the therapeutic strategy and it is not easily detected by image, the anatomopathological study of any and all suspicious lesions is of crucial importance. To the best of our knowledge, this is the first report of a metastasis inside a metastasis.

### 140. The Impact of COVID-19 Pandemic in Portuguese Cancer Patients: A Retrospective Study.

*Lima, A, Sousa, H, Nobre, A, Faria, AL and Machado, M. Int J Environ Res Public Health. 2021;18(16) [IF: 3.390]*

Literature reports that SARS-CoV-2 infection in cancer patients may be associated with higher severity and mortality, nevertheless the knowledge is limited. We aimed to describe patients' demographic characteristics and COVID-19 disease outcomes in Portuguese cancer patients. We conducted a retrospective study in a cohort of cancer patients diagnosed with COVID-19. A total of 127 individuals were included: 46.5% males and 53.5% females, with a median age of 72 years. Clinicopathological characteristics were used in univariate and multivariable logistic regression analyses to estimate odds ratios for each variable with outcomes adjusting for potential confounders. Our cohort revealed that 84.3% of patients had more than one risk factor for severe disease rather than cancer. In total, 36.2% of patients were admitted to the Department of Internal Medicine, 14.2% developed severe disease, 1.6% required Intensive Care Unit, and mortality was observed in 11.8%. Severe COVID-19 disease was associated with unfit (ECOG PS > 2) patients ( $p = 0.009$ ; OR = 6.39; 95% CI: 1.60-25.59), chronic kidney disease ( $p = 0.004$ ; OR = 20.7; 95% CI: 2.64-162.8), immunosuppression ( $p < 0.001$ ; OR = 10.3; 95% CI: 2.58-41.2), and presence of respiratory symptoms at diagnosis ( $p = 0.033$ ; OR = 5.05; 95% CI: 1.14-22.4). Increased risk for mortality was associated with unfit patients ( $p = 0.036$ ; OR = 4.22; 95% CI: 1.10-16.3), cardiac disease ( $p = 0.003$ ; OR = 8.26; 95% CI: 2.03-33.6) and immunosuppression ( $p = 0.022$ ; OR = 5.06; 95% CI: 1.27-20.18). Our results demonstrated that unfit and immunosuppressed patients, with chronic kidney disease and cardiac disease, have, respectively, an increased risk for severe disease and mortality related to COVID-19. Hence, this study provides important information on risk factors for severe COVID-19 disease and associated mortality in a Portuguese cancer population.

### 141. Improved survival in patients with thyroid function test abnormalities secondary to immune-checkpoint inhibitors.

*Lima Ferreira, J, Costa, C, Marques, B, Castro, S, Victor, M, Oliveira, J, Santos, AP, Sampaio, IL, Duarte, H, Marques, AP and Torres, I. Cancer Immunol Immunother. 2021;70(2):299-309 [IF: 6.968]*

Immune-checkpoint inhibitors (ICI) are monoclonal antibodies which target molecules to enhance antitumor response. Several adverse events have been described and the major ICI-related endocrinopathies are thyroid dysfunction and hypophysitis. Its occurrence has been associated with improved outcomes, but it is still to be proven. We performed a retrospective study of patients treated with ICI between 2014 and 2019 at an oncologic center to characterize thyroid function test abnormalities (TFTA) and to evaluate clinical outcomes. We excluded patients without regular monitoring of thyroid function, with previous thyroid or pituitary disease, previous head/neck radiotherapy and who performed only one ICI cycle. We included 161 of 205 patients treated with pembrolizumab, nivolumab or ipilimumab for several neoplasms, with a median duration of 18.9 weeks (9.1-42.6) of ICI treatment and 49.4 weeks (26.5-75.8) of follow-up. New-onset TFTA was diagnosed in 18% of patients ( $n = 29$ ), in median at 10.6

weeks (6.1-31.1) of ICI therapy. On the whole, 8.7% had primary hypothyroidism, 4.3% central hypothyroidism, 2.5% biphasic thyroiditis and 2.5% thyrotoxicosis. Patients who experienced primary or central thyroid dysfunction had a significantly improved overall response rate (58.6% vs 34.2%,  $p = 0.015$ ) and overall survival (3.27 vs 1.76 years,  $p = 0.030$ ), compared to the control group. The risk of mortality was two times higher for control group (adjusted HR = 2.43, 95% CI 1.13-5.23,  $p = 0.023$ ). This study recognizes that primary and central thyroid dysfunction can be a predictive clinical biomarker of a better response to ICI across several neoplasms.

#### 142. Bioinformatic analysis of dysregulated proteins in prostate cancer patients reveals putative urinary biomarkers and key biological pathways.

*Lima, T, Henrique, R, Vitorino, R and Fardilha, M. Med Oncol. 2021;38(1):9 [IF: 3.064]*

Prostate cancer (PCa) is one of the most common cancer types among men. The quantification of prostate-specific antigen used for PCa detection has revealed limited applicability. Thus, it is crucial to identify new minimally invasive biomarkers for PCa. It is believed that the integration of proteomics data from different studies is vital for identifying new biomarkers for PCa, but studies carried out in this regard have few converging results. Using a different approach, this study aimed to unveil molecular features consistently dysregulated in PCa and potential urinary biomarkers for PCa. The novelty of this analysis relies on the comparison of urinary and tissue proteomes from PCa patients and consequent exclusion of kidney and bladder cancer interference. The conducted bioinformatic analysis revealed molecular processes dysregulated in urine from PCa patients that mirror the alterations in prostate tumor tissue. To identify putative urinary biomarkers, proteins previously detected in kidney and bladder tissues were eliminated from the final list of potential urinary biomarkers for PCa. After a detailed analysis, MSMB, KLK3, ITIH4, ITIH2, HPX, GP2, APOA2 and AZU1 proteins stood out as candidate urinary biomarkers for PCa.

#### 143. KLK3 SNP-SNP interactions for prediction of prostate cancer aggressiveness.

*Lin, HY, Huang, PY, Cheng, CH, Tung, HY, Fang, Z, Berglund, AE, Chen, A, French-Kwawu, J, Harris, D, Pow-Sang, J, Yamoah, K, Cleveland, JL, Awasthi, S, Rounbehler, RJ, Gerke, T, Dhillon, J, Eeles, R, Kote-Jarai, Z, Muir, K, collaborators, U, Schleutker, J, Pashayan, N, Apcb, Neal, DE, Nielsen, SF, Nordestgaard, BG, Gronberg, H, Wiklund, F, Giles, GG, Haiman, CA, Travis, RC, Stanford, JL, Kibel, AS, Cybulski, C, Khaw, KT, Maier, C, Thibodeau, SN, Teixeira, MR, Cannon-Albright, L, Brenner, H, Kaneva, R, Pandha, H, consortium, P, Srinivasan, S, Clements, J, Batra, J and Park, JY. Sci Rep. 2021;11(1):9264 [IF: 4.379]*

Risk classification for prostate cancer (PCa) aggressiveness and underlying mechanisms remain inadequate. Interactions between single nucleotide polymorphisms (SNPs) may provide a solution to fill these gaps. To identify SNP-SNP interactions in the four pathways (the angiogenesis-, mitochondria-, miRNA-, and androgen metabolism-related pathways) associated with PCa aggressiveness, we tested 8587 SNPs for 20,729 cases from the PCa consortium. We identified 3 KLK3 SNPs, and 1083 ( $P < 3.5 \times 10^{-9}$ ) and 3145 ( $P < 1 \times 10^{-5}$ ) SNP-SNP interaction pairs significantly associated with PCa aggressiveness. These SNP pairs associated with PCa aggressiveness were more significant than each of their constituent SNP individual effects. The majority (98.6%) of the 3145 pairs involved KLK3. The 3 most common gene-gene interactions were KLK3-COL4A1:COL4A2, KLK3-CDH13, and KLK3-TGFBR3. Predictions from the SNP interaction-based polygenic risk score based on 24 SNP pairs are promising. The prevalence of PCa aggressiveness was 49.8%, 21.9%, and 7.0% for the PCa cases from our cohort with the top 1%, middle 50%, and bottom 1% risk profiles. Potential biological functions of the identified KLK3 SNP-SNP interactions were supported by gene expression and protein-protein interaction results. Our findings suggest KLK3 SNP interactions may play an important role in PCa aggressiveness.

#### 144. Cytohistological correlation in serous effusions using the newly proposed International System for Reporting Serous Fluid Cytopathology: Experience of an oncological center.

*Lobo, C, Costa, J, Petronilho, S, Monteiro, P, Leca, L and Schmitt, F. Diagn Cytopathol. 2021;49(5):596-605 [IF: 1.582]*

BACKGROUND: Cytological analysis is part of the initial etiological evaluation of serous effusions. The newly proposed International System for Reporting Serous Fluid Cytopathology (ISRSFC) aims to standardize reporting. METHODS: All pleural and peritoneal effusion samples admitted for cytological analysis at our

institution between 2012 and 2016, and pericardial effusion samples admitted between 2008 and 2018, were reviewed and reclassified according to the ISRSFC. Risk of malignancy (ROM) and performance parameters were calculated. RESULTS: 1496 pleural effusion samples were reclassified: 12(0.8%) non-diagnostic (ND), 944(63.1%) negative for malignancy (NFM), 9(0.6%) atypia of undetermined significance (AUS), 54(3.6%) suspicious of malignancy (SFM) and 477(31.9%) malignant (M). 64 pericardial effusion samples were reclassified: 23(35.9%) NFM, 1(1.6%) AUS, 4(6.3%) SFM and 36(56.2%) M. 763 peritoneal effusion samples were reclassified: 5(0.7%) ND, 457(59.9%) NFM, 12(1.6%) AUS, 37(4.8%) SFM and 252(33%) M. The ROM was, respectively, for each of the aforementioned categories, 57.1%, 23.9%, 50%, 76.2%, 100% in pleural effusions, 100%, 26.3%, 62.5%, 91.7%, 100% in peritoneal effusions and 0% for NFM, 0% for AUS and 100% for M in pericardial effusions. Sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy were, respectively, 61.6%, 100%, 100%, 73.3%, 81.3% for pleural, 100%, 100%, 100%, 100% for pericardial and 61.2%, 100%, 100%, 70%, 79.7% for peritoneal effusion samples. CONCLUSION: Serous effusion cytology has a high specificity and positive predictive value and a modest sensitivity and negative predictive value, supporting its role in confirming the diagnosis of malignancy. The ISRSFC will increase standardization and reproducibility in reporting, leading to improved clinical decision-making.

#### **145. Targeting Germ Cell Tumors with the Newly Synthesized Flavanone-Derived Compound MLo1302 Efficiently Reduces Tumor Cell Viability and Induces Apoptosis and Cell Cycle Arrest.**

*Lobo, J, Cardoso, AR, Miranda-Goncalves, V, Looijenga, LHJ, Lopez, M, Arimondo, PB, Henrique, R and Jeronimo, C. *Pharmaceutics*. 2021;13(1) [IF: 6.321]*

Less toxic treatment strategies for testicular germ cell tumor (TGCT) patients are needed, as overtreatment is a concern due to the long-term side effects of platin-based chemotherapy. Although clinical benefit from classical hypomethylating agents has to date been limited, TGCTs show an abnormal DNA methylome indicating the potential of treating TGCTs with hypomethylating drugs. We tested, for the first time in TGCT cell lines, a new synthetic flavonoid compound (MLo1302) from the 3-nitroflavanone family of DNA methyltransferase (DNMT) inhibitors. We show that MLo1302 reduces cell viability (including of cisplatin resistant cell line NCCIT-R), with IC50s (inhibitory concentration 50) within the nanomolar range for NCCIT and NTERA-2 cells, and proved its cytotoxic effect. Exposure to MLo1302 reduced DNMT protein expression, similar to decitabine, and showed a partial effect in cell differentiation, reducing protein expression of pluripotency markers. RT(2) profiler expression array indicated several dysregulated targets, related to activation of apoptosis, differentiation, and cell cycle arrest. We validated these data by showing increased apoptosis, increased protein expression of cleaved caspase 8 and activated caspase 2, and reduced proliferation (BrdU assay), with increase in CDKN1A and decrease in MIB-1 expression. Therefore, synthetic drugs designed to target DNA methylation in cells may uncover effective treatments for TGCT patients.

#### **146. Promoter methylation of DNA homologous recombination genes is predictive of the responsiveness to PARP inhibitor treatment in testicular germ cell tumors.**

*Lobo, J, Constancio, V, Guimaraes-Teixeira, C, Leite-Silva, P, Miranda-Goncalves, V, Sequeira, JP, Pistoni, L, Guimaraes, R, Cantante, M, Braga, I, Mauricio, J, Looijenga, LHJ, Henrique, R and Jeronimo, C. *Mol Oncol*. 2021;15(4):846-65 [IF: 6.603]*

Testicular germ cell tumors (TGCTs) are the most common cancers in men aged 15-39 years and are divided into two major groups, seminomas and nonseminomas. Novel treatment options are required for these patients, to limit side effects of chemotherapy. We hypothesized that promoter methylation of relevant homologous recombination (HR) genes might be predictive of response to poly-ADP ribose polymerase inhibitors (PARPis) in TGCTs. We report a study pipeline combining in silico, in vitro, and clinical steps. By using several databases and in silico tools, we identified BRCA1, RAD51C, PALB2, RAD54B, and SYCP3 as the most relevant genes for further investigation and pinpointed specific CpG sites with pronounced negative correlation to gene expression. Nonseminomas displayed significantly higher methylation levels for all target genes, where increased methylation was observed in patients with more differentiated subtypes and higher disease burden. We independently performed second-line targeted validation in tissue series from TGCT patients. A moderate and/or strong anti-correlation between gene expression (assessed by RNA-

sequencing) and promoter methylation (assessed by 450k array) was found, for all of the targets. As a proof of concept, we demonstrated the sensitivity of TGCT cell lines to Olaparib, which associated with differential methylation levels of a subset of targets, namely BRCA1 and RAD51C. Our findings support the use of HR genes promoter methylation as a predictor of the therapeutic response to PARPis in patients with TGCT.

**147. Differential methylation EPIC analysis discloses cisplatin-resistance related hypermethylation and tumor-specific heterogeneity within matched primary and metastatic testicular germ cell tumor patient tissue samples.**

*Lobo, J, Constancio, V, Leite-Silva, P, Guimaraes, R, Cantante, M, Braga, I, Mauricio, J, Looijenga, LHJ, Henrique, R and Jeronimo, C. Clin Epigenetics. 2021;13(1):70 [IF: 6.551]*

Testicular germ cell tumors (TGCTs) are among the most common solid malignancies in young-adult men, and currently most mortality is due to metastatic disease and emergence of resistance to cisplatin. There is some evidence that increased methylation is one mechanism behind this resistance, stemming from individual studies, but approaches based on matched primary and metastatic patient samples are lacking. Herein, we provide an EPIC array-based study of matched primary and metastatic TGCT samples. Histology was the major determinant of overall methylation pattern, but some clustering of samples related to response to cisplatin was observed. Further differential analysis of patients with the same histological subtype (embryonal carcinoma) disclosed a remarkable increase in net methylation levels (at both promoter and CpG site level) in the patient with cisplatin-resistant disease and poor outcome compared to the patient with complete response to chemotherapy. This further confirms the recent results of another study performed on isogenic clones of sensitive and resistant TGCT cell lines. Differentially methylated promoters among groups of samples were mostly not shared, disclosing heterogeneity in patient tissue samples. Finally, gene ontology analysis of cisplatin-resistant samples indicated enrichment of differentially hypermethylated promoters on pathways related to regulation of immune microenvironment, and enrichment of differentially hypomethylated promoters on pathways related to DNA/chromatin binding and regulation. This data supports not only the use of hypomethylating agents for targeting cisplatin-resistant disease, but also their use in combination with immunotherapies and chromatin remodelers.

**148. Targeted Methylation Analyses: From Bisulfite Treatment to Quantification.**

*Lobo, J, Gillis, AJM and Looijenga, LHJ. Methods Mol Biol. 2021;2195:167-80 [IF: NA]*

DNA methylation constitutes the most studied epigenetic mechanism, regulating gene expression in several physiological and pathological states. Targeted methylation polymerase chain reaction (PCR)-based analyses are among the most universal and commonly used techniques in research. They can be of use for validating methylation-based biomarkers to include in clinical practice. Optimal execution and interpretation of data is fundamental for achieving accurate and reproducible results. In this chapter we describe the backbone procedures behind targeted methylation analyses: bisulfite conversion and downstream PCR-based techniques, including real-time quantitative methylation-specific PCR (qMSP) and high-resolution melting (HRM) methylation-sensitive analyses. Specifically, we give details about the protocol, discuss the pros and cons of these methodologies, and give practical tips for achieving optimal results and for troubleshooting.

**149. Morphological and molecular heterogeneity in testicular germ cell tumors: implications for dedicated investigations.**

*Lobo, J, Jeronimo, C and Henrique, R. Virchows Arch. 2021;479(4):865-6 [IF: 4.064]*

**150. Utility of Serum miR-371a-3p in Predicting Relapse on Surveillance in Patients with Clinical Stage I Testicular Germ Cell Cancer.**

*Lobo, J, Leao, R, Gillis, AJM, van den Berg, A, Anson-Cartwright, L, Atenafu, EG, Kuhathaas, K, Chung, P, Hansen, A, Bedard, PL, Jewett, MAS, Warde, P, O'Malley, M, Sweet, J, Looijenga, LHJ and Hamilton, RJ. Eur Urol Oncol. 2021;4(3):483-91 [IF: 7.479]*

BACKGROUND: Optimal management of clinical stage I (CSI) testicular cancer is controversial due to lack of robust prognostic factors; miRNA-371a-3p holds promise as a biomarker, although its clinical utility for

identifying patients at risk of relapse is unknown. **OBJECTIVE:** To explore the association between serum miR-371a-3p and CSI surveillance relapse. **DESIGN, SETTING, AND PARTICIPANTS:** Serial banked sera from 151 CSI (101 seminomas and 50 nonseminomatous germ cell tumors [NSGCTs]) samples from our Princess Margaret active surveillance cohort were tested. **OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS:** Using the ampTsmiR test, miR-371a-3p was assayed. Multivariate logistic regression was used to assess the association between postorchietomy miRNA and relapse. **RESULTS AND LIMITATIONS:** Thirty-four (23%) patients relapsed. There was no association between postorchietomy miR-371a-3p (2.43 vs 2.74,  $p = 0.31$ ) or percent decline from before to after orchietomy (95.8% vs 93.1%,  $p = 0.14$ ) and relapse. After adjustment for clinical prognostic factors, there remained no association between postorchietomy miR-371a-3p and relapse (seminoma: odds ratio [OR] 1.33, 95% confidence interval [CI] 0.87-2.02,  $p = 0.18$ ; NSGCT: OR 0.45, 95% CI 0.21-1.00,  $p = 0.05$ ). Postorchietomy miR-371a-3p levels rose as the date of miRNA assessment approached relapse. At relapse, serum markers alpha-fetoprotein and human chorionic gonadotropin were normal in 62%; yet, miR-371a-3p was elevated in 32/34 (94.1%). The magnitude of miR-371a-3p elevation at relapse correlated with disease burden (N1/M0 122.5 vs N2-N3/M0: 521.1;  $p = 0.05$ ). Limitations include small numbers of relapses and variable time points of serum collection. **CONCLUSIONS:** In our cohort of CSI testis cancer patients on surveillance, postorchietomy miR-371a-3p levels were not associated with relapse, suggesting that miR-371a-3p may not be a useful biomarker for guiding adjuvant therapy. Our data suggest that miR-371a-3p holds potential as an early relapse marker and warrants a prospective study, as this may allow a window for less morbid relapse therapy. **PATIENT SUMMARY:** The promising novel blood biomarker for testis cancer miR-371a-3p may not provide information at testicle removal, but serial monitoring may lead to earlier detection of relapse.

#### 151. Liquid Biopsies in the Clinical Management of Germ Cell Tumor Patients: State-of-the-Art and Future Directions.

*Lobo, J, Leao, R, Jeronimo, C and Henrique, R. Int J Mol Sci. 2021;22(5) [IF: 5.923]*

Liquid biopsies constitute a minimally invasive means of managing cancer patients, entailing early diagnosis, follow-up and prediction of response to therapy. Their use in the germ cell tumor field is invaluable since diagnostic tissue biopsies (which are invasive) are often not performed, and therefore only a presumptive diagnosis can be made, confirmed upon examination of the surgical specimen. Herein, we provide an overall review of the current liquid biopsy-based biomarkers of this disease, including the classical, routinely used serum tumor markers-the promising microRNAs rapidly approaching the introduction into clinical practice-but also cell-free DNA markers (including DNA methylation) and circulating tumor cells. Finally, and importantly, we also explore novel strategies and challenges for liquid biopsy markers and methodologies, providing a critical view of the future directions for liquid biopsy tests in this field, highlighting gaps and unanswered questions.

#### 152. The Morphological Spectrum of Papillary Renal Cell Carcinoma and Prevalence of Provisional/Emerging Renal Tumor Entities with Papillary Growth.

*Lobo, J, Ohashi, R, Helmchen, BM, Rupp, NJ, Ruschoff, JH and Moch, H. Biomedicines. 2021;9(10) [IF: 6.081]*

Renal cell carcinoma (RCC) represents a heterogeneous disease, encompassing an increasing number of tumor subtypes. Post-2016, the World Health Organization (WHO) classification recognized that the spectrum of papillary renal cell carcinoma is evolving and has long surpassed the dichotomic simplistic "type 1 versus type 2" classification. The differential diagnosis of pRCC includes several new provisional/emerging entities with papillary growth. Type 2 tumors have been cleared out of several confounding entities, now regarded as independent tumors with specific clinical and molecular backgrounds. In this work we describe the prevalence and characteristics of emerging papillary tumor entities in two renal tumor cohorts (one consisting of consecutive papillary tumors from a single institute, the other consisting of consultation cases from several centers). After a review of 154 consecutive pRCC cases, 58% remained type 1 pRCC, and 34% type 2 pRCC. Papillary renal neoplasm with reversed polarity (1.3%), biphasic hyalinizing psammomatous RCC (1.3%), and biphasic squamoid/alveolar RCC (4.5%) were rare. Among 281 consultation cases, 121 (43%) tumors had a dominant papillary growth (most frequently MiT family translocation RCCs, mucinous tubular and spindle cell carcinoma and clear cell papillary RCC). Our data confirm that the spectrum of RCCs with papillary growth represents a major diagnostical

challenge, frequently requiring a second expert opinion. Papillary renal neoplasm with reversed polarity, biphasic hyalinizing psammomatous RCC, and biphasic squamoid/alveolar RCC are rarely sent out for a second opinion, but correct classification and knowledge of these variants will improve our understanding of the clinical behavior of renal tumors with papillary growth.

**153. Combining Hypermethylated RASSF1A Detection Using ddPCR with miR-371a-3p Testing: An Improved Panel of Liquid Biopsy Biomarkers for Testicular Germ Cell Tumor Patients.**

*Lobo, J, van Zogchel, LMJ, Nuru, MG, Gillis, AJM, van der Schoot, CE, Tytgat, GAM and Looijenga, LHJ. Cancers (Basel). 2021;13(20) [IF: 6.639]*

The classical serum tumor markers used routinely in the management of testicular germ cell tumor (TGCT) patients—alpha fetoprotein (AFP) and human chorionic gonadotropin (HCG)—show important limitations. miR-371a-3p is the most recent promising biomarker for TGCTs, but it is not sufficiently informative for detection of teratoma, which is therapeutically relevant. We aimed to test the feasibility of hypermethylated RASSF1A (RASSF1AM) detected in circulating cell-free DNA as a non-invasive diagnostic marker of testicular germ cell tumors, combined with miR-371a-3p. A total of 109 serum samples of patients and 29 sera of healthy young adult males were included, along with representative cell lines and tumor tissue samples. We describe a novel droplet digital polymerase chain reaction (ddPCR) method for quantitatively assessing RASSF1AM in liquid biopsies. Both miR-371a-3p (sensitivity = 85.7%) and RASSF1AM (sensitivity = 86.7%) outperformed the combination of AFP and HCG (sensitivity = 65.5%) for TGCT diagnosis. RASSF1AM detected 88% of teratomas. In this representative cohort, 14 cases were negative for miR-371a-3p, all of which were detected by RASSF1AM, resulting in a combined sensitivity of 100%. We have described a highly sensitive and specific panel of biomarkers for TGCT patients, to be validated in the context of patient follow-up and detection of minimal residual disease.

**154. Tackling tumor microenvironment through epigenetic tools to improve cancer immunotherapy.**

*Lodewijk, I, Nunes, SP, Henrique, R, Jeronimo, C, Duenas, M and Paramio, JM. Clin Epigenetics. 2021;13(1):63 [IF: 6.551]*

**BACKGROUND:** Epigenetic alterations are known contributors to cancer development and aggressiveness. Additional to alterations in cancer cells, aberrant epigenetic marks are present in cells of the tumor microenvironment, including lymphocytes and tumor-associated macrophages, which are often overlooked but known to be a contributing factor to a favorable environment for tumor growth. Therefore, the main aim of this review is to give an overview of the epigenetic alterations affecting immune cells in the tumor microenvironment to provoke an immunosuppressive function and contribute to cancer development. Moreover, immunotherapy is briefly discussed in the context of epigenetics, describing both its combination with epigenetic drugs and the need for epigenetic biomarkers to predict response to immune checkpoint blockage. **MAIN BODY:** Combining both topics, epigenetic machinery plays a central role in generating an immunosuppressive environment for cancer growth, which creates a barrier for immunotherapy to be successful. Furthermore, epigenetic-directed compounds may not only affect cancer cells but also immune cells in the tumor microenvironment, which could be beneficial for the clinical response to immunotherapy. **CONCLUSION:** Thus, modulating epigenetics in combination with immunotherapy might be a promising therapeutic option to improve the success of this therapy. Further studies are necessary to (1) understand in depth the impact of the epigenetic machinery in the tumor microenvironment; (2) how the epigenetic machinery can be modulated according to tumor type to increase response to immunotherapy and (3) find reliable biomarkers for a better selection of patients eligible to immunotherapy.

**155. Quality of life trajectories during the first three years after diagnosis of breast cancer: the NEON-BC study.**

*Lopes-Conceicao, L, Brandao, M, Araujo, N, Severo, M, Dias, T, Peleteiro, B, Fontes, F, Pereira, S and Lunet, N. J Public Health (Oxf). 2021;43(3):521-31 [IF: 2.341]*

**BACKGROUND:** We aimed to identify and characterize quality of life trajectories up to 3 years after breast cancer diagnosis. **METHODS:** A total of 460 patients were evaluated at baseline (before treatments), and after 1- and 3-years. Patient-reported outcomes, including quality of life (European Organization for

Research and Treatment of Cancer Quality of Life Questionnaire Core 30, QLQ-C30), anxiety, depression and sleep quality, were assessed in all evaluations. Model-based clustering was used to identify quality of life trajectories. RESULTS: We identified four trajectories without intersection during 3 years. The two trajectories characterized by better quality of life depicted relatively stable scores; in the other trajectories, quality of life worsened until 1 year, though in one of them the score at 3 years improved. Sociodemographic and clinical characteristics at baseline did not differ between trajectories, except for mastectomy, which was higher in the worst trajectory. Anxiety, depression and poor sleep quality increased from the best to the worst trajectory. CONCLUSIONS: The type of surgery and the variation of other patient-reported outcomes were associated with the course of quality of life over 3 years. More research to understand the heterogeneity of individual trajectories within these major patterns of variation is needed.

**156. Quality of life trajectories in breast cancer patients: an updated analysis 5 years after diagnosis.**

*Lopes-Conceicao, L, Brandao, M, Araujo, N, Severo, M, Dias, T, Peleteiro, B, Fontes, F, Pereira, S and Lunet, N. J Public Health (Oxf). 2021;43(1):e133-e4 [IF: 2.341]*

**157. Genetic Variations in Prostaglandin E2 Pathway Identified as Susceptibility Biomarkers for Gastric Cancer in an Intermediate Risk European Country.**

*Lopes, C, Pereira, C, Farinha, M, Medeiros, R and Dinis-Ribeiro, M. Int J Mol Sci. 2021;22(2) [IF: 5.923]*

The cyclooxygenase-2 (COX-2)/prostaglandin E2 (PGE2) pathway exerts deleterious pleiotropic effects in inflammation-induced gastric carcinogenesis. We aimed to assess the association of genetic variants in prostaglandin-endoperoxide synthase 2 (PTGS2), ATP binding cassette subfamily C member 4 (ABCC4), hydroxyprostaglandin dehydrogenase 15-(NAD) (HPGD), and solute carrier organic anion transporter family member 2A1 (SLCO2A1) PGE2 pathway-related genes with gastric cancer (GC) risk in a European Caucasian population. A hospital-based case-control study gathering 260 GC cases and 476 cancer-free controls was implemented. Using a tagSNP approach, 51 single nucleotide polymorphisms (SNPs) were genotyped through MassARRAY((R)) iPLEX Gold Technology or allelic discrimination by real-time polymerase chain reaction (PCR). Homozygous carriers of the minor allele for both rs689466 and rs10935090 SNPs were associated with a 2.98 and 4.30-fold increased risk for GC, respectively (95% confidence interval (CI): 1.14-7.74,  $p = 0.027$ ; 95% CI: 1.22-15.16,  $p = 0.026$ ), with the latter also being associated with an anticipated diagnosis age. A multifactor dimensionality reduction analysis identified an overall three-factor best interactive model composed of age, rs689466, and rs1678374 that was associated with a 17.6-fold GC increased risk (95% CI: 11.67-26.48,  $p < 0.0001$ , (cross-validation) CV consistency of 8/10 and accuracy of 0.807). In this preliminary study, several tagSNPs in PGE2 pathway-related genes were identified as risk biomarkers for GC development. This approach may help to identify higher-risk individuals and may contribute to the tailoring screening of GC in intermediate-risk European countries.

**158. ASCT2 and LAT1 Contribution to the Hallmarks of Cancer: From a Molecular Perspective to Clinical Translation.**

*Lopes, C, Pereira, C and Medeiros, R. Cancers (Basel). 2021;13(2) [IF: 6.639]*

The role of the amino acid transporters ASCT2 and LAT1 in cancer has been explored throughout the years. In this review, we report their impact on the hallmarks of cancer, as well as their clinical significance. Overall, both proteins have been associated with cell death resistance through dysregulation of caspases and sustainment of proliferative signaling through mTOR activation. Furthermore, ASCT2 appears to play an important role in cellular energetics regulation, whereas LAT1 expression is associated with angiogenesis and invasion and metastasis activation. The molecular impact of these proteins on the hallmarks of cancer translates into various clinical applications and both transporters have been identified as prognostic factors in many types of cancer. Concerning their role as therapeutic targets, efforts have been undertaken to synthesize competitive or irreversible ASCT2 and LAT1 inhibitors. However, JHP203, a selective inhibitor of the latter, is, to the best of our knowledge, the only compound included in a Phase 1 clinical trial. In conclusion, considering the usefulness of ASCT2 and LAT1 in a variety of cancer-related pathways and cancer therapy/diagnosis, the development and testing of novel inhibitors for these transporters that could be evaluated in clinical trials represents a promising approach to cancer prognosis improvement.

### 159. Results of the IROCA international clinical audit in prostate cancer radiotherapy at six comprehensive cancer centres.

*Lopes de Castro, C, Fundowicz, M, Rosello, A, Jove, J, Deantonio, L, Aguiar, A, Pisani, C, Villa, S, Boladeras, A, Konstanty, E, Kruszyna-Mochalska, M, Milecki, P, Jurado-Bruggeman, D, Lencart, J, Modolell, I, Munoz-Montplet, C, Aliste, L, Torras, MG, Puigdemont, M, Carvalho, L, Krengli, M, Guedea, F and Malicki, J. Sci Rep. 2021;11(1):12323 [IF: 4.379]*

To assess adherence to standard clinical practice for the diagnosis and treatment of patients undergoing prostate cancer (PCa) radiotherapy in four European countries using clinical audits as part of the international IROCA project. Multi-institutional, retrospective cohort study of 240 randomly-selected patients treated for PCa (n = 40/centre) in the year 2015 at six European hospitals. Clinical indicators applicable to general and PCa-specific radiotherapy processes were evaluated. All data were obtained directly from medical records. The audits were performed in the year 2017. Adherence to clinical protocols and practices was satisfactory, but with substantial inter-centre variability in numerous variables, as follows: staging MRI (range 27.5-87.5% of cases); presentation to multidisciplinary tumour board (2.5-100%); time elapsed between initial visit to the radiation oncology department and treatment initiation (42-102.5 days); number of treatment interruptions  $\geq 1$  day (7.5-97.5%). The most common deviation from standard clinical practice was inconsistent data registration, mainly failure to report data related to diagnosis, treatment, and/or adverse events. This clinical audit detected substantial inter-centre variability in adherence to standard clinical practice, most notably inconsistent record keeping. These findings confirm the value of performing clinical audits to detect deviations from standard clinical practices and procedures.

### 160. Loss of erythroblasts in acute myeloid leukemia causes iron redistribution with clinical implications.

*Lopes, M, Duarte, TL, Teles, MJ, Mosteo, L, Chacim, S, Aguiar, E, Pereira-Reis, J, Oliveira, M, Silva, AMN, Goncalves, N, Martins, G, Kong, IY, Zethoven, M, Vervoort, S, Martins, S, Quintela, M, Hawkins, ED, Trigo, F, Guimaraes, JT, Mariz, JM, Porto, G and Duarte, D. Blood Adv. 2021;5(16):3102-12 [IF: 6.686]*

Acute myeloid leukemia (AML) is a heterogeneous disease with poor prognosis and limited treatment strategies. Determining the role of cell-extrinsic regulators of leukemic cells is vital to gain clinical insights into the biology of AML. Iron is a key extrinsic regulator of cancer, but its systemic regulation remains poorly explored in AML. To address this question, we studied iron metabolism in patients with AML at diagnosis and explored the mechanisms involved using the syngeneic MLL-AF9-induced AML mouse model. We found that AML is a disorder with a unique iron profile, not associated with inflammation or transfusion, characterized by high ferritin, low transferrin, high transferrin saturation (TSAT), and high hepcidin. The increased TSAT in particular, contrasts with observations in other cancer types and in anemia of inflammation. Using the MLL-AF9 mouse model of AML, we demonstrated that the AML-induced loss of erythroblasts is responsible for iron redistribution and increased TSAT. We also show that AML progression is delayed in mouse models of systemic iron overload and that elevated TSAT at diagnosis is independently associated with increased overall survival in AML. We suggest that TSAT may be a relevant prognostic marker in AML.

### 161. Hydralazine and Enzalutamide: Synergistic Partners against Prostate Cancer.

*Lopes, N, Pacheco, MB, Soares-Fernandes, D, Correia, MP, Camilo, V, Henrique, R and Jeronimo, C. Biomedicines. 2021;9(8) [IF: 6.081]*

Advanced prostate cancers frequently develop resistance to androgen-deprivation therapy with serious implications for patient survival. Considering their importance in this type of neoplasia, epigenetic modifications have drawn attention as alternative treatment strategies. The aim of this study was to assess the antitumoral effects of the combination of hydralazine, a DNA methylation inhibitor, with enzalutamide, an antagonist of the androgen receptor, in prostate cancer cell lines. Several biological parameters, such as cell viability, proliferation, DNA damage, and apoptosis, as well as clonogenic and invasive potential, were evaluated. The individual treatments with hydralazine and enzalutamide exerted growth-inhibitory effects in prostate cancer cells and their combined treatment displayed synergistic effects. The combination of these two drugs was very effective in decreasing malignant features of prostate cancer and may become an alternative therapeutic option for prostate cancer patient management.

### 162. Recommendations for the introduction of metagenomic high-throughput sequencing in clinical virology, part I: Wet lab procedure.

*Lopez-Labrador, FX, Brown, JR, Fischer, N, Harvala, H, Van Boheemen, S, Cinek, O, Sayiner, A, Madsen, TV, Auvinen, E, Kufner, V, Huber, M, Rodriguez, C, Jonges, M, Honemann, M, Susi, P, Sousa, H, Klapper, PE, Perez-Cataluna, A, Hernandez, M, Molenkamp, R, der Hoek, LV, Schuurman, R, Couto, N, Leuzinger, K, Simmonds, P, Beer, M, Hoper, D, Kamminga, S, Feltkamp, MCW, Rodriguez-Diaz, J, Keyaerts, E, Nielsen, XC, Puchhammer-Stockl, E, Kroes, ACM, Buesa, J, Breuer, J, Claas, ECJ, de Vries, JJC and Sequencing, ENON-G. J Clin Virol. 2021;134:104691 [IF: 3.168]*

Metagenomic high-throughput sequencing (mHTS) is a hypothesis-free, universal pathogen detection technique for determination of the DNA/RNA sequences in a variety of sample types and infectious syndromes. mHTS is still in its early stages of translating into clinical application. To support the development, implementation and standardization of mHTS procedures for virus diagnostics, the European Society for Clinical Virology (ESCV) Network on Next-Generation Sequencing (ENNGS) has been established. The aim of ENNGS is to bring together professionals involved in mHTS for viral diagnostics to share methodologies and experiences, and to develop application recommendations. This manuscript aims to provide practical recommendations for the wet lab procedures necessary for implementation of mHTS for virus diagnostics and to give recommendations for development and validation of laboratory methods, including mHTS quality assurance, control and quality assessment protocols.

### 163. Urinary Extracellular Vesicles as Potential Biomarkers for Urologic Cancers: An Overview of Current Methods and Advances.

*Lourenco, C, Constanancio, V, Henrique, R, Carvalho, A and Jeronimo, C. Cancers (Basel). 2021;13(7) [IF: 6.639]*

Urologic cancers are a heterogeneous group of tumors, some of which have poor prognosis. This is partly due to the unavailability of specific and sensitive diagnostic techniques and monitoring tests, ideally non- or minimally invasive. Hence, liquid biopsies are promising tools that have been gaining significant attention over the last decade. Among the different classes of biomarkers that can be isolated from biofluids, urinary extracellular vesicles (uEVs) are a promising low-invasive source of biomarkers, with the potential to improve cancer diagnosis and disease management. Different techniques have been developed to isolate and characterize the cargo of these vesicles; however, no consensus has been reached, challenging the comparison among studies. This results in a vast number of studies portraying an extensive list of uEV-derived candidate biomarkers for urologic cancers, with the potential to improve clinical outcome; however, without significant validation. Herein, we review the current published research on miRNA and protein-derived uEV for prostate, bladder and kidney cancers, focusing on different uEV isolation methods, and its implications for biomarker studies.

### 164. Epigenetic mechanisms underlying prostate cancer radioresistance.

*Macedo-Silva, C, Benedetti, R, Ciardiello, F, Cappabianca, S, Jeronimo, C and Altucci, L. Clin Epigenetics. 2021;13(1):125 [IF: 6.551]*

Radiotherapy (RT) is one of the mainstay treatments for prostate cancer (PCa), a highly prevalent neoplasm among males worldwide. About 30% of newly diagnosed PCa patients receive RT with a curative intent. However, biochemical relapse occurs in 20-40% of advanced PCa treated with RT either alone or in combination with adjuvant-hormonal therapy. Epigenetic alterations, frequently associated with molecular variations in PCa, contribute to the acquisition of a radioresistant phenotype. Increased DNA damage repair and cell cycle deregulation decreases radio-response in PCa patients. Moreover, the interplay between epigenome and cell growth pathways is extensively described in published literature. Importantly, as the clinical pattern of PCa ranges from an indolent tumor to an aggressive disease, discovering specific targetable epigenetic molecules able to overcome and predict PCa radioresistance is urgently needed. Currently, histone-deacetylase and DNA-methyltransferase inhibitors are the most studied classes of chromatin-modifying drugs (so-called 'epidrugs') within cancer radiosensitization context. Nonetheless, the lack of reliable validation trials is a foremost drawback. This review summarizes the major epigenetically induced changes in radioresistant-like PCa cells and describes recently reported targeted epigenetic therapies in pre-clinical and clinical settings.

**165. The Use of Mobile Applications for Managing Care Processes During Chemotherapy Treatments: A Systematic Review.**

*Magalhaes, B, Fernandes, C, Santos, C and Martinez-Galiano, JM. Cancer Nurs. 2021;44(6):E339-E60 [IF: 2.592]*

BACKGROUND: The recent mobile technology advancements, such as the development of applications (apps) for mobile phones and tablets, can assist in the development of low-cost platforms to monitor therapeutic adherence or complications, providing easily accessible information or guidelines in self-care focused on the care recipient. OBJECTIVE: The aim of this study was to gather scientific evidence about the efficacy of the use of mobile apps during chemotherapy treatments. METHODS: A systematic review of quantitative studies was performed. All articles published until May 31, 2019 were identified in databases MEDLINE, CINAHL Psychology and Behavioral Sciences Collection, and Cochrane Library. RESULTS: A total of 10 quantitative studies were included. A set of metrics was identified that essentially analyze issues related to the devices' functionalities. The metrics associated with engagement and related to behavioral dimensions, associated with the use of/adherence to the mobile app, are predominant. The clinical metrics represent 25 of a total of 53 identified metrics. Beneficial and statistically significant results were identified related to fatigue, self-efficacy, and improvements in reports of complications. CONCLUSION: Based on the available research, mobile apps are likely to be a useful and acceptable tool to monitor interventions and complications. In addition, mobile apps can help in the self-management of treatment-related complications. Importantly, these apps need to bridge the academic context and clinical practice, by evaluating the impact of the use of mobile apps in patients. IMPLICATIONS FOR PRACTICE: The concept of prescribing apps is being addressed to ensure that apps work and have fair privacy and data security policies that address safety requirements.

**166. COVID-19 in gastroenterology: Where are we now? Current evidence on the impact of COVID-19 in gastroenterology.**

*Magro, F, Nuzzo, A, Abreu, C, Libanio, D, Rodriguez-Lago, I, Pawlak, K, Hollenbach, M, Brouwer, WP and Siau, K. United European Gastroenterol J. 2021;9(7):750-65 [IF: 4.623]*

BACKGROUND: The COVID-19 pandemic has created unprecedented challenges in all fields of society with social, economic, and health-related consequences worldwide. In this context, gastroenterology patients and healthcare systems and professionals have seen their routines changed and were forced to adapt, adopting measures to minimize the risk of infection while guaranteeing continuous medical care to chronic patients. OBJECTIVE: At this point, it is important to evaluate the impact of the pandemic on this field to further improve the quality of the services provided in this context. METHODS/RESULTS/CONCLUSION: We performed a literature review that summarizes the main aspects to consider in gastroenterology, during the pandemic crisis, and includes a deep discussion on the main changes affecting gastroenterology patients and healthcare systems, anticipating the pandemic recovery scenario with future practices and policies.

**167. A New Look into Cancer—A Review on the Contribution of Vibrational Spectroscopy on Early Diagnosis and Surgery Guidance.**

*Mamede, AP, Santos, IP, Batista de Carvalho, ALM, Figueiredo, P, Silva, MC, Tavares, MV, Marques, MPM and Batista de Carvalho, LAE. Cancers. 2021;13(21):5336 [IF: 6.639]*

*In 2020, approximately 10 million people died of cancer, rendering this disease the second leading cause of death worldwide. Detecting cancer in its early stages is paramount for patients' prognosis and survival. Hence, the scientific and medical communities are engaged in improving both therapeutic strategies and diagnostic methodologies, beyond prevention. Optical vibrational spectroscopy has been shown to be an ideal diagnostic method for early cancer diagnosis and surgical margins assessment, as a complement to histopathological analysis. Being highly sensitive, non-invasive and capable of real-time molecular imaging, Raman and Fourier transform infrared (FTIR) spectroscopies give information on the biochemical profile of the tissue under analysis, detecting the metabolic differences between healthy and cancerous portions of the same sample. This constitutes tremendous progress in the field, since the cancer-prompted morphological alterations often occur after the biochemical imbalances in the oncogenic process. Therefore,*

*the early cancer-associated metabolic changes are unnoticed by the histopathologist. Additionally, Raman and FTIR spectroscopies significantly reduce the subjectivity linked to cancer diagnosis. This review focuses on breast and head and neck cancers, their clinical needs and the progress made to date using vibrational spectroscopy as a diagnostic technique prior to surgical intervention and intraoperative margin assessment.*

#### 168. Where Did the Colon Cancer Go?

Marques-de-Sa, J, Pita, J, Coimbra, N and Dinis-Ribeiro, M. Am J Gastroenterol. 2021;116(1):10 [IF: 10.864]

#### 169. Anti-neoplastic and demethylating activity of a newly synthesized flavanone-derived compound in Renal Cell Carcinoma cell lines.

Marques-Magalhaes, A, Graca, I, Miranda-Goncalves, V, Henrique, R, Lopez, M, Arimondo, PB and Jeronimo, C. Biomed Pharmacother. 2021;141:111681 [IF: 6.529]

Renal Cell Carcinoma (RCC) is on the top 10 of the most incident cancers worldwide, being a third of patients diagnosed with advanced disease, for which no curative therapies are currently available. Thus, new effective therapeutic strategies are urgently needed. Herein, we tested the antineoplastic effect of newly synthesized 3-nitroflavanones (MLo1302) on RCC cell lines. 786-O, Caki2, and ACHN cell lines were cultured and treated with newly synthesized 3-nitroflavanones. IC50 values were calculated based on the effect on cell viability assessed by MTT assay, after 72 h of exposure. MLo1302 displayed antineoplastic properties in RCC cell lines through marked reduction of cell viability, increased apoptosis and DNA damage, and morphometric alterations indicating a less aggressive phenotype. MLo1302 induced a significant reduction of global DNA methylation and DNMT mRNA levels, increasing global DNA hydroxymethylation and TET expression. Moreover, MLo1302 decreased DNMT3A activity in RCC cell lines, demethylated and re-expressed hypermethylated genes in CAM-generated tumors. A marked in vivo decrease in tumor growth and angiogenesis was also disclosed. MLo1302 disclosed antineoplastic and demethylating activity in RCC cell lines, constituting a potential therapeutic agent for RCC patients.

#### 170. No evidence of benefit of routine ascitic fluid analysis in refractory ascites undergoing therapeutic paracentesis.

Marques de Sa, J, Bibi, M, Moura, M, Carvalhana, S and Cortez-Pinto, H. Eur J Gastroenterol Hepatol. 2021;33(6):942 [IF: 4.029]

#### 171. Prevalence of Barrett's esophagus in a Southern European country: a multicenter study.

Marques de Sa, J, Leal, C, Silva, J, Falcao, D, Felix, C, Nascimento, C, Boal Carvalho, P, Vasconcelos, H, Pedroto, I, Chagas, C, Cravo, M, Cotter, J, Sharma, P and Dinis-Ribeiro, M. Eur J Gastroenterol Hepatol. 2021;33(1S Suppl 1):e939-e43 [IF: 4.029]

**BACKGROUND:** Identification of Barrett's esophagus (BE) with the treatment of dysplasia is essential to prevent esophageal adenocarcinoma (EAC). Moreover, determination of BE prevalence is important to define subsequent management strategies. However, precise estimates on BE prevalence from several European countries are lacking. We aimed to determine BE prevalence in a Southern European country. **METHODS:** A cross-sectional, multicenter study from November 2019 to February 2020 was performed defining BE as a columnar extent in the distal esophagus greater than or equal to 1 cm with intestinal metaplasia. **RESULTS:** A total of 1550 individuals, 51% male with a mean age of 62 (SD = 15) years undergoing upper endoscopy were included. The overall BE prevalence was 1.29% (95% confidence interval: 0.73-1.85); significantly higher in men [2.05% (1.06-3.04)] vs. women [0.53% (0.01-1.04)]. Of the 20 BE patients, eight were newly diagnosed and 12 were under surveillance. The median extent was C3 (min 0; max 16) M4.5 (min 2; max 16). One patient each had EAC (0.06%) and high-grade dysplasia (0.06%) at the time of endoscopy. There was no difference in prevalence between geographical regions, centers, use of sedation or experience of endoscopists. Considering all reports, 93% used standardized terminology, 23% accurate photodocumentation and 69% photodocumented the esophagogastric junction (EGJ). Furthermore, 80% used Prague classification, 55% Seattle protocol, 60% distance to the squamocolumnar junction, 75% to the EGJ and 40% to the hiatal pinch. When considering only reports with EGJ photodocumentation or Prague classification, the prevalence was 1.78% (0.91-2.64) or 1.03% (0.53-1.53). **CONCLUSION:** We report for the first time BE prevalence in Southern Europe and report a low overall

prevalence in an unselected population. Future studies need to determine progression rates and how to improve quality metrics.

#### 172. Systematic review of the published guidelines on Barrett's esophagus: should we stress the consensus or the differences?

*Marques de Sa, I, Pereira, AD, Sharma, P and Dinis-Ribeiro, M. Dis Esophagus. 2021 [IF: 3.429]*

Multiple guidelines on Barrett's esophagus (BE) have been published in order to standardize and improve clinical practice. However, studies have shown poor adherence to them. Our aim was to synthesize, compare, and assess the quality of recommendations from recently published guidelines, stressing similarities and differences. We conducted a search in Pubmed and Scopus. When different guidelines from the same society were identified, the most recent one was considered. We used the GRADE system to assess the quality of evidence. We included 24 guidelines and position/consensus statements from the European Society of Gastrointestinal Endoscopy, British Society of Gastroenterology, American Society for Gastrointestinal Endoscopy, American Gastroenterological Association, American College of Gastroenterology, Australian guidelines, and Asia-Pacific consensus. All guidelines defend that BE should be diagnosed when there is an extension of columnar epithelium into the distal esophagus. However, there is still some controversy regarding length and histology criteria for BE diagnosis. All guidelines recommend expert pathologist review for dysplasia diagnosis. All guidelines recommend surveillance for non-dysplastic BE, and some recommend surveillance for indefinite dysplasia. While the majority of guidelines recommend ablation therapy for low-grade dysplasia without visible lesion, others recommend ablation therapy or endoscopic surveillance. However, controversy exists regarding surveillance intervals and biopsy protocols. All guidelines recommend endoscopic resection followed by ablation therapy for neoplastic visible lesion. Several guidelines use the GRADE system, but the majority of recommendations are based on low and moderate quality of evidence. Although there is considerable consensus among guidelines, there are some discrepancies resulting from low-quality evidence. The lack of high-quality evidence for the majority of recommendations highlights the importance of continued well-conducted research in this field.

#### 173. Identification of SPRY4 as a Novel Candidate Susceptibility Gene for Familial Nonmedullary Thyroid Cancer.

*Marques, IJ, Gomes, I, Pojo, M, Pires, C, Moura, MM, Cabrera, R, Santos, C, van, IWFJ, Teixeira, MR, Ramalho, JS, Leite, V and Cavaco, BM. Thyroid. 2021;31(9):1366-75 [IF: 6.568]*

Background: The molecular basis of familial nonmedullary thyroid cancer (FNMTC) is still poorly understood, representing a limitation for molecular diagnosis and clinical management. In this study, we aimed to identify new susceptibility genes for FNMTC through whole-exome sequencing (WES) analysis of leukocyte DNA of patients from a highly informative FNMTC family. Methods: We selected six affected family members to conduct WES analysis. Bioinformatic analyses were undertaken to filter and select the genetic variants shared by the affected members, which were subsequently validated by Sanger sequencing. To select the most likely pathogenic variants, several studies were performed, including family segregation analysis, in silico impact characterization, and gene expression (messenger RNA and protein) depiction in databases. For the most promising variant identified, we performed in vitro studies to validate its pathogenicity. Results: Several potentially pathogenic variants were identified in different candidate genes. After filtering with appropriate criteria, the variant c.701C>T, p.Thr234Met in the SPRY4 gene was prioritized for in vitro functional characterization. This SPRY4 variant led to an increase in cell viability and colony formation, indicating that it confers a proliferative advantage and potentiates clonogenic capacity. Phosphokinase array and Western blot analyses suggested that the effects of the SPRY4 variant were mediated through the mitogen-activated protein kinase/extracellular signal-regulated kinase pathway, which was further supported by a higher responsiveness of thyroid cancer cells with the SPRY4 variant to a MEK inhibitor. Conclusions: WES analysis in one family identified SPRY4 as a likely novel candidate susceptibility gene for FNMTC, allowing a better understanding of the cellular and molecular mechanisms underlying thyroid cancer development.

#### 174. Helicobacter pylori PqqE is a new virulence factor that cleaves junctional adhesion molecule A and disrupts gastric epithelial integrity.

*Marques, MS, Costa, AC, Osorio, H, Pinto, ML, Relvas, S, Dinis-Ribeiro, M, Carneiro, F, Leite, M and Figueiredo, C. Gut Microbes. 2021;13(1):1-21 [IF: 10.245]*

*Helicobacter pylori* infects approximately half of the world's population and is the strongest risk factor for peptic ulcer disease and gastric cancer, representing a major global health concern. *H. pylori* persistently colonizes the gastric epithelium, where it subverts the highly organized structures that maintain epithelial integrity. Here, a unique strategy used by *H. pylori* to disrupt the gastric epithelial junctional adhesion molecule-A (JAM-A) is disclosed, using various experimental models that include gastric cell lines, primary human gastric cells, and biopsy specimens of infected and non-infected individuals. *H. pylori* preferentially cleaves the cytoplasmic domain of JAM-A at Alanine 285. Cells stably transfected with full-length JAM-A or JAM-A lacking the cleaved sequence are used in a range of functional assays, which demonstrate that the *H. pylori* cleaved region is critical to the maintenance of the epithelial barrier and of cell-cell adhesion. Notably, by combining chromatography techniques and mass spectrometry, PqqE (HP1012) is purified and identified as the *H. pylori* virulence factor that cleaves JAM-A, uncovering a previously unreported function for this bacterial protease. These findings propose a novel mechanism for *H. pylori* to disrupt epithelial integrity and functions, breaking new ground in the understanding of the pathogenesis of this highly prevalent and clinically relevant infection.

**175. Familiar del3p syndrome: The uncertainty of the prognosis. A case report.**

*Martins, M, Arantes, R, Botelho, P, Souto, M, Moutinho, O and Pinto Leite, R. Clin Case Rep. 2021;9(4):2365-8 [IF: NA]*

The 3p deletion syndrome is an unusual condition. The few cases described are mainly de novo. We described a familial case detected in a prenatal diagnosis. Three members of the family had the 3p26.3-p26.1 deletion; however, only the son presented clinical features.

**176. Genetic testing for pheochromocytoma and paraganglioma: SDHx carriers' experiences.**

*Martins, RG and Carvalho, IP. J Genet Couns. 2021;30(3):872-84 [IF: 2.537]*

Pheochromocytoma and paraganglioma are frequently hereditary tumors commonly associated with succinate dehydrogenase (SDHx) pathogenic variants (PV). Genetic testing is recommended to relatives of patients carrying SDHx PV. This study aims to explore the experiences associated with genetic testing for this hereditary condition. Semi-structured interviews with 38 SDHx PV (tumor-affected and non-affected) carriers were transcribed and content-analyzed. Four ways of living with this genetic alteration emerged from the interviews: 'living as if not knowing', 'preventing others from going through this', 'feeling privileged', and 'still suffering'. Within each, negative, neutral, and positive reactions to the actual test result emerged initially, in addition to blame and guilt. Recognition of the importance of the genetic test and of the follow-up occurred in all four, but views on fecundity were divided between having and not having children. Consideration for the four different meanings of carrying an SDHx PV can improve participants' experiences and clinical practice.

**177. Risk factors for delayed autologous breast reconstruction using pedicled TRAM and latissimus dorsi flaps.**

*Mata Ribeiro, L, Meireles, RP, Brito, IM, Costa, PM, Rebelo, MA, Barbosa, RF, Choupina, MP, Pinho, CJ and Ribeiro, MP. European Journal of Plastic Surgery. 2020;44(3):333-44 [IF: NA]*

The purpose of this study was to compare outcomes between patients submitted to pedicled transverse rectus abdominis musculocutaneous (pTRAM) and latissimus dorsi musculocutaneous (LD) flaps for breast reconstructions and to investigate potential risk factors for complications in autologous reconstruction.

**178. Modulation of serine/threonine-protein phosphatase 1 (PP1) complexes: A promising approach in cancer treatment.**

*Matos, B, Howl, J, Jeronimo, C and Fardilha, M. Drug Discov Today. 2021;26(11):2680-98 [IF: 7.851]*

Cancer is the second leading cause of death worldwide. Despite the availability of numerous therapeutic options, tumor heterogeneity and chemoresistance have limited the success of these treatments, and the development of effective anticancer therapies remains a major focus in oncology research. The serine/threonine-protein phosphatase 1 (PP1) and its complexes have been recognized as potential drug

targets. Research on the modulation of PP1 complexes is currently at an early stage, but has immense potential. Chemically diverse compounds have been developed to disrupt or stabilize different PP1 complexes in various cancer types, with the objective of inhibiting disease progression. Beneficial results obtained in vitro now require further pre-clinical and clinical validation. In conclusion, the modulation of PP1 complexes seems to be a promising, albeit challenging, therapeutic strategy for cancer.

**179. Pteridium spp. and Bovine Papillomavirus: Partners in Cancer.**

*Medeiros-Fonseca, B, Abreu-Silva, AL, Medeiros, R, Oliveira, PA and Gil da Costa, RM. Front Vet Sci. 2021;8:758720 [IF: 3.412]*

Bovine papillomavirus (BPV) are a cause for global concern due to their wide distribution and the wide range of benign and malignant diseases they are able to induce. Those lesions include cutaneous and upper digestive papillomas, multiple histological types of urinary bladder cancers-most often associated with BPV1 and BPV2-and squamous cell carcinomas of the upper digestive system, associated with BPV4. Clinical, epidemiological and experimental evidence shows that exposure to bracken fern (*Pteridium* spp.) and other related ferns plays an important role in allowing viral persistence and promoting the malignant transformation of early viral lesions. This carcinogenic potential has been attributed to bracken illudane glycoside compounds with immune suppressive and mutagenic properties, such as ptaquiloside. This review addresses the role of BPV in tumorigenesis and its interactions with bracken illudane glycosides. Current data indicates that inactivation of cytotoxic T lymphocytes and natural killer cells by bracken fern illudanes plays a significant role in allowing viral persistence and lesion progression, while BPV drives unchecked cell proliferation and allows the accumulation of genetic damage caused by chemical mutagens. Despite limited progress in controlling bracken infestation in pasturelands, bracken toxins remain a threat to animal health. The number of recognized BPV types has steadily increased over the years and now reaches 24 genotypes with different pathogenic properties. It remains essential to widen the available knowledge concerning BPV and its synergistic interactions with bracken chemical carcinogens, in order to achieve satisfactory control of the livestock losses they induce worldwide.

**180. Experimental Models for Studying HPV-Positive and HPV-Negative Penile Cancer: New Tools for An Old Disease.**

*Medeiros-Fonseca, B, Cubilla, A, Brito, H, Martins, T, Medeiros, R, Oliveira, P and Gil da Costa, RM. Cancers (Basel). 2021;13(3) [IF: 6.639]*

Penile cancer is an uncommon malignancy that occurs most frequently in developing countries. Two pathways for penile carcinogenesis are currently recognized: one driven by human papillomavirus (HPV) infection and another HPV-independent route, associated with chronic inflammation. Progress on the clinical management of this disease has been slow, partly due to the lack of preclinical models for translational research. However, exciting recent developments are changing this landscape, with new in vitro and in vivo models becoming available. These include mouse models for HPV(+) and HPV(-) penile cancer and multiple cell lines representing HPV(-) lesions. The present review addresses these new advances, summarizing available models, comparing their characteristics and potential uses and discussing areas that require further improvement. Recent breakthroughs achieved using these models are also discussed, particularly those developments pertaining to HPV-driven cancer. Two key aspects that still require improvement are the establishment of cell lines that can represent HPV(+) penile carcinomas and the development of mouse models to study metastatic disease. Overall, the growing array of in vitro and in vivo models for penile cancer provides new and useful tools for researchers in the field and is expected to accelerate pre-clinical research on this disease.

**181. Effect of 1-Carbaldehyde-3,4-dimethoxyxanthone on Prostate and HPV-18 Positive Cervical Cancer Cell Lines and on Human THP-1 Macrophages.**

*Medeiros, R, Horta, B, Freitas-Silva, J, Silva, J, Dias, E, Sousa, E, Pinto, M and Cerqueira, F. Molecules. 2021;26(12) [IF: 4.411]*

Xanthone derivatives have shown promising antitumor properties, and 1-carbaldehyde-3,4-dimethoxyxanthone (1) has recently emerged as a potent tumor cell growth inhibitor. In this study, its effect was evaluated (MTT viability assay) against a new panel of cancer cells, namely cervical cancer

(HeLa), androgen-sensitive (LNCaP) and androgen-independent (PC-3) prostate cancer, and nonsolid tumor derived cancer (Jurkat) cell lines. The effect of xanthone 1 on macrophage functions was also evaluated. The effect of xanthone 1-conditioned THP-1 human macrophage supernatants on the metabolic viability of cervical and prostate cancer cell lines was determined along with its interference with cytokine expression characteristic of M1 profile (IL-1  $\leq$  beta; TNF-alpha) or M2 profile (IL-10; TGF-beta) (PCR and ELISA). Nitric oxide (NO) production by murine RAW264.7 macrophages was quantified by Griess reaction. Xanthone 1 (20  $\mu$ M) strongly inhibited the metabolic activity of the cell lines and was significantly more active against prostate cell lines compared to HeLa ( $p < 0.05$ ). Jurkat was the cell most sensitive to the effect of xanthone 1. Compound 1-conditioned IL-4-stimulated THP-1 macrophage supernatants significantly ( $p < 0.05$ ) inhibited the metabolic activity of HeLa, LNCaP, and PC-3. Xanthone 1 did not significantly affect the expression of cytokines by THP-1 macrophages. The inhibiting effect of compound 1 observed on the production of NO by RAW 264.7 macrophages was moderate. In conclusion, 1-carbaldehyde-3,4-dimethoxyxanthone (1) decreases the metabolic activity of cancer cells and seems to be able to modulate macrophage functions.

### 182. Prostate Cancer Aggressiveness Prediction Using CT Images.

*Mendes, B, Domingues, I, Silva, A and Santos, J. Life (Basel). 2021;11(11) [IF: 3.817]*

Prostate Cancer (PCa) is mostly asymptomatic at an early stage and often painless requiring active surveillance screening. Transrectal Ultrasound Guided Biopsy (TRUS) is the principal method to diagnose PCa following a histological examination by observing cell pattern irregularities and assigning the Gleason Score (GS) according to the recommended guidelines. This procedure presents sampling errors and, being invasive may cause complications to the patients. External Beam Radiotherapy Treatment (EBRT) is presented as curative option for localised and locally advanced disease, as a palliative option for metastatic low-volume disease or after prostatectomy for prostate bed and pelvic nodes salvage. In the EBRT workflow a Computed Tomography (CT) scan is performed as the basis for dose calculations and volume delineations. In this work, we evaluated the use of data-characterization algorithms (radiomics) from CT images for PCa aggressiveness assessment. The fundamental motivation relies on the wide availability of CT images and the need to provide tools to assess EBRT effectiveness. We used Pyradiomics and Local Image Features Extraction (LIFEx) to extract features and search for a radiomic signature within CT images. Finally, when applying Principal Component Analysis (PCA) to the features, we were able to show promising results.

### 183. Secondary Hyperparathyroidism Among Bariatric Patients: Unraveling the Prevalence of an Overlooked Foe.

*Mendonca, FM, Neves, JS, Silva, MM, Borges-Canha, M, Costa, C, Cabral, PM, Guerreiro, V, Lourenco, R, Meira, P, Ferreira, MJ, Salazar, D, Pedro, J, Viana, S, Souto, S, Varela, A, Belo, S, Lau, E, Freitas, P, Carvalho, D and group, C. Obes Surg. 2021;31(8):3768-75 [IF: 4.129]*

**INTRODUCTION:** Bariatric surgery (BS) is the most effective therapeutic approach to obesity. It is associated with great gastrointestinal anatomic changes, predisposing the patients to altered nutrient absorption that impacts phosphocalcium metabolism. This study aimed to clarify the prevalence of secondary hyperparathyroidism (SHPT) and its predictors in patients submitted to BS. **METHODS:** Retrospective study of 1431 patients who underwent metabolic surgery between January 2010 and June 2017 and who were followed for at least 1 year. We compared the clinical and biochemical characteristics of patients with and without secondary hyperparathyroidism (considering SHPT a PTH > 69 pg/mL). Two different analyses were performed: (1) paired analysis of participants before and 1 year after surgery (N = 441); (2) Cross sectional analysis of participants submitted to bariatric surgery before (N = 441), 1 year after (N = 1431) and 4 years after surgery (N = 333). Multiple logistic regression models were used to evaluate possible predictors of SHPT after BS. **RESULTS:** The overall prevalence of SHPT was 24.9% before surgery, 11.2% 1 year after surgery and 21.3% 4 years after surgery. Patients submitted to LAGB had the highest prevalence of SHPT 1 year after surgery (19.4%; vs RYGB, 12.8%, vs SG, 5.3%). Four years after surgery, RYGB had the highest prevalence of SHPT (27.0%), followed by LAGB (13.2%) and SG (6.9%). Higher body mass index and age, decreased levels of vitamin D and RYGB seem to be independent predictors of SHPT 1 year after surgery. The only independent predictor of SHPT 4 years after surgery was RYGB. **CONCLUSION:** The prevalence of SHPT is higher before and 4 years after BS than 1 year after surgery. This fact raises some questions about

the efficacy of the implemented follow-up plans of vitamin D supplementation on the long term, mainly among patients submitted to RYGB.

**184. Antimicrobials from Medicinal Plants: An Emergent Strategy to Control Oral Biofilms.**

*Milho, C, Silva, J, Guimarães, R, Ferreira, ICFR, Barros, L and Alves, MJ. Applied Sciences. 2021;11(9) [IF: 2.679]*

Oral microbial biofilms, directly related to oral diseases, particularly caries and periodontitis, exhibit virulence factors that include acidification of the oral microenvironment and the formation of biofilm enriched with exopolysaccharides, characteristics and common mechanisms that, ultimately, justify the increase in antibiotics resistance. In this line, the search for natural products, mainly obtained through plants, and derived compounds with bioactive potential, endorse unique biological properties in the prevention of colonization, adhesion, and growth of oral bacteria. The present review aims to provide a critical and comprehensive view of the in vitro antibiofilm activity of various medicinal plants, revealing numerous species with antimicrobial properties, among which, twenty-four with biofilm inhibition/reduction percentages greater than 95%. In particular, the essential oils of *Cymbopogon citratus* (DC.) Stapf and *Lippia alba* (Mill.) seem to be the most promising in fighting microbial biofilm in *Streptococcus mutans*, given their high capacity to reduce biofilm at low concentrations.

**185. The component of the m(6)A writer complex VIRMA is implicated in aggressive tumor phenotype, DNA damage response and cisplatin resistance in germ cell tumors.**

*Miranda-Goncalves, V, Lobo, J, Guimaraes-Teixeira, C, Barros-Silva, D, Guimaraes, R, Cantante, M, Braga, I, Mauricio, J, Oing, C, Honecker, F, Nettersheim, D, Looijenga, LHJ, Henrique, R and Jeronimo, C. J Exp Clin Cancer Res. 2021;40(1):268 [IF: 11.161]*

BACKGROUND: Germ cell tumors (GCTs) are developmental cancers, tightly linked to embryogenesis and germ cell development. The recent and expanding field of RNA modifications is being increasingly implicated in such molecular events, as well as in tumor progression and resistance to therapy, but still rarely explored in GCTs. In this work, and as a follow-up of our recent study on this topic in TGCT tissue samples, we aim to investigate the role of N6-methyladenosine (m(6)A), the most abundant of such modifications in mRNA, in in vitro and in vivo models representative of such tumors. METHODS: Four cell lines representative of GCTs (three testicular and one mediastinal), including an isogenic cisplatin resistant subline, were used. CRISPR/Cas9-mediated knockdown of VIRMA was established and the chorioallantoic membrane assay was used to study its phenotypic effect in vivo. RESULTS: We demonstrated the differential expression of the various m(6)A writers, readers and erasers in GCT cell lines representative of the major classes of these tumors, seminomas and non-seminomas, and we evidenced changes occurring upon differentiation with all-trans retinoic acid treatment. We showed differential expression also among cells sensitive and resistant to cisplatin treatment, implicating these players in acquisition of cisplatin resistant phenotype. Knockdown of VIRMA led to disruption of the remaining methyltransferase complex and decrease in m(6)A abundance, as well as overall reduced tumor aggressiveness (with decreased cell viability, tumor cell proliferation, migration, and invasion) and increased sensitivity to cisplatin treatment, both in vitro and confirmed in vivo. Enhanced response to cisplatin after VIRMA knockdown was related to significant increase in DNA damage (with higher gammaH2AX and GADD45B levels) and downregulation of XLF and MRE11. CONCLUSIONS: VIRMA has an oncogenic role in GCTs confirming our previous tissue-based study and is further involved in response to cisplatin by interfering with DNA repair. These data contribute to our better understanding of the emergence of cisplatin resistance in GCTs and support recent attempts to therapeutically target elements of the m(6)A writer complex.

**186. Secreted Extracellular Vesicle Molecular Cargo as a Novel Liquid Biopsy Diagnostics of Central Nervous System Diseases.**

*Monteiro-Reis, S, Carvalho-Maia, C, Bart, G, Vainio, SJ, Pedro, J, Silva, ER, Sales, G, Henrique, R and Jeronimo, C. Int J Mol Sci. 2021;22(6) [IF: 5.923]*

Secreted extracellular vesicles (EVs) are heterogeneous cell-derived membranous granules which carry a large diversity of molecules and participate in intercellular communication by transferring these molecules

to target cells by endocytosis. In the last decade, EVs' role in several pathological conditions, from etiology to disease progression or therapy evasion, has been consolidated, including in central nervous system (CNS)-related disorders. For this review, we performed a systematic search of original works published, reporting the presence of molecular components expressed in the CNS via EVs, which have been purified from plasma, serum or cerebrospinal fluid. Our aim is to provide a list of molecular EV components that have been identified from both nonpathological conditions and the most common CNS-related disorders. We discuss the methods used to isolate and enrich EVs from specific CNS-cells and the relevance of its components in each disease context.

**187. Epigenetic extracellular vesicle-based biomarkers for urological malignancies: is the hope worth the hype?**

Montezuma, D, Teixeira-Marques, A, Jeronimo, C and Henrique, R. Epigenomics. 2021;13(19):1514-21 [IF: 4.778]

**188. Designing a National Curriculum to Advance Surgical Oncology in Mozambique: A Delphi Consensus Study.**

Morais, A, Simao, M, Cossa, M, Come, J, Selemene, C, Tivane, A, Tulsidas, S, Lorenzoni, C, Rodrigues, J, Antunes, L, Brito, D, Costa, MJ, Sidat, M, Martins, M and Santos, LL. J Surg Educ. 2021;78(1):140-7 [IF: 2.891]

**OBJECTIVE:** Mozambique is currently experiencing an increase in chronic diseases including cancer. There is a large unmet need for cancer surgery in Mozambique. The aim of this study was to define the content and the design of a training program for practicing surgeons in surgical oncology that would be consensually regarded as adequate to care for oncological patients requiring surgical interventions. **DESIGN & SETTING:** A 3-round modified-Delphi approach was implemented to obtain consensus on surgical oncology training curriculum. The participants were purposefully selected experts in surgical oncology working in Mozambique. In round 1, participants answered a questionnaire with open-ended questions regarding the content of the curriculum and the timing and venue of training. In round 2, answers from the first round were presented to a purposeful selected sample of nationally recognized experts in oncology and surgical oncology, including members of the Mozambican College of Surgeons and leadership of the Ministry of Health. A final round was carried out to discuss the draft version of the training program aiming to achieve a predetermined consensus level of 80%. **PARTICIPANTS:** Fifteen of 23 experts (65.2%) responded to round one. The response rate for round 1 and 3 was 80% (12 of the 15 participants in round one). **RESULTS:** The responses collected in the first round were analyzed and revealed that basic principles of oncology and basic principles of surgical oncology should be included in the curriculum of surgical residency in Mozambique (80% of the experts agree; Cronbach alpha=0.93); a 24-months fellowship in surgical oncology should take place after residency in the surgical field (86.6% of experts agree; Cronbach alpha=0.97); and should occur at Maputo Central Hospital and at comprehensive cancer centers abroad (100% agree). In round 2 the proposal for the program of surgical oncology fellowship obtained a strong agreement amongst the experts (97.3%). The final proposal for the program was divided into the following structure: (1) theoretical components; (2) duration; (3) location; (4) methodology; (5) technical skills in oncology; and (6) competency and paid particular attention to the oncological diseases prevalent in Mozambique. The agreement amongst the experts was 97.3%. **CONCLUSIONS:** The experts reached a consensus regarding the general structure for a cancer surgery postgraduate training program in Mozambique, which should be a 24-months fellowship after residency in surgical disciplines. This fellowship should mostly take place in Mozambique, but it should also include dedicated internships in recognized cancer hospitals abroad. Such curricula embrace the Global Curriculum in Surgical Oncology including in particular the oncological nosology of Mozambique and should advance the quality of oncology surgical care provided in the country.

**189. Cancer Cells' Metabolism Dynamics in Renal Cell Carcinoma Patients' Outcome: Influence of GLUT-1-Related hsa-miR-144 and hsa-miR-186.**

Morais, M, Dias, F, Noqueira, I, Leao, A, Goncalves, N, Araujo, L, Granja, S, Baltazar, F, Teixeira, AL and Medeiros, R. Cancers (Basel). 2021;13(7) [IF: 6.639]

The cancer cells' metabolism is altered due to deregulation of key proteins, including glucose transporter 1

(GLUT-1), whose mRNA levels are influenced by microRNAs (miRNAs). Renal cell carcinoma (RCC) is the most common and lethal neoplasia in the adult kidney, mostly due to the lack of accurate diagnosis and follow-up biomarkers. Being a metabolic associated cancer, this study aimed to understand the hsa-miR-144-5p and hsa-miR-186-3p's potential as biomarkers of clear cell RCC (ccRCC), establishing their role in its glycolysis status. Using three ccRCC lines, the intra- and extracellular levels of both miRNAs, GLUT-1's mRNA expression and protein levels were assessed. Glucose consumption and lactate production were evaluated as glycolysis markers. A decrease of intracellular levels of these miRNAs and increase of their excretion was observed, associated with an increase of GLUT-1's levels and glycolysis' markers. Through a liquid biopsy approach, we found that RCC patients present higher plasmatic levels of hsa-miR-186-3p than healthy individuals. The Hsa-miR144-5p's higher levels were associated with early clinical stages. When patients were stratified according to miRNAs plasmatic levels, low plasmatic levels of hsa-miR-144-5p and high plasmatic levels of hsa-miR-186-3p (high-risk group) showed the worst overall survival. Thus, circulating levels of these miRNAs may be potential biomarkers of ccRCC prognosis.

#### 190. Starch-Capped AgNPs' as Potential Cytotoxic Agents against Prostate Cancer Cells.

*Morais, M, Machado, V, Dias, F, Palmeira, C, Martins, G, Fonseca, M, Martins, CSM, Teixeira, AL, Prior, JAV and Medeiros, R. Nanomaterials (Basel). 2021;11(2) [IF: 5.076]*

One of the major therapeutic approaches of prostate cancer (PC) is androgen deprivation therapy (ADT), but patients develop resistance within 2-3 years, making the development of new therapeutic approaches of great importance. Silver nanoparticles (AgNPs) synthesized through green approaches have been studied as anticancer agents because of their physical-chemical properties. This study explored the cytotoxic capacity of starch-capped AgNPs, synthesized through green methods, in LNCaP and in PC-3 cells, a hormonal-sensitive and hormone-resistant PC cell line, respectively. These AgNPs were synthesized in a microwave pressurized synthesizer and characterized by ultraviolet-visible (UV-Vis) spectroscopy, transmission electron microscopy (TEM), and energy-dispersive X-ray spectroscopy (EDX). Their cytotoxicity was assessed regarding their ability to alter morphological aspect (optical microscopy), induce damage in cytoplasmic membrane (Trypan Blue Assay), mitochondria (WST-1 assay), cellular proliferation (BrdU assay), and cell cycle (Propidium iodide and flow-cytometry). AgNPs showed surface plasmon resonance (SPR) of approximately 408 nm and average size of 3 nm. The starch-capped AgNPs successfully induced damage in cytoplasmic membrane and mitochondria, at concentrations equal and above 20 ppm. These damages lead to cell cycle arrest in G0/G1 and G2/M, blockage of proliferation and death in LNCaP and PC-3 cells, respectively. This data shows these AgNPs' potential as anticancer agents for the different stages of PC.

#### 191. The impact of the COVID-19 pandemic on the short-term survival of patients with cancer in Northern Portugal.

*Morais, S, Antunes, L, Rodrigues, J, Fontes, F, Bento, MJ and Lunet, N. Int J Cancer. 2021;149(2):287-96 [IF: 7.396]*

The COVID-19 pandemic led to potential delays in diagnosis and treatment of cancer patients, which may negatively affect the prognosis of these patients. Our study aimed to quantify the impact of COVID-19 on the short-term survival of cancer patients by comparing a period of 4 months after the outbreak began (2 March 2020) with an equal period from 2019. All cancer cases of the esophagus, stomach, colon and rectum, pancreas, lung, skin-melanoma, breast, cervix, and prostate, from the Portuguese Oncology Institute of Porto (IPO-Porto) and diagnosed between 2 March and 1 July of 2019 (before COVID-19) and 2020 (after COVID-19) were identified. Information regarding sociodemographic, clinical and treatment characteristics were collected from the cancer registry database and clinical files. Vital status was assessed to 31 October of the respective years. Cox proportional hazards regression was used to estimate crude and propensity score-adjusted hazards ratio (HR) and 95% confidence intervals (95% CIs) of death. During follow-up to 31 October, there were 154 (11.8%) deaths observed before COVID-19 and 131 (17.2%) after COVID-19, corresponding to crude and adjusted HRs (95% CI) of 1.51 (1.20-1.91) and 1.10 (0.86-1.40), respectively. Significantly higher adjusted hazards of death were observed for patients with Stage III cancer (HR = 2.37; 95% CI: 1.14-4.94) and those undergoing surgical treatment (HR = 3.97; 95% CI: 1.14-13.77) or receiving radiotherapy (HR = 1.96; 95% CI: 1.96-3.74), while patients who did not receive any treatment had

a lower mortality hazards (HR = 0.62; 95% CI: 0.46-0.83). The higher overall short-term mortality observed during the COVID-19 pandemic largely reflects the effects of the epidemic on the case-mix of patients being diagnosed with cancer.

**192. Urachal carcinoma: A case of a rare neoplasm.**

*Moreira, I, Coelho, S, Rodrigues, A, Patrao, AS and Mauricio, MJ. Curr Probl Cancer. 2021;45(6):100711 [IF: 3.187]*

INTRODUCTION: Urachal carcinoma is a rare type of non-urothelial malignancy that arises from the urachal ligament, a remnant of fetal development. It frequently involves the dome of the bladder or its midline, with adenocarcinoma being the most common histological type. This malignancy is generally diagnosed in advanced stages and is associated with poor prognosis. CASE REPORT: A 40-year-old woman was referred to hospital due to recurrent urinary tract infections. Imaging studies showed the presence of a 3.7 cm tumor in the bladder dome that extended to the posterior region of the umbilicus. A biopsy through cystoscopy confirmed the diagnosis of urachal carcinoma. Since there were no metastases, the patient underwent partial cystectomy and resection of the urachal ligament and the umbilicus. Surgical margins were negative and it was considered a complete resection. Nine months later, disease progression occurred, with peritoneal carcinomatosis, multiple adenopathies and a 4 cm mass in the pelvic cavity with invasion of the vagina, rectum, and sigmoid colon. She began palliative chemotherapy with cisplatin and 5-fluorouracil. After 7 cycles, progression was again observed, with an increase of the pelvic mass, vaginal and rectal hemorrhage, multiple intramuscular implants, bilateral axillary adenopathies, as well as lesion in the right breast, which was compatible with metastasis from urachal carcinoma. She underwent hemostatic radiotherapy to the pelvic mass and second line palliative chemotherapy with gemcitabine and paclitaxel. After 4 cycles, the patient clinically deteriorated and eventually died. CONCLUSION: Urachal carcinoma is an aggressive malignancy. Although systemic treatment may be effective in disease control, a standard chemotherapy regimen is yet to be determined. Multicenter trials are needed to clarify the best treatment approach in these patients.

**193. A prodigious intracerebral lesion infiltrating the adjacent skull.**

*Moreira, I, Ferreira, A, Verdelho, A, Pereira, B, Fitas, D, Coelho, F, Faria, F, Lima, JA, Jacome, M, Isidoro, R and Martins, A. Curr Probl Cancer. 2021;45(2):100642 [IF: 3.187]*

**194. Lumen-Apposing Metal Stents (Lams) in the Management of Refractory Gi Stenosis: A Series of 3 Cases.**

*Moreira, M, Pita, I, Fernandes, J, Azevedo, R, Canena, J and Lopes, L. GE Port J Gastroenterol. 2022;29(1):64-7 [IF: NA]*

**195. The Dynamic Interface Between the Bone Marrow Vascular Niche and Hematopoietic Stem Cells in Myeloid Malignancy.**

*Mosteo, L, Storer, J, Batta, K, Searle, EJ, Duarte, D and Wiseman, DH. Front Cell Dev Biol. 2021;9:635189 [IF: 6.684]*

Hematopoietic stem cells interact with bone marrow niches, including highly specialized blood vessels. Recent studies have revealed the phenotypic and functional heterogeneity of bone marrow endothelial cells. This has facilitated the analysis of the vascular microenvironment in steady state and malignant hematopoiesis. In this review, we provide an overview of the bone marrow microenvironment, focusing on refined analyses of the marrow vascular compartment performed in mouse studies. We also discuss the emerging role of the vascular niche in "inflamm-aging" and clonal hematopoiesis, and how the endothelial microenvironment influences, supports and interacts with hematopoietic cells in acute myeloid leukemia and myelodysplastic syndromes, as exemplar states of malignant myelopoiesis. Finally, we provide an overview of strategies for modulating these bidirectional interactions to therapeutic effect in myeloid malignancies.

**196. Adaptação ao Cancro da Mama: Validação da Versão Portuguesa da Psychological Adaption Scale.**

*Neto, V, Jönsson, C, Castro, S, R. Silva, E and Lencastre, L. Revista Iberoamericana de Diagnóstico y*

*Evaluación – e Avaliação Psicológica. 2021;60(3):55-69 [IF: NA]*

**197. Immunotherapy and Radiotherapy for Older Cancer Patients during the COVID-19 Era: Proposed Paradigm by the International Geriatric Radiotherapy Group.**

*Nguyen, NP, Baumert, BG, Oboite, E, Motta, M, Appalanaido, GK, Arenas, M, Lara, PC, Bonet, M, Zamagni, A, Vuong, T, Popescu, T, Karlsson, U, Trigo, L, Sun Myint, A, Thariat, J and Vinh-Hung, V. Gerontology. 2021;67(4):379-85 [IF: 5.140]*

BACKGROUND: Older cancer patients with locally advanced or metastatic disease may benefit from chemotherapy alone or combined with radiotherapy. However, chemotherapy is often omitted either because of physician bias or because of its underlying comorbidity, thus compromising their survival. The coronavirus disease 19 (COVID-19) pandemic is compounding this issue because of the fear of immunosuppression induced by chemotherapy on the elderly which makes them more vulnerable to the virus. SUMMARY: Immunotherapy has less effect on the patient bone marrow compared to chemotherapy. The potential synergy between radiotherapy and immunotherapy may improve local control and survival for older patients with selected cancer. Preliminary data are encouraging because of better survival and local control in diseases which are traditionally resistant to radiotherapy and chemotherapy such as melanoma and renal cell carcinoma. Key Message: We propose a new paradigm combining immunotherapy at a reduced dose and/or extended dosing intervals and hypofractionated radiotherapy for older patients with selected cancer which needs to be tested in future clinical trials.

**198. Recommendations for the use of active personal dosimeters (APDs) in interventional workplaces in hospitals.**

*O'Connor, U, Carinou, E, Clairand, I, Ciraj-Bjelac, O, De Monte, F, Domienik-Andrzejewska, J, Ferrari, P, Ginjaume, M, Hrsak, H, Hupe, O, Knezevic, Z, Sans Merce, M, Sarmento, S, Siiskonen, T and Vanhavere, F. Phys Med. 2021;87:131-5 [IF: 2.685]*

Occupational radiation doses from interventional procedures have the potential to be relatively high. The requirement to optimise these doses encourages the use of electronic or active personal dosimeters (APDs) which are now increasingly used in hospitals. They are typically used in tandem with a routine passive dosimetry monitoring programme, with APDs used for real-time readings, for training purposes and when new imaging technology is introduced. However, there are limitations when using APDs. A survey in hospitals to identify issues related to the use of APDs was recently completed, along with an extensive series of APD tests by the EURADOS Working Group 12 on Dosimetry for Medical Imaging. The aim of this review paper is to summarise the state of the art regarding the use of APDs. We also used the results of our survey and our tests to develop a set of recommendations for the use of APDs in the clinical interventional radiology/cardiology settings, and draw attention to some of the current challenges.

**199. Preference for the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection in patients with HER2-positive early breast cancer (PHranceSCa): A randomised, open-label phase II study.**

*O'Shaughnessy, J, Sousa, S, Cruz, J, Fallowfield, L, Auvinen, P, Pulido, C, Cvetanovic, A, Wilks, S, Ribeiro, L, Burotto, M, Klingbiel, D, Messeri, D, Alexandrou, A, Trask, P, Fredriksson, J, Machackova, Z, Stamatovic, L and group, PHs. Eur J Cancer. 2021;152:223-32 [IF: 9.162]*

AIM: The aim of the study was to assess patient preference for the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection (PH FDC SC) in patients with HER2-positive early breast cancer in PHranceSCa (NCT03674112). MATERIALS AND METHODS: Patients who completed neoadjuvant P + H + chemotherapy + surgery were randomised 1:1 to three intravenous (IV) P + H cycles followed by three cycles of PH FDC SC or vice versa (crossover) and then chose subcutaneous (SC) injection or IV infusion to continue up to 18 cycles (continuation). Assessments were via patient and healthcare professional (HCP) questionnaires. RESULTS: One hundred and sixty patients were randomised (cut-off: 24 February 2020); 136 (85.0%, 95% confidence interval: 78.5-90.2%) preferred SC; 22 (13.8%) preferred IV; 2 (1.3%) had no preference. The main reasons for SC preference were reduced clinic time (n = 119) and comfort during administration (n = 73). One hundred and forty-one patients (88.1%) were very satisfied/satisfied with SC injection versus 108 (67.5%) with IV infusion; 86.9% chose PH FDC SC continuation. HCP perceptions of

median patient treatment room time ranged from 33.0-50.0 min with SC and 130.0-300.0 min with IV. Most adverse events (AEs) were grade 1/2 (no 4/5s); serious AE rates were low. AE rates before and after switching were similar (cycles 1-3 IV --> cycles 4-6 SC: 77.5% --> 72.5%; cycles 1-3 SC --> cycles 4-6 IV: 77.5% --> 63.8%). CONCLUSION: Most patients strongly preferred PH FDC SC over P + H IV. PH FDC SC was generally well tolerated, with no new safety signals (even when switching), and offers a quicker alternative to IV infusion.

**200. Occupational management of healthcare workers exposed to COVID-19.**

*Ochoa-Leite, C, Bento, J, Rocha, DR, Vasques, I, Cunha, R, Oliveira, A and Rocha, L. Occup Med (Lond). 2021;71(8):359-65 [IF: 1.611]*

BACKGROUND: The year 2020 was marked by the new coronavirus pandemic, resulting in millions of cases and deaths, placing healthcare workers at high risk of infection. AIMS: The aim of this study was to describe the role of an occupational health service during coronavirus disease 2019 pandemic in an oncologic hospital and characterize the most likely sources of viral infection. METHODS: The information of all healthcare workers with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection from 11 March to 15 December 2020 was collected through an epidemiological survey conducted during contact tracing. The data extracted included gender, age, comorbidities, occupational group, source of infection, clinical presentation, duration of the disease, need for hospitalization and persistent or late symptoms after disease or upon returning to work. RESULTS: Out of a total of 2300 workers, 157 were infected, consisting of nurses (36%), nurse assistants (33%) and diagnostic and therapeutic professionals (10%). Physicians and administrative staff accounted for 8% each. The most frequently reported source of infection was occupational (43%), owing to worker-to-worker transmission (45%) and patient-to-worker transmission (36%). The most frequent moments of infection perceived corresponded to the removal of protective equipment during meals and moments of rest in the staff and changing rooms. CONCLUSIONS: The study revealed that occupational transmission from patients and colleagues might be an important source of SARS-CoV-2 infection in healthcare workers. Spread between colleagues accounted for 45% of the occupational source infections reported. Implementing physical distancing measures and limiting the number of people in changing and rest rooms could significantly reduce infection and related absenteeism.

**201. Stress-Related Growth Scale-Short Form: A Portuguese validation for cancer patients.**

*Oliveira, MA, Guerra, MP, Lencastre, L, Castro, S, Moutinho, S and Park, CL. Int J Clin Health Psychol. 2021;21(3):100255 [IF: 5.350]*

Abstract Background/Objective: Cancer can be extremely disruptive, triggering high levels of distress, and at the same time transformative, promoting perceptions of positive life changes and growth. This study aims to analyze the psychometric proprieties of the Stress-Related Growth Scale Short-Form (SRGS-SF) in cancer patients. Method: 209 Cancer patients heterogeneous in disease stage and diagnosis completed: clinical and sociodemographic information, Distress Thermometer, Positive and Negative Affect Schedule, Visual-analogue Scale of Perceived Positive Life Changes, and Stress-Related Growth Scale-Short Form. Results: The analysis of internal structure pointed to an one-dimensional scale, with high reliability (.92) measured through the McDonald's omega coefficient. Validity was also evidenced through significant correlations with other variables. Conclusions: The Portuguese version of the SRGS-SF seems to present the necessary psychometric proprieties to be considered a valid and reliable short tool, to assess perceptions of growth following cancer and contribute to targeted and integrative psycho-oncological interventions.

**202. CAD systems for colorectal cancer from WSI are still not ready for clinical acceptance.**

*Oliveira, SP, Neto, PC, Fraga, J, Montezuma, D, Monteiro, A, Monteiro, J, Ribeiro, L, Goncalves, S, Pinto, IM and Cardoso, JS. Sci Rep. 2021;11(1):14358 [IF: 4.379]*

Most oncological cases can be detected by imaging techniques, but diagnosis is based on pathological assessment of tissue samples. In recent years, the pathology field has evolved to a digital era where tissue samples are digitised and evaluated on screen. As a result, digital pathology opened up many research opportunities, allowing the development of more advanced image processing techniques, as well as artificial intelligence (AI) methodologies. Nevertheless, despite colorectal cancer (CRC) being the second deadliest cancer type worldwide, with increasing incidence rates, the application of AI for CRC diagnosis,

particularly on whole-slide images (WSI), is still a young field. In this review, we analyse some relevant works published on this particular task and highlight the limitations that hinder the application of these works in clinical practice. We also empirically investigate the feasibility of using weakly annotated datasets to support the development of computer-aided diagnosis systems for CRC from WSI. Our study underscores the need for large datasets in this field and the use of an appropriate learning methodology to gain the most benefit from partially annotated datasets. The CRC WSI dataset used in this study, containing 1,133 colorectal biopsy and polypectomy samples, is available upon reasonable request.

### 203. Psychometric validity of the Portuguese version of SWAL-QOL for head and neck cancer.

*Oliveira Vieira, D, Bolle Antunes, E, Dinis-Ribeiro, M and Monteiro, E. Revista de Logopedia, Foniatria y Audiología. 2021;41(3):133-41 [IF: NA]*

**Introduction and aim** In Portugal there are no instruments that measure the impact of dysphagia on the quality of life. The aim of this study was the assessment of the psychometric properties of the Portuguese version of SWAL-QOL, in a head and neck cancer population. **Materials and methods** It was a case-control study, with a consecutive sample of 300 subjects that was divided into 3 groups (2 controls and 1 case). We performed principal components analysis, assessed reliability and clinical validity. For concurrent validity of the Portuguese version of SWAL-QOL, the Functional Scale of Oral Intake (FOIS) and the Performance Status Scale (PSS) for patients with head and neck cancer were used. **Results** The sample was predominantly male (66%) with a mean age of 57 years. Regarding the patients with head and neck cancer, 22% were in stage IIIA, and 43% had lesions on the larynx. As to the treatment provided, 33% underwent surgery and radiotherapy, and 80% of cases had oral feeding. The psychometric validity of SWAL-QOL was established, with good results for internal consistency (from .665 to .952), reproducibility (from .628 to .877) and construct validity. SWAL-QOL also showed good correlation with the clinical variable dysphagics vs. non-dysphagics. There were no statistical significant differences for the consistency of food and fluids, and oral vs. non-oral nutrition. **Conclusions** The validation of SWAL-QOL for the Portuguese language revealed that this instrument is psychometrically valid and appropriate for use with dysphagic patients with head and neck cancer. **Resumen** **Introducción y objetivo** En Portugal no existen instrumentos que midan el impacto de la disfagia en la calidad de vida. El objetivo de este estudio fue evaluar las propiedades psicométricas de la versión portuguesa de SWAL-QOL, en una población de pacientes de cáncer de cabeza y cuello. **Materiales y métodos** Estudio de control de casos, con una muestra consecutiva de 300 sujetos, que se dividió en 3 grupos (2 grupos control y un caso). Realizamos un análisis de los componentes principales, y evaluamos la fiabilidad y la validez clínica. Para la validez concurrente de la versión portuguesa de SWAL-QOL, utilizamos la Functional Scale of Oral Intake (FOIS) y la Performance Status Scale (PSS) para los pacientes de cáncer de cabeza y cuello. **Resultados** La muestra se compuso fundamentalmente de varones (66%), con una edad media de 57 años. Con relación a los pacientes de cáncer de cabeza y cuello, el 22% estaba en estadio IIIA y el 43% tenía lesiones en la laringe. En cuanto a la terapia suministrada, el 33% recibió cirugía y radioterapia y el 80% de los casos recibió alimentación oral. Se estableció la validez psicométrica de SWAL-QOL, con buenos resultados para consistencia interna (de 0,665 a 0,952), reproducibilidad (de 0,628 a 0,877), y validez del constructo. SWAL-QOL reflejó también una buena correlación con la variable clínica disfágicos vs no disfágicos. No se produjeron diferencias estadísticamente significativas para la consistencia de alimentos y líquidos y nutrición oral vs no oral. **Conclusiones** La validación de SWAL-QOL para el idioma portugués reveló que se trata de un instrumento psicométricamente válido para uso con pacientes disfágicos de cáncer de cabeza y cuello.

### 204. Cold versus hot polypectomy/endoscopic mucosal resection-A review of current evidence.

*Ortiqao, R, Weigt, J, Afifi, A and Libanio, D. United European Gastroenterol J. 2021;9(8):938-46 [IF: 4.623]*

**BACKGROUND:** Colonoscopy with polypectomy substantially reduces the risk of colorectal cancer (CRC) but interval cancers still account for 9% of all CRCs, some of which are due to incomplete resection. **AIM:** The aim of this review is to compare the outcomes of cold and hot endoscopic resection and provide technical tips and tricks for optimizing cold snare polypectomy. **RESULTS:** Cold snare polypectomy (CSP) is the standard technique for small ( $\leq 10$  mm) colorectal polyps. For large colonic polyps ( $>10$  mm), hot resection techniques with use of electrocautery (polypectomy or endoscopic mucosal resection) were

recommended until recently. However, the use of electrocoagulation brings serious adverse effects in up to 9% of the patients, such as delayed bleeding, post-polypectomy syndrome and perforation. In recent years, efforts have been made to improve the polypectomy with cold snare in order to avoid these adverse effects of electrocoagulation without compromising the efficacy of the resection. Several authors have recently shown that the complication rates of CSP of polyps >10 mm is close to zero and recurrence rates varies between 5-18%. Lower recurrence rates are found in serrated lesions (<8%).

#### 205. Hydralazine and Panobinostat Attenuate Malignant Properties of Prostate Cancer Cell Lines.

*Pacheco, MB, Camilo, V, Lopes, N, Moreira-Silva, F, Correia, MP, Henrique, R and Jeronimo, C. Pharmaceuticals (Basel). 2021;14(7) [IF: 5.863]*

Among the well-established alterations contributing to prostate cancer (PCa) pathogenesis, epigenetics is an important player in its development and aggressive disease state. Moreover, since no curative therapies are available for advanced stage disease, there is an urgent need for novel therapeutic strategies targeting this subset of patients. Thus, we aimed to evaluate the combined antineoplastic effects of DNA methylation inhibitor hydralazine and histone deacetylase inhibitors panobinostat and valproic acid in several prostate cell lines. The effect of these drugs was assessed in four PCa (LNCaP, 22Rv1, DU145 and PC-3) cell lines, as well as in non-malignant epithelial (RWPE-1) and stromal (WPMY-1) cell lines, using several assays to evaluate cell viability, apoptosis, proliferation, DNA damage and clonogenic potential. We found that exposure to each drug separately reduced viability of all PCa cells in a dose-dependent manner and that combined treatments led to synergic growth inhibitory effects, impacting also on colony formation, invasion, apoptotic and proliferation rates. Interestingly, antitumoral effects of combined treatment were particularly expressive in DU145 cells. We concluded that hydralazine and panobinostat attenuate malignant properties of PCa cells, constituting a potential therapeutic tool to counteract PCa progression.

#### 206. European Cancer Organisation Essential Requirements for Quality Cancer Care (ERQCC): Pancreatic Cancer.

*Partelli, S, Sclafani, F, Barbu, ST, Beishon, M, Bonomo, P, Braz, G, de Braud, F, Brunner, T, Cavestro, GM, Crul, M, Trill, MD, Ferolla, P, Herrmann, K, Karamitopoulou, E, Neuzillet, C, Orsi, F, Seppanen, H, Torchio, M, Valenti, D, Zamboni, G, Zins, M, Costa, A and Poortmans, P. Cancer Treat Rev. 2021;99:102208 [IF: 12.111]*

European Cancer Organisation Essential Requirements for Quality Cancer Care (ERQCC) are written by experts representing all disciplines involved in cancer care in Europe. They give patients, health professionals, managers and policymakers a guide to essential care throughout the patient journey. Pancreatic cancer is an increasing cause of cancer mortality and has wide variation in treatment and care in Europe. It is a major healthcare burden and has complex diagnosis and treatment challenges. Care must be carried out only in pancreatic cancer units or centres that have a core multidisciplinary team (MDT) and an extended team of health professionals detailed here. Such units are far from universal in European countries. To meet European aspirations for comprehensive cancer control, healthcare organisations must consider the requirements in this paper, paying particular attention to multidisciplinary and patient-centred pathways from diagnosis, to treatment, to survivorship.

#### 207. Evidence of psychological and biological effects of structured Mindfulness-Based Interventions for cancer patients and survivors: A meta-review.

*Pedro, J, Monteiro-Reis, S, Carvalho-Maia, C, Henrique, R, Jeronimo, C and Silva, ER. Psychooncology. 2021;30(11):1836-48 [IF: 3.894]*

**OBJECTIVE:** A large number of studies have been conducted exploring the effects of mindfulness programs on health outcomes, such as psychological and biological outcomes. However, there is substantial heterogeneity among studies and, consequently, in the systematic reviews/meta-analyses. Since clinical practice is massively informed by evidence on review studies, our main objective was to summarize the reported evidence regarding the effects of structured mindfulness-based programs on psychological, biological, and quality-of-life outcomes in cancer patients. **METHODS:** We conducted a meta-review, using a literature search from inception to June 2020 in several electronic databases using a combination of keywords including MBSR, MBCT, cancer, and meta-analysis OR "systematic review" (PROSPERO registration CRD42020186511). **RESULTS:** Ten studies met the eligibility criteria and were included. The

main findings were beneficial small to medium effect sizes of Mindfulness-Based Stress Reduction (MBSR)/Mindfulness-Based Cognitive Therapy (MBCT)/Mindfulness-Based Cancer Recovery (MBCR) on psychological health, such as anxiety, depression, stress, and quality of life. A beneficial effect was found for biological outcomes, albeit based on a reduced number of studies. Studies were moderate homogenous regarding the intervention, population, and outcomes explored. Results on long-term follow-up seem to indicate that the effects tend not to be maintained, namely in shorter follow-ups (6 months).

CONCLUSIONS: This meta-review brings a broad perspective on the actual evidence regarding MBSR/MBCT/MBCR. We expect to contribute to future project design, focused on developing high-quality studies and exploring the moderating effects that might contribute to biased results, as well as exploring who might benefit more from MBSR/MBCT/MBCT interventions.

#### 208. Is the ASA Classification Universal?

*Pedrosa, E, Silva, M, Lobo, A, Barbosa, J and Mourao, J. Turk J Anaesthesiol Reanim. 2021;49(4):298-303 [IF: NA]*

OBJECTIVE: The physical status classification of the American Society of Anaesthesiology (ASA) is the most used score in the preoperative evaluation, but inconsistent evaluations and low reliability have been reported. The aim of this study is to evaluate the variability in the evaluation of ASA physical status classification among Portuguese anaesthesiologists. METHODS: Cross-sectional study, in which an electronic questionnaire, was distributed to Portuguese anaesthesiologists with questions regarding their demographic characteristics, professional experience, place of work and how they would categorise 15 clinical cases regarding ASA classification. Three anaesthesiologists and a medicine student wrote the cases. Data analyses were done using R suite version 1.0.143 and IBM SPSS Statistics. The agreement among participants was evaluated through intraclass correlation coefficient (ICC). A value of  $P < .05$  was assumed as statistically significant. RESULTS: 1,850 e-mails were sent, and 259 answers were obtained. Median age of participants was 47 years. 172 were female and 87 males. Ninety percent of work is in the public sector, and 99.6% use this classification on their daily practice. Participants' agreement ranged from 3 to 15 responses, with a mean of 9.2 (SD 6 2.4). In none of the cases was observed a total agreement with the author's classification. The ICC among the participants was 0.726 (0.585; 0.869;  $P < .001$ ), showing a moderate degree of agreement. CONCLUSION: The results of this sample revealed that the agreement among Portuguese anaesthetists is satisfactory and similar to the values observed in other countries where there were no significant differences between trainees and specialists.

#### 209. Placental site trophoblastic tumour: five challenges of patient clinical management.

*Peixinho, C, Almeida, A, Bartosch, C and Cruz Pires, M. BMJ Case Rep. 2021;14(1) [IF: NA]*

Placental site trophoblastic tumour is a rare form of gestational trophoblastic disease accounting for about 1%-2% of all trophoblastic tumours. Diagnosis and management of placental site trophoblastic tumour can be difficult. We report a case of a 30-year-old woman diagnosed with a placental site trophoblastic tumour and identify the challenges in diagnosis and treatment of this rare situation. The presenting sign was abnormal vaginal bleeding that started 3 months after delivery. Image exams revealed an enlarged uterus with a heterogeneous mass, with vesicular pattern, and the increased vascularisation serum human chorionic gonadotropin level was above normal range. The histological diagnosis was achieved through hysteroscopic biopsy. Staging exams revealed pulmonary micronodules. The patient was successfully treated with hysterectomy and chemotherapy. The latest follow-up (37 months after diagnosis) was uneventful, and the patient exhibited no signs of recurrence or metastasis.

#### 210. The Tumour Microenvironment and Circulating Tumour Cells: A Partnership Driving Metastasis and Glycan-Based Opportunities for Cancer Control.

*Peixoto, A, Cotton, S, Santos, LL and Ferreira, JA. Adv Exp Med Biol. 2021;1329:1-33 [IF: 2.622]*

Circulating tumour cells (CTC) are rare cells that actively detach or are shed from primary tumours into the lymph and blood. Some CTC subpopulations gain the capacity to survive, home and colonize distant locations, forming metastasis. This results from a multifactorial process in which cancer cells optimize motility, invasion, immune escape and cooperative relationships with microenvironmental cues. Here we present evidences of a self-fuelling molecular crosstalk between cancer cells and the tumour stroma

supporting the main milestones leading to metastasis. We discuss how the tumour microenvironment supports pre-metastatic niches and CTC development and ultimately dictates CTC fate in targeted organs. Finally, we highlight the key role played by protein glycosylation in metastasis development, its prompt response to microenvironmental stimuli and the tremendous potential of glycan-based molecular signatures for liquid biopsies and targeted therapeutics.

#### **211. Glycoproteomics identifies HOMER3 as a potentially targetable biomarker triggered by hypoxia and glucose deprivation in bladder cancer.**

*Peixoto, A, Ferreira, D, Azevedo, R, Freitas, R, Fernandes, E, Relvas-Santos, M, Gaitero, C, Soares, J, Cotton, S, Teixeira, B, Paulo, P, Lima, L, Palmeira, C, Martins, G, Oliveira, MJ, Silva, AMN, Santos, LL and Ferreira, JA. J Exp Clin Cancer Res. 2021;40(1):191 [IF: 11.161]*

**BACKGROUND:** Muscle invasive bladder cancer (MIBC) remains amongst the deadliest genitourinary malignancies due to treatment failure and extensive molecular heterogeneity, delaying effective targeted therapeutics. Hypoxia and nutrient deprivation, oversialylation and O-glycans shortening are salient features of aggressive tumours, creating cell surface glycoproteome fingerprints with theranostics potential. **METHODS:** A glycomics guided glycoproteomics workflow was employed to identify potentially targetable biomarkers using invasive bladder cancer cell models. The 5637 and T24 cells O-glycome was characterized by mass spectrometry (MS), and the obtained information was used to guide glycoproteomics experiments, combining sialidase, lectin affinity and bottom-up protein identification by nanoLC-ESI-MS/MS. Data was curated by a bioinformatics approach developed in-house, sorting clinically relevant molecular signatures based on Human Protein Atlas insights. Top-ranked targets and glycoforms were validated in cell models, bladder tumours and metastases by MS and immunoassays. Cells grown under hypoxia and glucose deprivation disclosed the contribution of tumour microenvironment to the expression of relevant biomarkers. Cancer-specificity was validated in healthy tissues by immunohistochemistry and MS in 20 types of tissues/cells of different individuals. **RESULTS:** Sialylated T (ST) antigens were found to be the most abundant glycans in cell lines and over 900 glycoproteins were identified potentially carrying these glycans. HOMER3, typically a cytosolic protein, emerged as a top-ranked targetable glycoprotein at the cell surface carrying short-chain O-glycans. Plasma membrane HOMER3 was observed in more aggressive primary tumours and distant metastases, being an independent predictor of worst prognosis. This phenotype was triggered by nutrient deprivation and concomitant to increased cellular invasion. T24 HOMER3 knockdown significantly decreased proliferation and, to some extent, invasion in normoxia and hypoxia; whereas HOMER3 knock-in increased its membrane expression, which was more pronounced under glucose deprivation. HOMER3 overexpression was associated with increased cell proliferation in normoxia and potentiated invasion under hypoxia. Finally, the mapping of HOMER3-glycosites by EThcD-MS/MS in bladder tumours revealed potentially targetable domains not detected in healthy tissues. **CONCLUSION:** HOMER3-glycoforms allow the identification of patients' subsets facing worst prognosis, holding potential to address more aggressive hypoxic cells with limited off-target effects. The molecular rationale for identifying novel bladder cancer molecular targets has been established.

#### **212. Multi-Gene Panel Testing in Gastroenterology: Are We Ready for the Results?**

*Pereira, F, Teixeira, MR, Dinis Ribeiro, M and Brandao, C. GE Port J Gastroenterol. 2021;28(6):403-9 [IF: NA]*

Genetic testing aims to identify patients at risk for inherited cancer susceptibility. In the last decade, there was a significant increase in the request of broader panels of genes as multi-gene panel testing became widely available. However, physicians may be faced with genetic findings for which there is lack of management evidence, despite some progress in understanding their clinical relevance. In this short review, we discuss the advantages and the drawbacks related to multi-gene panel testing in the setting of a Gastrointestinal Familial Cancer Risk clinic. We also summarize the available recommendations on management of pathogenic variant carriers.

#### **213. The CIREL Cohort: A Prospective Controlled Registry Studying the Real-Life Use of Irinotecan-Loaded Chemoembolisation in Colorectal Cancer Liver Metastases: Interim Analysis.**

*Pereira, PL, Iezzi, R, Manfredi, R, Carchesio, F, Bansaghi, Z, Brountzos, E, Spiliopoulos, S, Echevarria-Uraga,*

JJ, Goncalves, B, Inchingolo, R, Nardella, M, Pellerin, O, Sousa, M, Arnold, D, de Baere, T, Gomez, F, Helmlberger, T, Maleux, G, Prenen, H, Sangro, B, Zeka, B, Kaufmann, N and Taieb, J. *Cardiovasc Intervent Radiol*. 2021;44(1):50-62 [IF: 2.740]

**PURPOSE:** Transarterial chemoembolisation (TACE) using irinotecan-eluting beads is an additional treatment option for colorectal cancer liver metastases (CRLM) patients that are not eligible for curative treatment approaches. This interim analysis focuses on feasibility of the planned statistical analysis regarding data distribution and completeness, treatment intention, safety and health-related quality of life (HRQOL) of the first 50 patients prospectively enrolled in the Cirse REgistry for LifePearl microspheres (CIREL), an observational multicentre study conducted across Europe. **METHODS:** In total, 50 patients  $\geq$  18 years diagnosed with CRLM and decided to be treated with irinotecan-eluting LifePearl microspheres TACE (LP-irinotecan TACE) by a multidisciplinary tumour board. There were no further inclusion or exclusion criteria. The primary endpoint is the categorisation of treatment intention, and secondary endpoints presented in this interim analysis are safety, treatment considerations and HRQOL. **RESULTS:** LP-irinotecan TACE was conducted in 42% of patients as salvage therapy, 20% as an intensification treatment, 16% as a first-line treatment, 14% a consolidation treatment and 8% combination treatment with ablation with curative intent. Grade 3 and 4 adverse events were reported by 4% of patients during procedure and by 10% within 30 days. While 38% reported a worse, 62% reported a stable or better global health score, and 54% of patients with worse global health score were treated as salvage therapy patients. **CONCLUSION:** This interim analysis confirms in a prospective analysis the feasibility of the study, with an acceptable toxicity profile. More patients reported a stable or improved HRQOL than deterioration. Deterioration of HRQOL was seen especially in salvage therapy patients. **TRIAL REGISTRATION:** NCT03086096.

#### 214. Prognostic Value of Histone Modifying Enzyme EZH2 in RCHOP-Treated Diffuse Large B-Cell Lymphoma and High Grade B-Cell Lymphoma.

Petronilho, S, Sequeira, JP, Paulino, S, Lopes, P, Lisboa, S, Chacim, S, Lobo, J, Teixeira, M, Jeronimo, C and Henrique, R. *J Pers Med*. 2021;11(12) [IF: 4.945]

**BACKGROUND:** DLBCL represent a heterogeneous group of aggressive diseases. High grade B-cell lymphomas (HGBCL) were recently individualized from DLBCL as a discrete diagnostic entity due to their worse prognosis. Currently, although most patients are successfully treated with RCHOP regimens, 1/3 will either not respond or ultimately relapse. Alterations in histone modifying enzymes have emerged as the most common alterations in DLBCL, but their role as prognostic biomarkers is controversial. We aimed to ascertain the prognostic value of EZH2 immunoexpression in RCHOP-treated DLBCL and HGBCL. **RESULTS:** We performed a retrospective cohort study including 125 patients with RCHOP-treated DLBCL or HGBCL. EZH2 expression levels did not differ between diagnostic groups or between DLBCL-NOS molecular groups. We found no associations between EZH2 expression levels and outcome, including in the subgroup analysis (GC versus non-GC). Nonetheless, EZH2/BCL2 co-expression was significantly associated with worse outcome (event free survival and overall survival). **CONCLUSION:** Although EZH2 mutations are almost exclusively found in GC-DLBCL, we found similar EZH2 expression levels in both DLBCL-NOS molecular groups, suggesting non-mutational mechanisms of EZH2 deregulation. These findings suggest that the use of EZH2 antagonists might be extended to non-GC DLBCL patients with clinical benefit. EZH2/BCL2 co-expression was associated with a worse outcome.

#### 215. Metastatic feline mammary cancer: prognostic factors, outcome and comparison of different treatment modalities - a retrospective multicentre study.

Petrucci, G, Henriques, J, Gregorio, H, Vicente, G, Prada, J, Pires, I, Lobo, L, Medeiros, R and Queiroga, F. *J Feline Med Surg*. 2021;23(6):549-56 [IF: 2.015]

**OBJECTIVES:** Although feline mammary carcinomas (FMCs) are highly metastatic, the literature and treatment options pertaining to advanced tumours are scarce. This study aimed to investigate the clinical outcome of metastatic FMC with or without adjuvant treatment. **METHODS:** The medical records of 73 cats with metastatic FMC (stage IV) were reviewed and included in this study. Metastatic disease was detected by distinct imaging techniques (radiography, ultrasound and CT) and confirmed by cytology and/or histopathology. Cats with adjuvant chemotherapy treatment (n = 34) were divided into three groups: group 1 (n = 9) cats receiving maximum tolerated dose chemotherapy; group 2 (n = 15) cats receiving metronomic

chemotherapy; and group 3 (n = 10) cats treated with toceranib phosphate. The study endpoints were time to progression (TTP) and tumour-specific survival (TSS). Treatment-related toxicity was evaluated according to the Veterinary Co-operative Oncology Group's Common Terminology Criteria for Adverse Events version 1.1 (VCOG-CTCAE). RESULTS: Overall mean TTP and TSS were 23 and 44 days, respectively. Cats with clinical signs at the time of diagnosis had a lower TSS (14 days) than asymptomatic cats (128 days;  $P < 0.001$ ). Cats with pleural effusion had a lower TSS (16 days) than cats without ( $P < 0.001$ ). Median TSS was 58, 75 and 63 days in groups 1, 2 and 3, respectively ( $P = 0.197$ ). Toxicity was observed in 66.7%, 20% and 30% of cats in groups 1, 2 and 3, respectively. CONCLUSIONS AND RELEVANCE: To the best of our knowledge, this study includes the highest number of patients with metastatic FMC assessed. Despite the overall poor prognosis, some cats survived  $>6$  months, indicating that adjuvant treatment may be an option to consider in metastatic disease. More studies are warranted for better understanding and management of stage IV patients.

#### 216. Predictive factors of non-sentinel lymph node disease in breast cancer patients with positive sentinel lymph node.

*Peyroteo, M, Canotilho, R, Correia, AM, Baia, C, Ribeiro, C, Reis, P and de Sousa, A. Cir Esp (Engl Ed). 2020 [IF: 1.653]*

INTRODUCTION: Management of positive sentinel lymph node biopsy (SLNB) in breast cancer remains a matter of debate. Our aim was to evaluate the incidence and identify predictive factors of non-sentinel lymph node metastases. METHODS: Retrospective review of all cN0 breast cancer patients treated between January 2013 and December 2017, with positive SLNB that were submitted to ALND. RESULTS: Of the 328 patients included, the majority of tumors were cT1 or cT2, with lymphovascular invasion in 58.4% of cases. The mean isolated nodes in SLNB was 2.7, with a mean of 1.6 positive nodes, 60.7% with extracapsular extension. Regarding ALND, a mean of 13.9 nodes were isolated, with a mean of 2.1 positive nodes. There was no residual disease in the ALND in 50.9% of patients, with 18.9% having  $\geq$  four positive nodes. In the multivariate analysis, lymphovascular invasion, extracapsular extension in SLN, largest SLN metastases size ( $>10$  mm) and ratio of positive SNL ( $> 50\%$ ) were independent predictors of non-sentinel lymph node metastases. These four factors were used to build a non-pondered score to predict the probability of a positive ALND after a positive SLNB. The AUC of the model was 0.69 and 81% of patients with score = 0 and 65.6% with score = 1 had no additional disease in ALND. CONCLUSION: The absence of non-sentinel lymph node metastases in the majority of patients with 1-2 positive SLN with low risk score questions the need of ALND in this population. The identified predictive factors may help select patients in which ALND can be omitted.

#### 217. Time to invest on research during medical training.

*Peyroteo, M, Moitinho de Almeida, M, Cunha, M, Simoes, J, Alagoa Joao, A, Moreira Azevedo, J, Vieira, B, Cordeiro Sousa, D, Leite, D, Gaio-Lima, C and Sampaio Soares, A. Postgrad Med J. 2021;97(1144):128-9 [IF: 2.401]*

#### 218. Gastric microbiome profile throughout gastric carcinogenesis: beyond helicobacter.

*Pimentel-Nunes, P, Barros, A, Pita, J, Miranda, I, Conceicao, G, Borges-Canha, M, Leite-Moreira, AF, Libanio, D and Dinis-Ribeiro, M. Scand J Gastroenterol. 2021;56(6):708-16 [IF: 2.423]*

BACKGROUND: Gastric dysbiosis has been hinted as a potential cause of gastric cancer. However, changes in microbiome throughout the major stages of gastric carcinogenesis remain mostly unknown. OBJECTIVE: To describe gastric microbiome at different stages, analysing for the first time dysbiosis specifically in patients with early gastric cancer (EGC). METHODS: Cross-sectional study including patients (n = 77) with endoscopically and histologically confirmed normal stomachs (controls; n = 25), advanced atrophic gastritis with intestinal metaplasia (IM; n = 18) and EGC (n = 34). Endoscopic biopsies from antrum and corpus (n = 154) were analyzed. Next-generation sequencing was performed characterizing microbial communities down to the species level based on full-length 16SrRNA gene profiling. RESULTS: Significant differences were found in the microbiome profile between the groups. Firmicutes were more frequent ( $p = .012$ ) and Proteobacteria were less frequent ( $p = .04$ ) both in the IM and EGC when comparing to controls. Relative frequency of *Helicobacter pylori*, when present, was much higher in the controls (83%) when comparing to

the other groups (IM 1%, EGC 27%;  $p = .006$ ), being the dominant bacteria only in the controls. Dysbiosis was present already and more significantly at the IM stage, with two bacteria progressively increasing from controls to IM then to cancer: *Gemella* from 1.48 to 3.9% ( $p = .014$ ); and *Streptococcus* from 19.3 to 33.7% ( $p = .04$ ), being the EGC dominant bacteria. CONCLUSIONS: Our results confirm *Helicobacter pylori* dominance in non-atrophic stomachs and progressive dysbiosis throughout gastric carcinogenesis. *Gemella* but particularly *Streptococcus* is significantly increased in patients with EGC. Specific modulation of these bacteria may change gastric cancer risk.

**219. GE - Portuguese Journal of Gastroenterology: Farewell and Good Luck.**

*Pimentel-Nunes, P, Bispo, M, Almeida, N and Machado, M. GE Port J Gastroenterol. 2021;28(4):227-30 [IF: NA]*

**220. Pain management in cancer patients in the main hospitals in Mozambique.**

*Pinto, E, Goncalves, F, Sacarlal, J, Castro, L and Rego, G. Ann Palliat Med. 2021;10(4):4069-79 [IF: 2.595]*

BACKGROUND: Pain is the most feared and distressing symptom in palliative care. In advanced stages of cancer, its incidence is 70-80%. In Mozambique there is little published information concerning to the prevalence, intensity, and pain's management in cancer patients. METHODS: A cross-sectional observational study was conducted between August 2018 and January 2019, in Mozambique's main hospitals, and in the only hospital with an isolated provision of palliative care service. The analyzed data included demographic data, pain intensity and its treatment. The Pain Management Index was used to calculate the adequacy of the analgesia. RESULTS: A total of 294 patients were included. The mean patients' age was 46.1 years old. Concerning to pain, 83.7% of the patients had pain, most of them moderate to severe pain. The prevalence of pain was frequent in women mainly in cervical cancer (84.3%) and in men with Kaposi sarcoma (80%). The main analgesic used for severe pain was paracetamol, and it was used alone in 40.9% of the patients. Morphine was used in 8.1% and adjuvants less than 10%. Pain Management Index was negative for 68.7% of the sample, meaning an inadequate analgesia. Significant differences were found in Pain Management Index levels between hospitals. CONCLUSIONS: The prevalence of pain in the main health institutions in Mozambique is high. Paracetamol was the analgesic most used in severe pain. Further studies are needed to understand the main reasons of patients' suffering.

**221. Urinary Volatilomics Unveils a Candidate Biomarker Panel for Noninvasive Detection of Clear Cell Renal Cell Carcinoma.**

*Pinto, J, Amaro, F, Lima, AR, Carvalho-Maia, C, Jeronimo, C, Henrique, R, Bastos, ML, Carvalho, M and Guedes de Pinho, P. J Proteome Res. 2021;20(6):3068-77 [IF: 4.466]*

Clear cell renal cell carcinoma (ccRCC) is the most common type of kidney cancer usually associated with asymptomatic development and risk of systemic progression. Hence, reliable molecular biomarkers of ccRCC are needed to provide early and minimally invasive detection. In this study, urinary volatilome profiling of patients diagnosed with ccRCC ( $n = 75$ ), and cancer-free controls ( $n = 75$ ), was performed to investigate the presence of a volatile signature characteristic of ccRCC. Volatile organic compounds (VOCs) in general, and more specifically volatile carbonyl compounds (VCCs), present in urine were extracted by headspace solid-phase microextraction coupled with gas chromatography-mass spectrometry (HS-SPME-GC-MS). Supervised multivariate models showed a good discriminatory power of ccRCC patients from controls in urine. Overall, 22 volatile metabolites were found significantly altered between the two groups, including aldehydes, ketones, aromatic hydrocarbons, and terpenoids. A candidate six-biomarker panel, comprising octanal, 3-methylbutanal, benzaldehyde, 2-furaldehyde, 4-heptanone, and p-cresol, depicted the best performance for ccRCC detection with 83% sensitivity, 79% specificity, and 81% accuracy. Moreover, the ccRCC urinary volatilome signature suggested dysregulation of energy metabolism and overexpression of enzymes associated with carcinogenesis. These findings provide the molecular basis for the fine-tuning of gas-sensing materials for application in the development of a bioelectronic sensor.

**222. Discovery of Volatile Biomarkers for Bladder Cancer Detection and Staging through Urine Metabolomics.**

*Pinto, J, Carapito, A, Amaro, F, Lima, AR, Carvalho-Maia, C, Martins, MC, Jeronimo, C, Henrique, R, Bastos,*

*ML and Guedes de Pinho, P. Metabolites. 2021;11(4) [IF: 4.932]*

Timely diagnosis is crucial to improve the long-term survival of bladder cancer (BC) patients. The discovery of new BC biomarkers based in urine analysis is very attractive because this biofluid is in direct contact with the inner bladder layer, in which most of the neoplasms develop, and is non-invasively collected. Hence, this work aimed to unveil alterations in the urinary volatile profile of patients diagnosed with BC compared with cancer-free individuals, as well as differences among patients diagnosed at different tumor stages, to identify candidate biomarkers for non-invasive BC diagnosis and staging. Urine analysis was performed by headspace solid-phase microextraction coupled with gas chromatography-mass spectrometry (HS-SPME-GC-MS). The results unveiled that BC patients have a distinct urinary volatile profile characterized by higher levels of several alkanes and aromatic compounds, and lower levels of aldehydes, ketones and monoterpenes. Seventeen significantly altered volatiles were used to evaluate the performance for overall BC detection, disclosing 70% sensitivity, 89% specificity and 80% accuracy. Moreover, distinct urinary volatile profiles were found among patients diagnosed at different tumor stages (Ta/Tis, T1 and  $\geq$ T2). This work identified distinct urinary volatile signatures of BC patients with potential for non-invasive detection and staging of bladder cancer.

**223. Pachymeningeal carcinomatosis: an unusual location of metastization of adenoid cystic carcinoma.**

*Pires, A, Vieira, C, Jacome, M, Moreira, D and Arantes, M. Braz J Otorhinolaryngol. 2021;87(4):489-92 [IF: 1.811]*

**224. Original Article: MicroRNA Dysregulation in the Gastric Carcinogenesis Cascade: Can We Anticipate Its Role in Individualized Care?**

*Pita, I, Libanio, D, Dias, F, Teixeira, AL, Noqueira, I, Medeiros, R, Dinis-Ribeiro, M and Pimentel-Nunes, P. Pathobiology. 2021;88(5):338-50 [IF: 4.342]*

**BACKGROUND:** Gastric carcinogenesis progresses from normal mucosa, atrophic/metaplastic gastritis, and dysplasia to adenocarcinoma. MicroRNAs (miRNAs) regulate DNA expression and have been implicated; however, their role is not fully established. **AIMS:** The aim of this study was to characterize plasma and tissue expression of several miRNAs in gastric carcinogenesis stages. **METHODS:** Single-center cross-sectional study in 64 patients: 19 controls (normal mucosa); 15 with extensive atrophic/metaplastic gastritis; and 30 with early gastric neoplasia (EGN). Seven miRNAs (miR-21, miR-146a, miR-181b, miR-370, miR-375, miR 181b, and miR-490) were quantified by real time-qPCR in peripheral blood and endoscopic biopsy samples. **RESULTS:** We found a significant upregulation of miR-181b, miR-490, and miR-21 in the EGN mucosa (overexpression 2-14-times higher than controls). We observed a significant underexpression of miR-146a and miR-370 in atrophic/metaplastic gastritis (86 and 66% decrease,  $p = 0.008$  and  $p = 0.001$ ) and in EGN (89 and 62% reduction,  $p = 0.034$  and  $p = 0.032$ ) compared with controls. There were no differences between lesions and nonneoplastic mucosa and no dysregulation of plasma miRNAs.

**CONCLUSION:** We found significant dysregulation of 5 miRNAs in gastric carcinogenesis, suggesting a tumor suppressor role for miR-146a and miR-370 and oncogenic potential for miR-21, miR-181, and miR-490.

These changes happen diffusely in the gastric mucosa, suggesting a high-risk field defect, which may influence these patients' surveillance.

**225. Endoscopic ultrasound-guided sampling of gastrointestinal subepithelial lesions: just wet it.**

*Pita, I, Pimentel-Nunes, P, Dinis-Ribeiro, M and Bastos, P. Eur J Gastroenterol Hepatol. 2021;33(12):1533-8 [IF: 4.029]*

**INTRODUCTION:** Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) is the main method for acquisition of tissue from gastrointestinal subepithelial lesions (SELs). Despite the development of new needles, diagnostic yield remains low. A new method of aspiration has been described, where the needle is filled with saline [wet-suction technique (WST)], with promising results in pancreatic lesions. This method has not been tested in SELs. **AIMS AND METHODS:** Prospective single center study to assess the diagnostic yield of EUS-FNA+WST in the diagnosis of SELs, without the use of rapid on-site evaluation. In mesenchymal tumors, the diagnosis was considered positive only when immunohistochemistry could differentiate between gastrointestinal stromal tumor and leiomyoma. **RESULTS:** Eighty-seven patients with SELs were included (55% male, mean age 66 years). Mean SEL size was 25 mm (min 10 mm, max 120 mm), mean

number of passes was 3 (+/-0.8). A 22G needle was used in 72 patients (83%), 19G in 10 (12%) and 25G in 5 (6%). We obtained a conclusive cytopathological diagnosis in 74 cases (diagnostic yield of 85%) and immunohistochemistry was performed in 70 cases (81%). The most frequent diagnoses were gastrointestinal stromal tumor (n = 34, 37%), leiomyoma (n = 13, 15%) and metastases (n = 10, 11%). CONCLUSION: Wet suction technique allowed an excellent diagnostic yield in the EUS-guided evaluation of SELs. We suggest that, after proper replication of these results, WST may become the first-line method in the management of these lesions.

## 226. Endoscopic tissue sampling - Part 1: Upper gastrointestinal and hepatopancreatobiliary tracts. European Society of Gastrointestinal Endoscopy (ESGE) Guideline.

*Pouw, RE, Barret, M, Biermann, K, Bisschops, R, Czako, L, Gecse, KB, de Hertogh, G, Hucl, T, Iacucci, M, Jansen, M, Rutter, M, Savarino, E, Spaander, MCW, Schmidt, PT, Vieth, M, Dinis-Ribeiro, M and van Hooft, JE. Endoscopy. 2021;53(11):1174-88 [IF: 10.093]*

1: ESGE recommends that, where there is a suspicion of eosinophilic esophagitis, at least six biopsies should be taken, two to four biopsies from the distal esophagus and two to four biopsies from the proximal esophagus, targeting areas with endoscopic mucosal abnormalities. Distal and proximal biopsies should be placed in separate containers. Strong recommendation, low quality of evidence. 2: ESGE recommends obtaining six biopsies, including from the base and edge of the esophageal ulcers, for histologic analysis in patients with suspected viral esophagitis. Strong recommendation, low quality of evidence. 3: ESGE recommends at least six biopsies are taken in cases of suspected advanced esophageal cancer and suspected advanced gastric cancer. Strong recommendation, moderate quality of evidence. 4: ESGE recommends taking only one to two targeted biopsies for lesions in the esophagus or stomach that are potentially amenable to endoscopic resection (Paris classification 0-I, 0-II) in order to confirm the diagnosis and not compromise subsequent endoscopic resection. Strong recommendation, low quality of evidence. 5: ESGE recommends obtaining two biopsies from the antrum and two from the corpus in patients with suspected *Helicobacter pylori* infection and for gastritis staging. Strong recommendation, low quality of evidence. 6: ESGE recommends biopsies from or, if endoscopically resectable, resection of gastric adenomas. Strong recommendation, moderate quality of evidence. 7: ESGE recommends fine-needle aspiration (FNA) and fine-needle biopsy (FNB) needles equally for sampling of solid pancreatic masses. Strong recommendation, high quality evidence. 8: ESGE suggests performing peroral cholangioscopy (POC) and/or endoscopic ultrasound (EUS)-guided tissue acquisition in indeterminate biliary strictures. For proximal and intrinsic strictures, POC is preferred. For distal and extrinsic strictures, EUS-guided sampling is preferred, with POC where this is not diagnostic. Weak recommendation, low quality evidence. 9: ESGE suggests obtaining possible non-neoplastic biopsies before sampling suspected malignant lesions to prevent intraluminal spread of malignant disease. Weak recommendation, low quality of evidence. 10: ESGE suggests dividing EUS-FNA material into smears (two per pass) and liquid-based cytology (LBC), or the whole of the EUS-FNA material can be processed as LBC, depending on local experience. Weak recommendation, low quality evidence.

## 227. Endoscopic tissue sampling - Part 2: Lower gastrointestinal tract. European Society of Gastrointestinal Endoscopy (ESGE) Guideline.

*Pouw, RE, Bisschops, R, Gecse, KB, de Hertogh, G, Iacucci, M, Rutter, M, Barret, M, Biermann, K, Czako, L, Hucl, T, Jansen, M, Savarino, E, Spaander, MCW, Schmidt, PT, Dinis-Ribeiro, M, Vieth, M and van Hooft, JE. Endoscopy. 2021;53(12):1261-73 [IF: 10.093]*

1: ESGE suggests performing segmental biopsies (at least two from each segment), which should be placed in different specimen containers (ileum, cecum, ascending, transverse, descending, and sigmoid colon, and rectum) in patients with clinical and endoscopic signs of colitis. Weak recommendation, low quality of evidence. 2: ESGE recommends taking two biopsies from the right hemicolon (ascending and transverse colon) and, in a separate container, two biopsies from the left hemicolon (descending and sigmoid colon) when microscopic colitis is suspected. Strong recommendation, low quality of evidence. 3: ESGE recommends pancolonial dye-based chromoendoscopy or virtual chromoendoscopy with targeted biopsies of any visible lesions during surveillance endoscopy in patients with inflammatory bowel disease. Strong recommendation, moderate quality of evidence. 4: ESGE suggests that, in high risk patients with a history

of colonic neoplasia, tubular-appearing colon, strictures, ongoing therapy-refractory inflammation, or primary sclerosing cholangitis, chromoendoscopy with targeted biopsies can be combined with four-quadrant non-targeted biopsies every 10 cm along the colon. Weak recommendation, low quality of evidence. 5: ESGE recommends that, if pouch surveillance for dysplasia is performed, visible abnormalities should be biopsied, with at least two biopsies systematically taken from each of the afferent ileal loop, the efferent blind loop, the pouch, and the anorectal cuff. Strong recommendation, low quality of evidence. 6: ESGE recommends that, in patients with known ulcerative colitis and endoscopic signs of inflammation, at least two biopsies be obtained from the worst affected areas for the assessment of activity or the presence of cytomegalovirus; for those with no evident endoscopic signs of inflammation, advanced imaging technologies may be useful in identifying areas for targeted biopsies to assess histologic remission if this would have therapeutic consequences. Strong recommendation, low quality of evidence. 7: ESGE suggests not biopsying endoscopically visible inflammation or normal-appearing mucosa to assess disease activity in known Crohn's disease. Weak recommendation, low quality of evidence. 8: ESGE recommends that adequately assessed colorectal polyps that are judged to be premalignant should be fully excised rather than biopsied. Strong recommendation, low quality of evidence. 9: ESGE recommends that, where endoscopically feasible, potentially malignant colorectal polyps should be excised en bloc rather than being biopsied. If the endoscopist cannot confidently perform en bloc excision at that time, careful representative images (rather than biopsies) should be taken of the potential focus of cancer, and the patient should be rescheduled or referred to an expert center. Strong recommendation, low quality of evidence. 10: ESGE recommends that, in malignant lesions not amenable to endoscopic excision owing to deep invasion, six carefully targeted biopsies should be taken from the potential focus of cancer. Strong recommendation, low quality of evidence.

#### **228. An Iterative Algorithm for Semisupervised Classification of Hotspots on Bone Scintigraphies of Patients with Prostate Cancer.**

*Providencia, L, Domingues, I and Santos, J. J Imaging. 2021;7(8) [IF: NA]*

Prostate cancer (PCa) is the second most diagnosed cancer in men. Patients with PCa often develop metastases, with more than 80% of this metastases occurring in bone. The most common imaging technique used for screening, diagnosis and follow-up of disease evolution is bone scintigraphy, due to its high sensitivity and widespread availability at nuclear medicine facilities. To date, the assessment of bone scans relies solely on the interpretation of an expert physician who visually assesses the scan. Besides this being a time consuming task, it is also subjective, as there is no absolute criteria neither to identify bone metastases neither to quantify them by a straightforward and universally accepted procedure. In this paper, a new algorithm for the false positives reduction of automatically detected hotspots in bone scintigraphy images is proposed. The motivation relies in the difficulty of building a fully annotated database. In this way, our algorithm is a semisupervised method that works in an iterative way. The ultimate goal is to provide the physician with a fast, precise and reliable tool to quantify bone scans and evaluate disease progression and response to treatment. The algorithm is tested in a set of bone scans manually labeled according to the patient's medical record. The achieved classification sensitivity, specificity and false negative rate were 63%, 58% and 37%, respectively. Comparison with other state-of-the-art classification algorithms shows superiority of the proposed method.

#### **229. Implementing ICHOM standard set for cataract surgery at IPO-Porto (Portugal): clinical outcomes, quality of life and costs.**

*Queiros, L, Redondo, P, Franca, M, Silva, SE, Borges, P, de Melo, AB, Pereira, N, da Costa, PF, Carvalho, N, Borges, M, Sequeira, I, Goncalves, FNR and Lemos, J. BMC Ophthalmol. 2021;21(1):119 [IF: 2.209]*

**BACKGROUND:** This paper fills a gap in the applied research field, for a local context, by addressing the topics of describing cataract surgery' clinical outcomes; quality of life (QoL); and costs of the patients treated after the implementation of the ICHOM standard set. **METHODS:** This is a retrospective observational study using real-world data (RWD). We included all patients subjected to cataract surgery at the Portuguese Institute of oncology - Porto (IPO-Porto), Portugal, after 3 months follow up period completed between 5th June 2017 and 21st May 2018. The following inclusion criteria: corrected visual acuity of  $\leq 6/10$  or other significant visual disturbance due to lens opacity or the existence of a large

anisometropia. A circuit was implemented based on the ICHOM standard for cataract, to measure clinical variables (e.g. visual acuity) and QoL (CATQUEST-9SF) before and after surgery, and cost of treatment. The results were explored by means of a paired-sample t-test, considering normality assumptions. RESULTS: Data refers to 268 patients (73 P25-P75:32-95 years old), regarding 374 eyes. The cataract surgery had a positive effect on visual acuity ( $p < 0.001$ ), refraction (right and left cylinder;  $p < 0.001$ ) and all QoL dimensions. The vast majority of patients, around 98%, reported improvements in QoL. Based on IPO-Porto administrative records, the direct cost of treating cataracts (per eye) is of 500euro, representing a total cost of 187,000euro for the number of patients operated herein. CONCLUSION: This study reports the successful implementation of the ICHOM standard set for cataracts in a Portuguese institution and confirms that cataract surgery provides a rapid visual recovery, with excellent visual outcomes and minimal complications in most patients, while also having a positive impact on patients' quality of life.

### 230. Drug Repurposing Opportunities in Pancreatic Ductal Adenocarcinoma.

Rebelo, R, Polonia, B, Santos, LL, Vasconcelos, MH and Xavier, CPR. *Pharmaceuticals (Basel)*. 2021;14(3) [IF: 5.863]

Pancreatic ductal adenocarcinoma (PDAC) is considered one of the deadliest tumors worldwide. The diagnosis is often possible only in the latter stages of the disease, with patients already presenting an advanced or metastatic tumor. It is also one of the cancers with poorest prognosis, presenting a five-year survival rate of around 5%. Treatment of PDAC is still a major challenge, with cytotoxic chemotherapy remaining the basis of systemic therapy. However, no major advances have been made recently, and therapeutic options are limited and highly toxic. Thus, novel therapeutic options are urgently needed. Drug repurposing is a strategy for the development of novel treatments using approved or investigational drugs outside the scope of the original clinical indication. Since repurposed drugs have already completed several stages of the drug development process, a broad range of data is already available. Thus, when compared with de novo drug development, drug repurposing is time-efficient, inexpensive and has less risk of failure in future clinical trials. Several repurposing candidates have been investigated in the past years for the treatment of PDAC, as single agents or in combination with conventional chemotherapy. This review gives an overview of the main drugs that have been investigated as repurposing candidates, for the potential treatment of PDAC, in preclinical studies and clinical trials.

### 231. Inflammation as a Possible Trigger for Mitoxantrone-Induced Cardiotoxicity: An In Vivo Study in Adult and Infant Mice.

Reis-Mendes, A, Dorés-Sousa, JL, Padrao, AI, Duarte-Araujo, M, Duarte, JA, Seabra, V, Gonçalves-Monteiro, S, Remiao, F, Carvalho, F, Sousa, E, Bastos, ML and Costa, VM. *Pharmaceuticals (Basel)*. 2021;14(6) [IF: 5.863]

Mitoxantrone (MTX) is a pharmaceutical drug used in the treatment of several cancers and refractory multiple sclerosis (MS). Despite its therapeutic value, adverse effects may be severe, namely the frequently reported cardiotoxicity, whose mechanisms need further research. This work aimed to assess if inflammation or oxidative stress-related pathways participate in the cardiotoxicity of MTX, using the mouse as an animal model, at two different age periods (infant or adult mice) using two therapeutic relevant cumulative doses. Histopathology findings showed that MTX caused higher cardiac toxicity in adults. In MTX-treated adults, at the highest dose, noradrenaline cardiac levels decreased, whereas at the lowest cumulative dose, protein carbonylation increased and the expression of nuclear factor kappa B (NF-kappaB) p65 subunit and of M1 macrophage marker increased. Moreover, MTX-treated adult mice had enhanced expression of NF-kappaB p52 and tumour necrosis factor (TNF-alpha), while decreasing interleukin-6 (IL-6). Moreover, while catalase expression significantly increased in both adult and infant mice treated with the lowest MTX cumulative dose, the expression of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and glutathione peroxidase only significantly increased in infant animals. Nevertheless, the ratio of GAPDH to ATP synthase subunit beta decreased in adult animals. In conclusion, clinically relevant doses of MTX caused dissimilar responses in adult and infant mice, being that inflammation may be an important trigger to MTX-induced cardiotoxicity.

### 232. Role of Inflammation and Redox Status on Doxorubicin-Induced Cardiotoxicity in Infant and Adult

**CD-1 Male Mice.**

*Reis-Mendes, A, Padrao, AI, Duarte, JA, Goncalves-Monteiro, S, Duarte-Araujo, M, Remiao, F, Carvalho, F, Sousa, E, Bastos, ML and Costa, VM. Biomolecules. 2021;11(11) [IF: 5.863]*

Doxorubicin (DOX) is a topoisomerase II inhibitor commonly used in the treatment of several types of cancer. Despite its efficacy, DOX can potentially cause fatal adverse effects, like cardiotoxicity. This work aimed to assess the role of inflammation in DOX-treated infant and adult mice and its possible link to underlying cardiotoxicity. Two groups of CD-1 male mice of different ages (infants or adults) were subjected to biweekly DOX administrations, to reach a cumulative dose of 18.0 mg/kg, which corresponds approximately in humans to 100.6 mg/m<sup>2</sup> for infants and 108.9 mg/m<sup>2</sup> for adults a clinically relevant dose in humans. The classic plasmatic markers of cardiotoxicity increased, and that damage was confirmed by histopathological findings in both groups, although it was higher in adults. Moreover, in DOX-treated adults, an increase of cardiac fibrosis was observed, which was accompanied by an increase in specific inflammatory parameters, namely, macrophage M1 and nuclear factor kappa B (NF-kappaB) p65 subunit, with a trend toward increased levels of the tumor necrosis factor receptor 2 (TNFR2). On the other hand, the levels of myeloperoxidase (MPO) and interleukin (IL)-6 significantly decreased in DOX-treated adult animals. In infants, a significant increase in cardiac protein carbonylation and in the levels of nuclear factor erythroid-2 related factor 2 (Nrf2) was observed. In both groups, no differences were found in the levels of tumor necrosis factor (TNF-alpha), IL-1beta, p38 mitogen-activated protein kinase (p38 MAPK) or NF-kappaB p52 subunit. In conclusion, using a clinically relevant dose of DOX, our study demonstrated that cardiac effects are associated not only with the intensity of the inflammatory response but also with redox response. Adult mice seemed to be more prone to DOX-induced cardiotoxicity by mechanisms related to inflammation, while infant mice seem to be protected from the damage caused by DOX, possibly by activating such antioxidant defenses as Nrf2.

### **233. Impact of Body Mass Index, Age and Tobacco Use on the Outcomes of Immediate Breast Reconstruction with Implants and Acellular Dermal Matrix.**

*Ribeiro, LM, Meireles, RP, Brito, IM, Costa, PM, Rebelo, MA, Barbosa, RF, Choupina, MP, Pinho, CJ and Ribeiro, MP. Indian J Plast Surg. 2021;54(3):350-7 [IF: NA]*

**Background** This study aimed to analyze the effect of body mass index (BMI), age, and tobacco use on alloplastic breast reconstruction. **Methods** We conducted a retrospective study of patients who submitted to immediate breast reconstructions with an anatomical implant and acellular dermal matrix in a single center between 2016 and 2018. Outcomes evaluated included immediate complications, early complications, reinterventions, readmissions, and reconstruction failure. Patients were divided into two groups concerning each potential risk factor (BMI < or >=25; age < or >= 50 years; and smokers vs nonsmokers). Simple descriptive statistics and univariate analysis were performed. **Results** A total of 101 breast reconstructions (73 patients) were included in the analysis. The mean BMI was 24, and the mean age was 44.5 years old. Smokers accounted for 14 breast reconstructions (13.9%). The rate of early infections, mastectomy flap necrosis, and implant removal was significantly higher in overweight patients. The total volume of breast drainage was higher in the age >= 50 years group. Smoking did not alter the outcomes. **Conclusions** A BMI >= 25 is a risk factor for early infections and reconstructive failure. Age >= 50 years is associated with a higher volume of breast drainage but does not seem to impact the success of the reconstruction. Smoking does not appear to affect the outcomes significantly in this type of reconstruction. Surgeons should consider delaying the reconstruction or using autologous tissue when patients are overweight.

### **234. El análisis semicuantitativo de la PET con [18F]FDG interim es superior para predecir la evolución en los pacientes con linfoma de Hodgkin en comparación con el análisis visual.**

*Ribeiro, T, Marques, A, Ferreira, G, Castro, C, Tavares, M, Espírito-Santo, A, Moreira, C and Mariz, J. Revista Española de Medicina Nuclear e Imagen Molecular. 2021;40(5):281-6 [IF: 1.359]*

**PURPOSE:** To investigate the prognostic value of interim PET (PETi) in adult HL patients, comparing visual with semiquantitative analysis. **MATERIAL AND METHODS:** Retrospective analysis of Hodgkin's Lymphoma (HL) patients diagnosed between 2012 and 2016 in the Onco-Hematology Department of Instituto Portugues de Oncologia - Porto (median follow-up: 46.5 months [2,6-66,4]). Fifty-eight patients with

available PET at diagnosis (PET0) and PETi data were included. PETi scans were analysed according to Deauville 5-point scale (5-PS), and cut-off values for changes in maximum standardized uptake value [SUVmax], peak SUV [SUVpeak], metabolic tumour volume [MTV] and total lesion glycolysis index [TLG] between PETi and PET0 were computed using ROC analysis. Visual and semiquantitative data were compared with each other in the prediction of patient outcomes. RESULTS: Semiquantitative analysis obtained a higher sensitivity for persistent/relapsed disease compared to the 5-PS (70% vs. 10%, respectively), but lower specificity. It also demonstrated better predictive performance for response to first-line therapy (negative predictive value > 92%). The positive predictive value was similar for all five measurements. At 60 months of follow-up, there was a significant difference between the progression free survival (PFS) curves of patients with positive and negative PETi according to DeltaSUVmax (56.9% vs. 88.0%,  $p < 0.05$ ), DeltaSUVpeak (55.9% vs 88.1%,  $p < 0.05$ ), DeltaMTV (35.3% vs. 88.7%,  $p < 0.05$ ), and DeltaTLG (42.4% vs. 88.1%,  $p < 0.05$ ). Statistical significance wasn't reached when considering 5-PS results. DISCUSSION: PETi interpretation according to a semiquantitative approach appears to discriminate HL patients better than the visual 5-PS analysis. This could allow better detection of persistent or early relapsed disease, while a negative PETi result could support de-escalating therapy intensity.

### 235. The Porto European Cancer Research Summit 2021.

Ringborg, U, Berns, A, Celis, JE, Heitor, M, Tabernero, J, Schuz, J, Baumann, M, Henrique, R, Apro, M, Basu, P, Beets-Tan, R, Besse, B, Cardoso, F, Carneiro, F, van den Eede, G, Eggermont, A, Frohling, S, Galbraith, S, Garralda, E, Hanahan, D, Hofmarcher, T, Jonsson, B, Kallioniemi, O, Kasler, M, Kondorosi, E, Korbel, J, Lacombe, D, Carlos Machado, J, Martin-Moreno, JM, Meunier, F, Nagy, P, Nuciforo, P, Oberst, S, Oliveiera, J, Papatriantafyllou, M, Ricciardi, W, Roediger, A, Ryll, B, Schilsky, R, Scocca, G, Seruca, R, Soares, M, Steindorf, K, Valentini, V, Voest, E, Weiderpass, E, Wilking, N, Wren, A and Zitvogel, L. *Mol Oncol*. 2021;15(10):2507-43 [IF: 6.603]

Key stakeholders from the cancer research continuum met in May 2021 at the European Cancer Research Summit in Porto to discuss priorities and specific action points required for the successful implementation of the European Cancer Mission and Europe's Beating Cancer Plan (EBCP). Speakers presented a unified view about the need to establish high-quality, networked infrastructures to decrease cancer incidence, increase the cure rate, improve patient's survival and quality of life, and deal with research and care inequalities across the European Union (EU). These infrastructures, featuring Comprehensive Cancer Centres (CCCs) as key components, will integrate care, prevention and research across the entire cancer continuum to support the development of personalized/precision cancer medicine in Europe. The three pillars of the recommended European infrastructures - namely translational research, clinical/prevention trials and outcomes research - were pondered at length. Speakers addressing the future needs of translational research focused on the prospects of multiomics assisted preclinical research, progress in Molecular and Digital Pathology, immunotherapy, liquid biopsy and science data. The clinical/prevention trial session presented the requirements for next-generation, multicentric trials entailing unified strategies for patient stratification, imaging, and biospecimen acquisition and storage. The third session highlighted the need for establishing outcomes research infrastructures to cover primary prevention, early detection, clinical effectiveness of innovations, health-related quality-of-life assessment, survivorship research and health economics. An important outcome of the Summit was the presentation of the Porto Declaration, which called for a collective and committed action throughout Europe to develop the cancer research infrastructures indispensable for fostering innovation and decreasing inequalities within and between member states. Moreover, the Summit guidelines will assist decision making in the context of a unique EU-wide cancer initiative that, if expertly implemented, will decrease the cancer death toll and improve the quality of life of those confronted with cancer, and this is carried out at an affordable cost.

### 236. Promoter Demethylation Upregulates STEAP1 Gene Expression in Human Prostate Cancer: In Vitro and In Silico Analysis.

Rocha, SM, Sousa, I, Gomes, IM, Arinto, P, Costa-Pinheiro, P, Coutinho, E, Santos, CR, Jeronimo, C, Lemos, MC, Passarinha, LA, Socorro, S and Maia, CJ. *Life (Basel)*. 2021;11(11) [IF: 3.817]

The Six Transmembrane Epithelial Antigen of the Prostate (STEAP1) is an oncogene overexpressed in several human tumors, particularly in prostate cancer (PCa). However, the mechanisms involved in its

overexpression remain unknown. It is well known that epigenetic modifications may result in abnormal gene expression patterns, contributing to tumor initiation and progression. Therefore, this study aimed to analyze the methylation pattern of the STEAP1 gene in PCa versus non-neoplastic cells. Bisulfite amplicon sequencing of the CpG island at the STEAP1 gene promoter showed a higher methylation level in non-neoplastic PNT1A prostate cells than in human PCa samples. Bioinformatic analysis of the GEO datasets also showed the STEAP1 gene promoter as being demethylated in human PCa, and a negative association with STEAP1 mRNA expression was observed. These results are supported by the treatment of non-neoplastic PNT1A cells with DNMT and HDAC inhibitors, which induced a significant increase in STEAP1 mRNA expression. In addition, the involvement of HDAC in the regulation of STEAP1 mRNA expression was corroborated by a negative association between STEAP1 mRNA expression and HDAC4,5,7 and 9 in human PCa. In conclusion, our work indicates that STEAP1 overexpression in PCa can be driven by the hypomethylation of STEAP1 gene promoter.

### **237. Effectiveness of a pharmacist-led intervention on inhalation technique for asthma and COPD patients: The INSPIRA pilot cluster-randomized controlled trial.**

*Rodrigues, AT, Romano, S, Romao, M, Figueira, D, Bulhosa, C, Madeira, A, Rocha, L and Alves, J. Respir Med. 2021;185:106507 [IF: 3.451]*

**INTRODUCTION:** Asthma and COPD are leading causes of disability-adjusted life-years worldwide representing a huge burden on the health system and among patients. One of the reasons for the lack of disease control is poor inhalation technique, with impact on quality of life and symptom control. **OBJECTIVE:** To assess the effectiveness of a community pharmacist-led educational intervention on asthma and COPD patients' inhalation technique. **METHODS:** The INspira study is a 6-month pilot cluster randomized controlled trial, conducted in community pharmacies of Portugal, enrolling adults aged 18 years or older, with a self-reported diagnosis of asthma or COPD and on inhaled therapy. Pharmacies were randomly allocated to Intervention or Control group. Intervention focused mainly on inhalation technique education via demonstration and repetition. Primary outcome was the proportion of patients scoring 100% in at least one inhaler. **RESULTS:** From January to November 2019, 48 pharmacies recruited 201 asthma and COPD patients, of which 132 completed the 6-month follow-up. At the end of follow-up, the odds of intervention group patients score 100% compared to the control group were 5.63 (95% CI, [2.21; 14.35]) in all inhalers in use and 6.77 (95% CI, [2.52; 18.20]) considering at least one inhaler. Intervention group patients reported having a significantly lower number of scheduled appointments compared with the control group (OR = 0.17; 95% CI, [0.037; 0.79]; p = 0.0135). No other significant differences were found between groups. **CONCLUSION:** This pilot study suggested that pharmacist interventions can improve patients' inhalation technique, with possible positive impact in healthcare resource use.

### **238. Clinical Characteristics, Treatment and Evolution of Splenic and Nodal Marginal Zone Lymphomas- Retrospective and Multicentric Analysis of Portuguese Centers.**

*Rodrigues, CD, Peixeiro, RP, Viegas, D, Choro, P, Couto, ME, Gaspar, CL, Fernandes, JP, Alves, D, Ribeiro, LA, de Vasconcelos, MP, Tome, AL, Badior, M, Coelho, H, Principe, F, Chacim, S, da Silva, MG and Coutinho, R. Clin Lymphoma Myeloma Leuk. 2021;21(11):e839-e44 [IF: 3.231]*

**INTRODUCTION:** Treatment of Splenic (SMZL) and Nodal (NMZL) Marginal Zone Lymphoma is not consensual. Histologic transformation (HT) to aggressive lymphoma is a poorly understood event, with an unfavorable outcome. **OBJECTIVES:** Describe the clinical characteristics, treatment, outcomes and incidence of HT. **METHODS:** Characteristics of patients with SMZL and NMZL consecutively diagnosed in 8 Portuguese centers were retrospectively reviewed. Endpoints were overall survival (OS), time to first systemic treatment (TTFST), frequency of HT and time to transformation (TTT). **RESULTS:** This study included 122 SMZL and 68 NMZL, most of them received systemic treatment: 55.4% and 76.5%, respectively. Splenectomy was performed in 58.7% of patients with SMZL. Different treatment protocols were used. OS or TTFST did not differ significantly according to treatments. Given the small sample size, no conclusion can be made concerning the role of Rituximab in the treatment of NMZL and SMZL based in these results. HT was documented in 18 patients, mainly in SMZL, with a cumulative incidence at 5 years of 4.2%. We confirmed that age is a prognostic factor. **CONCLUSION:** Randomized prospective trials are needed to standardize treatment in MZL. Patients with HT did appear to have shorter OS in comparison with those

who did not experience HT (OS 5 years of 68.4% vs. 80.4%), but the number of HT was too small to reach statistical significance.

**239. Pathological stage, surgical margin and lymphovascular invasion as prognostic factors after salvage radiotherapy for post-prostatectomy relapsed prostate cancer - outcomes and optimization strategies.**

*Rodrigues, J, Ferreira, C, Goncalves, J, Carvalho, L, Oliveira, J, Castro, C and Oliveira, A. Rep Pract Oncol Radiother. 2021;26(4):535-44 [IF: NA]*

Background: Salvage radiotherapy (sRT) is the main potentially curative treatment after biochemical failure/locoregional relapse post-radical prostatectomy (RP). The aim of the study was to characterize the population who underwent sRT after RP at our Department, to understand the influence of several potential prognosis factors, and to determine possible optimization strategies. Materials and methods: We retrospectively analyzed patients undergoing sRT at our department between 2012 and 2017, evaluating patient, tumor and treatment characteristics, restaging procedures and clinical outcomes - namely biochemical relapse-free survival (BC-RFS), clinical relapse-free survival (C-RFS), additional hormone therapy-free survival (HT-FS) and overall survival (OS). We assessed potential prognostic factors by univariate and multivariate models (MVA). Results: We included 277 patients (median age 68 years). Median pre-sRT PSA was  $> 0.5$  ng/mL in 54.9%. All underwent prostate bed irradiation. Pelvic lymph nodes were included in 9.7%. Outcome analysis was performed for 264 patients (35.6 months median follow-up). At 3 years, BC-RFS was 61.4%, C-RFS was 81.3%, HT-FS was 79.9% and OS was 96.6%. Most relapses occurred in regional lymph nodes only (47.9% patients who relapsed). On MVA, lymphovascular invasion, advanced pT-stages and negative margins negatively influenced BC-RFS ( $p = 0.029$ ,  $p = 0.002$  and  $p < 0.001$ ) and HT-FS ( $p = 0.001$ ,  $p = 0.029$  and  $p = 0.002$ ). C-RFS was worsened by lymphovascular invasion ( $p = 0.009$ ) and negative margins ( $p = 0.015$ ). These had no effect on OS. BC-RFS and HT-FS were improved when sRT started while PSA  $\leq 0.5$  ng/mL ( $p < 0.05$ ). Conclusion: Lymphovascular invasion, higher pT-stages and negative margins negatively affected prognosis. An early start of sRT (PSA  $\leq 0.5$  ng/mL) predicted better BC-RFS and HT-FS.

**240. Long-Term Outcomes After Autologous Versus Allogeneic Stem Cell Transplantation in Molecularly-Stratified Patients With Intermediate Cytogenetic Risk Acute Myeloid Leukemia: A PETHEMA Study.**

*Rodriguez-Arboli, E, Martinez-Cuadron, D, Rodriguez-Veiga, R, Carrillo-Cruz, E, Gil-Cortes, C, Serrano-Lopez, J, Bernal Del Castillo, T, Martinez-Sanchez, MDP, Rodriguez-Medina, C, Vidriales, B, Bergua, JM, Benavente, C, Garcia-Boyero, R, Herrera-Puente, P, Algarra, L, Sayas-Lloris, MJ, Fernandez, R, Labrador, J, Lavilla-Rubira, E, Barrios-Garcia, M, Tormo, M, Serrano-Maestro, A, Sossa-Melo, CL, Garcia-Belmonte, D, Vives, S, Rodriguez-Gutierrez, JI, Albo-Lopez, C, Garrastazul-Sanchez, MP, Colorado-Araujo, M, Mariz, J, Sanz, MA, Perez-Simon, JA, Montesinos, P, Pethema and Groups, GC. Transplant Cell Ther. 2021;27(4):311 e1- e10 [IF: NA]*

Acute myeloid leukemia (AML) with intermediate risk cytogenetics (IRcyto) comprises a variety of biological entities with distinct mutational landscapes that translate into differential risks of relapse and prognosis. Optimal postremission therapy choice in this heterogeneous patient population is currently unsettled. In the current study, we compared outcomes in IRcyto AML recipients of autologous (autoSCT) ( $n = 312$ ) or allogeneic stem cell transplantation (alloSCT) ( $n = 279$ ) in first complete remission (CR1). Molecular risk was defined based on CEBPA, NPM1, and FLT3-ITD mutational status, per European LeukemiaNet 2017 criteria. Five-year overall survival (OS) in patients with favorable molecular risk (FRmol) was 62% (95% confidence interval [CI], 50-72) after autoSCT and 66% (95% CI, 41-83) after matched sibling donor (MSD) alloSCT ( $P = .68$ ). For patients of intermediate molecular risk (IRmol), MSD alloSCT was associated with lower cumulative incidence of relapse ( $P < .001$ ), as well as with increased nonrelapse mortality ( $P = .01$ ), as compared to autoSCT. The 5-year OS was 47% (95% CI, 34-58) after autoSCT and 70% (95% CI, 59-79) after MSD alloSCT ( $P = .02$ ) in this patient subgroup. In a propensity-score matched IRmol subcohort ( $n = 106$ ), MSD alloSCT was associated with superior leukemia-free survival (hazard ratio [HR] 0.33,  $P = .004$ ) and increased OS in patients alive 1 year after transplantation (HR 0.20,  $P = .004$ ). These results indicate that, within IRcyto AML in CR1, autoSCT may be a valid option for FRmol patients, whereas MSD alloSCT should be the preferred postremission strategy in IRmol patients.

**241. COVID-19 and endoscopic management of superficial gastrointestinal neoplastic lesions: a multinational cross-sectional survey.**

*Rodriguez-Carrasco, M, Albeniz, E, Bhandari, P, Beyna, T, Bourke, MJ, Min, A, Chiu, PWY, Chu, S, Yip, HC, Deprez, PH, Emura, F, Repici, A, Suzuki, N, Yahagi, N, Kubosawa, Y, Hassan, C and Dinis-Ribeiro, M. Endoscopy. 2021;53(2):173-7 [IF: 10.093]*

INTRODUCTION: We aimed to report the impact of the pandemic lockdown period on the treatment and prognosis of superficial gastrointestinal neoplastic lesions. METHODS: A survey was completed by 11 centers from four continents regarding postponements during the early lockdown period of the pandemic, and the same period in 2019. RESULTS: In 2020, 55 % of the scheduled procedures were deferred, which was 11 times higher than in 2019; the main reasons were directly related to COVID-19. In countries that were highly affected, this proportion rose to 76 % vs. 26 % in those where there was less impact. Despite the absolute reduction, the relative distribution in 2019 vs. 2020 was similar, the only exception being duodenal lesions (affected by a 92 % reduction in mucosectomies). Although it is expected that the majority of postponements will not affect the stage (based on the results from biopsies and/or endoscopic appearance), 3 % of delayed procedures will probably require surgery. CONCLUSIONS: The lockdown period caused by the SARS-CoV-2 pandemic led to a substantial reduction in the number of endoscopic resections for neoplastic lesions. Nevertheless, based on clinical judgment, the planned median delay will not worsen the prognosis of the affected patients.

**242. Clipping a gastric lesion before resection: not a contraindication for endoscopic submucosal dissection.**

*Rodriguez-Carrasco, M, Souto Moura, M, Cunha, AL and Dinis-Ribeiro, M. Endoscopy. 2021;53(11):E405-E6 [IF: 10.093]*

**243. Optimization and Clinical Evaluation of a Multi-Target Loop-Mediated Isothermal Amplification Assay for the Detection of SARS-CoV-2 in Nasopharyngeal Samples.**

*Roumani, F, Azinheiro, S, Sousa, H, Sousa, A, Timoteo, M, Varandas, T, Fonseca-Silva, D, Baldaque, I, Carvalho, J, Prado, M and Garrido-Maestu, A. Viruses. 2021;13(5) [IF: 5.048]*

SARS-CoV-2 is the coronavirus responsible for COVID-19, which has spread worldwide, affecting more than 200 countries, infecting over 140 million people in one year. The gold standard to identify infected people is RT-qPCR, which is highly sensitive, but needs specialized equipment and trained personnel. The demand for these reagents has caused shortages in certain countries. Isothermal nucleic acid techniques, such as loop-mediated isothermal amplification (LAMP) have emerged as an alternative or as a complement to RT-qPCR. In this study, we developed and evaluated a multi-target RT-LAMP for the detection of SARS-CoV-2. The method was evaluated against an RT-qPCR in 152 clinical nasopharyngeal swab samples. The results obtained indicated that both assays presented a "good concordance" (Cohen's k of 0.69), the RT-LAMP was highly specific (99%) but had lower sensitivity compared to the gold standard (63.3%). The calculated low sensitivity was associated with samples with very low viral load (RT-qPCR Cq values higher than 35) which may be associated with non-infectious individuals. If an internal Cq threshold below 35 was set, the sensitivity and Cohen's k increased to 90.9% and 0.92, respectively. The interpretation of the Cohen's k for this was "very good concordance". The RT-LAMP is an attractive approach for frequent individual testing in decentralized setups.

**244. Performance of DNA methylation-based biomarkers in the cervical cancer screening program of northern Portugal: A feasibility study.**

*Salta, S, Maia-Moco, L, Estevas-Pereira, H, Sequeira, JP, Vieira, R, Bartosch, C, Petronilho, S, Monteiro, P, Sousa, A, Baldaque, I, Rodrigues, J, Sousa, H, Tavares, F, Henrique, R and Jeronimo, C. Int J Cancer. 2021;149(11):1916-25 [IF: 7.396]*

Cervical cancer remains a health concern. Effective screening programs are critical to reduce the incidence and mortality. High-risk HPV (hr-HPV) testing as primary screening tool discloses high sensitivity but suboptimal specificity. Adequate triage tests to reduce unnecessary colposcopy referrals and overdiagnosis/overtreatment are crucial. Hence, we aimed to validate a panel of DNA methylation-based markers as triage test for women hr-HPV+ in the population-based Regional Cervical Cancer Screening

Program of Northern Portugal. Firstly, CADM1, MAL, FAM19A4 and hsa-miR124-2 promoter methylation levels were assessed by multiplex QMSP in a testing set of 402 FFPE tissue samples (159 normal samples and 243 cervical lesions, including 39 low-grade intraepithelial squamous lesions [LSIL], 59 high-grade intraepithelial squamous lesions [HSIL] and 145 cancerous lesions). Then, preliminary validation was performed in 125 hr-HPV+ cervical scrapes (including 59 normal samples, 30 LSIL, 34 HSIL and 2 cancerous lesions). Higher MAL(me), FAM19A4(me) and hsa-miR124-2(me) methylation levels were disclosed in histological HSIL or worse (HSIL+) in testing set. Individually, markers depicted over 86% specificity for HSIL+ detection. In validation set, all these genes significantly differed between histological HSIL+ and low-grade squamous intraepithelial lesions or less. In combination, these markers reached 74% specificity and 61% sensitivity for identification of histological HSIL+. We concluded that host gene methylation might constitute a useful referral triage tool of hr-HPV+ women enrolled in the Cervical Cancer Screening Program of Northern Portugal.

#### 245. Optimized method for in vivo dosimetry with small films in pelvic IOERT for rectal cancer.

*Santos, J, Silva, S and Sarmiento, S. Phys Med. 2021;81:20-30 [IF: 2.685]*

**PURPOSE:** Intra-Operative Electron Radiation Therapy (IOERT) is used to treat rectal cancer at our institution, and in vivo measurements with Gafchromic EBT3(R) films were introduced as quality assurance. The purpose of this work was to quantify the uncertainties associated with digitization of very small EBT3 films irradiated simultaneously, in order to optimize in vivo dosimetry for IOERT. **METHODS:** Film samples of different sizes - M1 (5x5cm(2)), M2 (1.5x1.5 cm(2)), M3 (1.0x1.5 cm(2)) and M4 (0.75x1.5 cm(2)) - were used to quantify typical variations (uncertainties) due to scanner fluctuations, misalignment, film inhomogeneity, long-term effect of film cutting, small rotations, film curling, edge effects and the influence of opaque templates. Fitting functions and temporal validity of sensitometric curves were also assessed. **RESULTS:** Film curling, intra-film variability and scanner fluctuations are important effects that need to be minimized or considered in the uncertainty budget. Small rotations, misalignments and film cutting have little or no influence on the readings. Most fitting functions perform well, but the quantity used for dose quantification determines over- or under-valuation of dose in the long term. Edge effects and the influence of opaque templates need to be well understood, to allow optimization of methodology to the intended purpose. **CONCLUSION:** The proposed method allows practical and simultaneous digitization of up to ten small irradiated film samples, with an experimental uncertainty of 1%.

#### 246. Towards Drug Repurposing in Cancer Cachexia: Potential Targets and Candidates.

*Santos, JMO, Costa, AC, Dias, TR, Satari, S, Costa, ESMP, da Costa, RMG and Medeiros, R. Pharmaceuticals (Basel). 2021;14(11) [IF: 5.863]*

As a multifactorial and multiorgan syndrome, cancer cachexia is associated with decreased tolerance to antitumor treatments and increased morbidity and mortality rates. The current approaches for the treatment of this syndrome are not always effective and well established. Drug repurposing or repositioning consists of the investigation of pharmacological components that are already available or in clinical trials for certain diseases and explores if they can be used for new indications. Its advantages comparing to de novo drugs development are the reduced amount of time spent and costs. In this paper, we selected drugs already available or in clinical trials for non-cachexia indications and that are related to the pathways and molecular components involved in the different phenotypes of cancer cachexia syndrome. Thus, we introduce known drugs as possible candidates for drug repurposing in the treatment of cancer-induced cachexia.

#### 247. Urogenital Schistosomiasis-History, Pathogenesis, and Bladder Cancer.

*Santos, LL, Santos, J, Gouveia, MJ, Bernardo, C, Lopes, C, Rinaldi, G, Brindley, PJ and Costa, J. J Clin Med. 2021;10(2) [IF: 4.241]*

Schistosomiasis is the most important helminthiasis worldwide in terms of morbidity and mortality. Most of the infections occurs in Africa, which about two thirds are caused by *Schistosoma haematobium*. The infection with *S. haematobium* is considered carcinogenic leading to squamous cell carcinoma (SCC) and urothelial carcinoma of the urinary bladder. Additionally, it is responsible for female genital schistosomiasis leading to infertility and higher risk of human immunodeficiency virus (HIV) transmission. Remarkably, a

recent outbreak in Corsica (France) drew attention to its potential re-mergence in Southern Europe. Thus far, little is known related to host-parasite interactions that trigger carcinogenesis. However, recent studies have opened new avenues to understand mechanisms on how the parasite infection can lead cancer and other associated pathologies. Here, we present a historical perspective of schistosomiasis, and review the infection-associated pathologies and studies on host-parasite interactions that unveil tentative mechanisms underlying schistosomiasis-associated carcinogenesis.

#### 248. Is Increased Time From Diagnosis to Treatment in Advanced Hypopharynx Cancer Associated With Poorer Outcomes: A Single-Centre Analysis.

*Santos, M and Monteiro, E. Ear Nose Throat J. 2021;100(6):454-9 [IF: 1.697]*

**OBJECTIVE:** To assess the potential influence of increased time from diagnosis to treatment on survival outcomes in patients with locoregionally advanced hypopharyngeal squamous cell carcinoma (HSCC). **METHODS:** Retrospective study of patients with a primary diagnosis of HSCC proposed for primary surgical treatment. **RESULTS:** The study population included a total of 121 Caucasian patients (121 males) with HSCC. Mean age at diagnosis was 60.4 years (range: 43-83 years). All patients had cT3 or cT4 hypopharyngeal tumors. The sample presented a 5-year overall survival (OS) of 59.6% and a disease-specific survival of 74.9%. Considering univariable analysis (unadjusted), duration of adjuvant treatment (T5), pN, margins, and extracapsular spread (ECS) are factors associated with poorer survival outcomes. An increase in T5 was associated with lower OS. Results revealed that T5 higher than 43 days, pN1, pN2, pN3, no free margins, and presence of ECS were associated with lower OS. These patients have 7.465 higher hazard of death. **CONCLUSION:** This study suggests that duration of adjuvant therapy may be more important than other timing metrics from diagnosis to treatment. For locoregionally advanced HSCC, duration of adjuvant therapy after primary surgery higher than 6 weeks is an important feature for worse survival outcome. Preventing strategies in order to avoid radiotherapy or chemoradiotherapy breaks should be developed and optimized.

#### 249. Time between Diagnosis and Treatment of Hypopharynx and Larynx Cancer: Are Longer Delays Associated with Higher Discrepancy between Clinical and Pathological Staging?

*Santos, M and Monteiro, E. Int Arch Otorhinolaryngol. 2021;25(1):e108-e114 [IF: NA]*

**Introduction** At the time of diagnosis, treatment strategies for cancer are largely based upon clinical staging. However, discrepancy between clinical and pathological staging has been reported. **Objective** To assess the rate of staging discrepancy in Laryngeal and Hypopharyngeal Squamous Cell Carcinoma (LHSCC), the potential influence of higher interval of time from diagnosis to primary surgical treatment, and whether this has any impact on survival outcomes. **Methods** Retrospective study of patients with LHSCC proposed for primary surgical treatment. **Results** The study population included 125 Caucasian patients with LHSCC. The level of agreement between clinical and pathological tumor staging was moderate (Cohen's Kappa: 0.400;  $p < 0.001$ ) and similar result was found for node staging (Cohen's Kappa: 0.520;  $p < 0.001$ ). The mean time between diagnosis and surgical treatment was 26.66 days and no statistically significant influence was found with staging discrepancy. The sample presented a 5-year Overall Survival (OS) of 58.2% and a Disease-specific survival (DSS) of 72.6%. No statistically significant impact of staging discrepancy on survival was found. **Conclusion** For advanced LHSCC, based on the findings of physical examination, endoscopy and imaging, is possible to achieve a moderate accuracy between clinical and pathological staging which allows a reliable counselling and treatment planning. Interval of time under 3-4 weeks between diagnosis and surgical treatment does not influence the rate of discrepancy. However, almost 30% of staging discrepancy is expected due to false negatives of imaging and limitations of physical exams.

#### 250. Hematopoietic stem cell transplantation for adults with relapsed acute promyelocytic leukemia in second complete remission.

*Sanz, J, Labopin, M, Sanz, MA, Aljurf, M, Sousa, AB, Craddock, C, Zuckerman, T, Labussiere-Wallet, H, Campos, A, Grillo, G, Ozkurt, ZN, Cornelissen, JJ, Remenyi, P, Martino, M, Porras, RP, Nagler, A, Gorin, NC, Mohty, M, Acute Leukemia Working Party of the European Society for, B and Marrow, T. Bone Marrow Transplant. 2021;56(6):1272-80 [IF: 5.483]*

We retrospectively compared outcomes of a large series of adult patients with APL in CR2 receiving

alloHSCT (n = 228) or autoHSCT (n = 341) reported to the European Society for Blood and Marrow Transplantation from January 2004 to December 2018. The 2-year cumulative incidence of non-relapse mortality was significantly higher for alloHSCT 17.3% (95% CI 12.5-22.8) compared with autoHSCT 2.7% (95% CI 1.2-5) (p = 0.001), while differences in relapse rate were not significant (28% versus 22.9%; p = 0.28). Leukemia-free survival (LFS) and overall survival (OS) favored autoHSCT with 74.5% (95% CI 69-79.2) and 82.4% (95% CI 77.3-86.5) compared with alloHSCT with 54.7% (95% CI 47.5-61.3) (p = 0.001) and 64.3% (95% CI 57.2-70.6), respectively (p = 0.001 and p = 0.001). Multivariable analysis showed significantly worse LFS after alloHSCT (HR 0.49; 95% CI 0.37-0.67; p < 0.0001), older age (p = 0.001), and shorter time from diagnosis to transplant (p = 0.00015). Similar results were obtained for OS. The study shows that autoHSCT resulted in better survival outcomes (LFS and OS) for APL in CR2. These results were mainly due to reduced NRM in the autoHSCT as compared to alloHSCT.

### 251. Demographic, clinical and pathological characterisation of patients with colorectal and anal cancer followed between 2013 and 2016 at Maputo Central Hospital, Mozambique.

*Selemane, C, Jamisse, L, Arroz, J, Tulsidas, S, Morais, AG, Carrilho, C, Modcoicar, P, Sidat, M, Rodrigues, J, Moreira-Goncalves, D, Ismail, M and Santos, LL. Ecancermedicalscience. 2021;15:1205 [IF: NA]*

Purpose: The aim of this study was to investigate colorectal cancer (CRC) data and anal cancer data from Maputo Central Hospital (MCH), the largest hospital and a reference for oncological diseases in Mozambique, with the aim of characterising the disease profile in view to define an appropriate control programme. Methods: MCH records from the Pathology and Surgery Services and MCH Cancer Registry database were assessed to obtain retrospective clinical and pathologic data of patients with CRC or anal cancer admitted to and treated between 13 December 2013 and 23 March 2016. Results: The female gender was more prevalent (54.8%), even when anal cancers were excluded. Median age was 54 years (20-99). Most patients (51.6%) lived in the city of Maputo. The most common presenting symptom was found to be rectal bleeding. Adenocarcinoma was the most frequent histological type, and the most prevalent anatomical site was the rectum. Most of the cases were diagnosed at MCH in advanced stages. Colostomy was the most frequent surgical procedure and performed in 38.7% of the patients. Most cases of anal cancer occurred in human immunodeficiency virus-infected patients. Most patients had a poor prognosis due to advanced stage at first diagnosis. Conclusion: We observed an increase in cases of CRC and anal cancer in Mozambique and mostly diagnosed at advanced stages, which anticipates a dismal prognosis. Our data supports the urgent need of a comprehensive public health programme dedicated to solving this growing concern.

### 252. Unveiling the World of Circulating and Exosomal microRNAs in Renal Cell Carcinoma.

*Sequeira, JP, Constanco, V, Lobo, J, Henrique, R and Jeronimo, C. Cancers (Basel). 2021;13(21):5252 [IF: 6.639]*

Renal cell carcinoma is the third most common urological cancer. Despite recent advances, late diagnosis and poor prognosis of advanced-stage disease remain a major problem, entailing the need for novel early diagnosis tools. Liquid biopsies represent a promising minimally invasive clinical tool, providing real-time feedback of tumor behavior and biological potential, addressing its clonal evolution and representing its heterogeneity. In particular, the study of circulating microRNAs and exosomal microRNAs in liquid biopsies experienced an exponential increase in recent years, considering the potential clinical utility and available technology that facilitates implementation. Herein, we provide a systematic review on the applicability of these biomarkers in the context of renal cell carcinoma. Issues such as additional benefit from extracting microRNAs transported in extracellular vesicles, use for subtyping and representation of different histological types, correlation with tumor burden, and prediction of patient outcome are also addressed. Despite the need for more conclusive research, available data indicate that exosomal microRNAs represent a robust minimally invasive biomarker for renal cell carcinoma. Thus, innovative research on microRNAs and novel detection techniques are likely to provide clinically relevant biomarkers, overcome current clinical challenges, and improve patient management.

### 253. Airway stents in malignant central airway obstruction.

*Serino, M, Freitas, C, Saleiro, S, Cabrita, B, Conde, M, Fernandes, MGO and Magalhaes, A. Pulmonology.*

2021;27(5):466-9 [IF: 3.575]

**254. Indications and outcomes of endoscopic resection for non-pedunculated colorectal lesions: A narrative review.**

*Shahini, E, Libanio, D, Lo Secco, G, Pisani, A and Arezzo, A. World J Gastrointest Endosc. 2021;13(8):275-95 [IF: 9.427]*

In the last years, endoscopic techniques gained a crucial role in the treatment of colorectal flat lesions. At the same time, the importance of a reliable assessment of such lesions to predict the malignancy and the depth of invasion of the colonic wall emerged. The current unsolved dilemma about the endoscopic excision techniques concerns the necessity of a reliable submucosal invasive cancer assessment system that can stratify the risk of the post-procedural need for surgery. Accordingly, this narrative literature review aims to compare the available diagnostic strategies in predicting malignancy and to give a guide about the best techniques to employ. We performed a literature search using electronic databases (MEDLINE/PubMed, EMBASE, and Cochrane Library). We collected all articles about endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) registering the outcomes. Moreover, we analyzed all meta-analyses comparing EMR vs ESD outcomes for colorectal sessile or non-polypoid lesions of any size, preoperatively estimated as non-invasive. Seven meta-analysis studies, mainly Eastern, were included in the analysis comparing 124 studies and overall 22954 patients who underwent EMR and ESD procedures. Of these, eighty-two were retrospective, twenty-four perspective, nine case-control, and six cohorts, while three were randomized clinical trials. A total of 18118 EMR and 10379 ESD were completed for a whole of 28497 colorectal sessile or non-polypoid lesions > 5-10 mm in size. In conclusion, it is crucial to enhance the preoperative diagnostic workup, especially in deciding the most suitable endoscopic method for radical resection of flat colorectal lesions at risk of underlying malignancy. Additionally, the ESD necessitates further improvement because of the excessively time-consuming as well as the intraprocedural technical hindrances and related complications. We found a higher rate of en bloc resections and R0 for ESD than EMR for non-pedunculated colorectal lesions. Nevertheless, despite the lower local recurrence rates, ESD had greater perforation rates and needed lengthier procedural times. The prevailing risk for additional surgery in ESD rather than EMR for complications or oncologic reasons is still uncertain.

**255. Prevalence of Neisseria gonorrhoeae and Trichomonas vaginalis in Portuguese women of childbearing age.**

*Silva, J, Cerqueira, F, Teixeira, AL, Campaignha, R, Amorim, J and Medeiros, R. J Obstet Gynaecol. 2021;41(2):254-8 [IF: 1.246]*

The purpose of this study was to evaluate the prevalence of Neisseria gonorrhoeae (NG) and Trichomonas vaginalis (TV) in Portuguese women of childbearing age. Cervicovaginal self-collected samples of 680 childbearing-age women (15-44 years) were tested for NG and TV by polymerase chain reaction. Sociodemographic, clinical and behavioural data were assessed through an anonymous self-administered questionnaire. NG and TV prevalence was 1.3% (95% confidence interval (CI) 0.7-2.5%) and 1.0% (95% CI 0.5-2.1%), respectively. The prevalence of TV was significantly higher in women aged >22 years ( $p = .003$ ), with >6 years after sexual intercourse ( $p = .003$ ), and who reported previous pregnancy ( $p = .004$ ). Our study suggests that NG and TV are rare in Portuguese women of childbearing age. However, larger epidemiological studies with a nationally representative sample of female subjects are warranted, to clarify the need for screening of these microorganisms in Portuguese women, since its prevalence is probably underestimated. **IMPACT STATEMENT** What is already known on this subject? Studies on the prevalence of NG and TV have been performed in several developed and developing countries. However, limited data is available in Portuguese women. The detection of NG and TV is necessary because, beside the risk of transmission to sex partners, these STIs may be associated with an increased risk of HIV acquisition and transmission, and ultimately with reproductive, pregnancy and perinatal complications. What do the results of this study add? Our study adds new findings to the body of knowledge on NG and TV prevalence in Portuguese women of reproductive age. As so, we found a low prevalence of both NG (1.3%) and TV (1.0%) in the studied population. What are the implications of these findings for clinical practice and/or further research? Our results may be a step ahead to encourage future nationally representative studies evaluating

the prevalence of NG and TV genital infection and, consequently, to clarify the need for screening of these microorganisms. In clinical practice, it should be highlighted the appropriate management of NG and TV infection in specific situations, such as pregnancy. Also, sexual partners must be treated to prevent the recurrences in the index cases and reduce transmission to other partners.

**256. Helicobacter pylori lipopolysaccharide structural domains and their recognition by immune proteins revealed with carbohydrate microarrays.**

*Silva, LM, Correia, VG, Moreira, ASP, Domingues, MRM, Ferreira, RM, Figueiredo, C, Azevedo, NF, Marcos-Pinto, R, Carneiro, F, Magalhaes, A, Reis, CA, Feizi, T, Ferreira, JA, Coimbra, MA and Palma, AS. Carbohydr Polym. 2021;253:117350 [IF: 9.381]*

The structural diversity of the lipopolysaccharides (LPSs) from *Helicobacter pylori* poses a challenge to establish accurate and strain-specific structure-function relationships in interactions with the host. Here, LPS structural domains from five clinical isolates were obtained and compared with the reference strain 26695. This was achieved combining information from structural analysis (GC-MS and ESI-MS(n)) with binding data after interrogation of a LPS-derived carbohydrate microarray with sequence-specific proteins. All LPSs expressed Lewis(x/y) and N-acetyllactosamine determinants. Ribans were also detected in LPSs from all clinical isolates, allowing their distinction from the 26695 LPS. There was evidence for 1,3-d-galactans and blood group H-type 2 sequences in two of the clinical isolates, the latter not yet described for *H. pylori* LPS. Furthermore, carbohydrate microarray analyses showed a strain-associated LPS recognition by the immune lectins DC-SIGN and galectin-3 and revealed distinctive LPS binding patterns by IgG antibodies in the serum from *H. pylori*-infected patients.

**257. Methodological approach for determining the Minimal Important Difference and Minimal Important Change scores for the European Organisation for Research and Treatment of Cancer Head and Neck Cancer Module (EORTC QLQ-HN43) exemplified by the Swallowing scale.**

*Singer, S, Hammerlid, E, Tomaszewska, IM, Amdal, CD, Bjordal, K, Herlofson, BB, Santos, M, Silva, JC, Mehanna, H, Fullerton, A, Brannan, C, Gonzalez, LF, Inhestern, J, Pinto, M, Arraras, JI, Yarom, N, Bonomo, P, Baumann, I, Galalae, R, Nicolatou-Galitis, O, Kiyota, N, Raber-Durlacher, J, Salem, D, Fabian, A, Boehm, A, Krejovic-Trivic, S, Chie, WC, Taylor, K, Simon, C, Licitra, L, Sherman, AC, Group, EQoL, the, EH and Neck Cancer, G. Qual Life Res. 2021 [IF: 4.147]*

**PURPOSE:** The aim of this study was to explore what methods should be used to determine the minimal important difference (MID) and minimal important change (MIC) in scores for the European Organisation for Research and Treatment of Cancer Head and Neck Cancer Module, the EORTC QLQ-HN43. **METHODS:** In an international multi-centre study, patients with head and neck cancer completed the EORTC QLQ-HN43 before the onset of treatment (t1), three months after baseline (t2), and six months after baseline (t3). The methods explored for determining the MID were: (1) group comparisons based on performance status; (2) 0.5 and 0.3 standard deviation and standard error of the mean. The methods examined for the MIC were patients' subjective change ratings and receiver-operating characteristics (ROC) curves, predictive modelling, standard deviation, and standard error of the mean. The EORTC QLQ-HN43 Swallowing scale was used to investigate these methods. **RESULTS:** From 28 hospitals in 18 countries, 503 patients participated. Correlations with the performance status were  $|r| < 0.4$  in 17 out of 19 scales; hence, performance status was regarded as an unsuitable anchor. The ROC approach yielded an implausible MIC and was also discarded. The remaining approaches worked well and delivered MID values ranging from 10 to 14; the MIC for deterioration ranged from 8 to 16 and the MIC for improvement from - 3 to - 14. **CONCLUSIONS:** For determining MIDs of the remaining scales of the EORTC QLQ-HN43, we will omit comparisons of groups based on the Karnofsky Performance Score. Other external anchors are needed instead. Distribution-based methods worked well and will be applied as a starting strategy for analyses. For the calculation of MICs, subjective change ratings, predictive modelling, and standard-deviation based approaches are suitable methods whereas ROC analyses seem to be inappropriate.

**258. CNS-3 status remains an independent adverse prognosis factor in children with acute lymphoblastic leukemia (ALL) treated without cranial irradiation: Results of EORTC Children Leukemia Group study 58951.**

Sirvent, N, Suciú, S, De Moerloose, B, Ferster, A, Mazingue, F, Plat, G, Yakouben, K, Uyttebroeck, A, Paillard, C, Costa, V, Simon, P, Pluchart, C, Poiree, M, Minckes, O, Millot, F, Freycon, C, Maes, P, Hoyoux, C, Cave, H, Rohrllich, P, Bertrand, Y, Benoit, Y and Children's Leukemia Group of the European Organisation for Research Treatment of, C. *Arch Pediatr.* 2021;28(5):411-6 [IF: 1.180]

AIM: To evaluate the prognostic significance of initial central nervous system (CNS) involvement of children with acute lymphoblastic leukemia (ALL) enrolled in the EORTC 58951 trial. PATIENTS AND METHODS: From 1998 to 2008, 1930 ALL patients were included in the randomized EORTC 58951 trial. Overall treatment intensity was adjusted according to known prognostic factors including the level of minimal residual disease after induction treatment. CNS-directed therapy comprised four to 11 courses of i.v. methotrexate (5g/m<sup>2</sup>), and 10 to 19 intrathecal chemotherapy injections, depending on risk group and CNS status. Cranial irradiation was omitted for all patients. RESULTS: The overall 8-year event-free survival (EFS) and overall survival (OS) rates were 81.3% and 88.1%, respectively. In the CNS-1, TPL+, CNS-2, and CNS-3 groups, the 8-year EFS rates were 82.1%, 77.1%, 78.3%, and 57.4%, respectively. Multivariable analysis indicated that initial CNS-3 status, but not CNS-2 or TLP+, was an independent adverse predictor of outcome. The 8-year incidence of isolated CNS relapse was 1.7% and of isolated or combined CNS relapse it was 3.7%. NCI high-risk group, male sex, CNS-2 and CNS-3 status were independent predictors for a higher incidence of any CNS relapse. CONCLUSIONS: CNS-3 status remains associated with poor prognosis and requires intensification of both systemic and CNS-directed therapy. This trial was registered at <https://clinicaltrials.gov/under/NCT00003728>.

#### 259. Alterations in functional connectivity are associated with white matter lesions and information processing efficiency in multiple sclerosis.

Soares, JM, Conde, R, Magalhaes, R, Marques, P, Magalhaes, R, Gomes, L, Goncalves, OF, Arantes, M and Sampaio, A. *Brain Imaging Behav.* 2021;15(1):375-88 [IF: 3.978]

Functional connectivity (FC) is typically altered in individuals with Multiple Sclerosis (MS). However, in relapsing-remitting multiple sclerosis (RRMS) patients, the relationship between brain FC, tissue integrity and cognitive impairment is still unclear as contradictory findings have been documented. In this exploratory study we compared both the whole brain connectome and resting state networks (RSNs) FC of twenty-one RRMS and seventeen healthy controls (HCs), using combined network based statistics and independent component analyses. The total white matter (WM) lesion volume and information processing efficiency were also correlated with FC in the RRMS group. Both whole brain connectome and individual RSNs FC were diminished in patients with RRMS compared to HC. Additionally, the reduction in FC was found to be a function of the total WM lesion volume, with greatest impact in those harboring the largest lesion volume. Finally, a positive correlation between FC and information processing efficiency was observed in RRMS. This complimentary whole brain and RSNs FC approach can contribute to clarify literature inconsistencies regarding FC alterations and provide new insights on the white matter structural damage in explaining functional abnormalities in RRMS.

#### 260. Small cell lung cancer treatment and survival in Portugal: A retrospective analysis from the I-O Optimise initiative.

Soares, M, Antunes, L, Redondo, P, Borges, M, Grimson, F, Hermans, R, Chaib, C, Lacoín, L, Juarez-Garcia, A, Daumont, MJ, Penrod, JR, Bento, MJ and Goncalves, FR. *Eur J Cancer Care (Engl).* 2021;30(6):e13496 [IF: 9.162]

OBJECTIVE: We aim to describe treatment patterns and overall survival (OS) among a Portuguese cohort of patients with small cell lung cancer (SCLC). METHODS: This study utilised a database held by IPO-Porto, Portugal's largest oncology hospital. Adult patients diagnosed with SCLC at IPO-Porto between January 2012 and June 2017, with follow-up to December 2017, were included. Patients were stratified into subgroups with limited disease (LD) or extensive disease (ED). Treatment analyses were performed from 2015 onwards. RESULTS: Overall, 227 patients diagnosed with SCLC (37 LD; 190 ED) were analysed. Median OS (interquartile range [IQR]) was 15.0 months (3.8-39.3) for LD-SCLC and 5.0 months (1.7-10.3) for ED-SCLC. Among 19 patients diagnosed with LD-SCLC from 2015 onwards, 12 (63.2%) received initial treatment with systemic anticancer therapy (SACT) +/- radiotherapy; 6 (31.6%) received best supportive care (BSC). Among 89 patients with ED-SCLC, 57 (68.5%) received SACT +/- palliative radiotherapy; 28 (31.5%) received

BSC. For patients receiving platinum doublet chemotherapy (+/-radiotherapy), median OS (IQR) was not reached for LD-SCLC and 5.4 months (2.3-10.9) for ED-SCLC. CONCLUSION: This real-world data analysis from a large Portuguese oncology hospital demonstrates a high disease burden for patients diagnosed with SCLC, particularly those with ED, and highlights a need for more effective therapies.

**261. Treatment and outcomes for early non-small-cell lung cancer: a retrospective analysis of a Portuguese hospital database.**

*Soares, M, Antunes, L, Redondo, P, Borges, M, Hermans, R, Patel, D, Grimson, F, Munro, R, Chaib, C, Lacoïn, L, Daumont, M, Penrod, JR, O'Donnell, JC, Bento, MJ and Goncalves, FR. Lung Cancer Manag. 2021;10(2):LMT46 [IF: NA]*

Aim: This observational study evaluated treatment patterns and survival for patients with stage I-IIIa non-small-cell lung cancer (NSCLC). Materials & methods: Adults newly diagnosed with NSCLC in 2012-2016 at IPO-Porto hospital were included. Treatment data were available for patients diagnosed in 2015-2016. Results: 495 patients were included (median age: 67 years). The most common treatments were surgery alone or with another therapy (stage I: 66%) and systemic anticancer therapy plus radiotherapy (stage II: 54%; stage IIIa: 59%). One-year OS (95% CI) for patients with stage I, II and IIIa NSCLC (diagnosed 2012-2016) were 92% (88-96), 71% (62-82) and 69% (63-75), respectively; one-year OS (95% CI) for treated patients with stage I-II or stage IIIa NSCLC (diagnosed 2015-2016) were 89% (81-97) and 86% (75-98) for non-squamous cell and 76% (60-95) and 49% (34-70) for squamous cell NSCLC. Conclusion: Treatment advances are strongly needed for stage I-IIIa NSCLC, especially for patients with squamous cell histology.

**262. Optimizing classical risk scores to predict complications in head and neck surgery: a new approach.**

*Sousa Menezes, A, Fernandes, A, Rocha Rodrigues, J, Salome, C, Machado, F, Antunes, L, Castro Silva, J, Monteiro, E and Lara Santos, L. Eur Arch Otorhinolaryngol. 2021;278(1):191-202 [IF: 2.503]*

PURPOSE: To validate tools to identify patients at risk for perioperative complications to implement prehabilitation programmes in head and neck surgery (H&N). METHODS: Retrospective cohort including 128 patients submitted to H&N, with postoperative Intermediate Care Unit admittance. The accuracy of the risk calculators ASA, P-POSSUM, ACS-NSQIP and ARISCAT to predict postoperative complications and mortality was assessed. A multivariable analysis was subsequently performed to create a new risk prediction model for serious postoperative complications in our institution. RESULTS: Our 30-day morbidity and mortality were 45.3% and 0.8%, respectively. The ACS-NSQIP failed to predict complications and had an acceptable discrimination ability for predicting death. The discrimination ability of ARISCAT for predicting respiratory complications was acceptable. ASA and P-POSSUM were poor predictors for mortality and morbidity. Our new prediction model included ACS-NSQIP and ARISCAT (area under the curve 0.750, 95% confidence intervals: 0.63-0.87). CONCLUSION: Despite the insufficient value of these risk calculators when analysed individually, we designed a risk tool combining them which better predicts the risk of serious complications.

**263. (177)Lu-Dotatate plus long-acting octreotide versus high-dose long-acting octreotide in patients with midgut neuroendocrine tumours (NETTER-1): final overall survival and long-term safety results from an open-label, randomised, controlled, phase 3 trial.**

*Strosberg, JR, Caplin, ME, Kunz, PL, Ruzniewski, PB, Bodei, L, Hendifar, A, Mittra, E, Wolin, EM, Yao, JC, Pavel, ME, Grande, E, Van Cutsem, E, Seregni, E, Duarte, H, Gericke, G, Bartalotta, A, Mariani, MF, Demange, A, Mutevelic, S, Krenning, EP and investigators, N-. Lancet Oncol. 2021;22(12):1752-63 [IF: 41.316]*

BACKGROUND: The primary analysis of the phase 3 NETTER-1 trial showed significant improvement in progression-free survival with (177)Lu-Dotatate plus long-acting octreotide versus high-dose long-acting octreotide alone in patients with advanced midgut neuroendocrine tumours. Here, we report the prespecified final analysis of overall survival and long-term safety results. METHODS: This open-label, randomised, phase 3 trial enrolled patients from 41 sites in eight countries across Europe and the USA. Patients were 18 years and older with locally advanced or metastatic, well differentiated, somatostatin receptor-positive midgut neuroendocrine tumours (Karnofsky performance status score  $\geq$ 60) and disease progression on fixed-dose long-acting octreotide. Patients were randomly assigned (1:1) via an interactive

web-based response system to intravenous (177)Lu-Dotatate 7.4 GBq (200 mCi) every 8 weeks (four cycles) plus intramuscular long-acting octreotide 30 mg ((177)Lu-Dotatate group) or high-dose long-acting octreotide 60 mg every 4 weeks (control group). The primary endpoint of progression-free survival has been previously reported; here, we report the key secondary endpoint of overall survival in the intention-to-treat population. Final overall survival analysis was prespecified to occur either after 158 deaths or 5 years after the last patient was randomised, whichever occurred first. During long-term follow-up, adverse events of special interest were reported in the (177)Lu-Dotatate group only. This trial is registered with ClinicalTrials.gov, NCT01578239. FINDINGS: From Sept 6, 2012, to Jan 14, 2016, 231 patients were enrolled and randomly assigned for treatment. The prespecified final analysis occurred 5 years after the last patient was randomly assigned (when 142 deaths had occurred); median follow-up was 76.3 months (range 0.4-95.0) in the (177)Lu-Dotatate group and 76.5 months (0.1-92.3) in the control group. The secondary endpoint of overall survival was not met: median overall survival was 48.0 months (95% CI 37.4-55.2) in the (177)Lu-Dotatate group and 36.3 months (25.9-51.7) in the control group (HR 0.84 [95% CI 0.60-1.17]; two-sided  $p=0.30$ ). During long-term follow-up, treatment-related serious adverse events of grade 3 or worse were recorded in three (3%) of 111 patients in the (177)Lu-Dotatate group, but no new treatment-related serious adverse events were reported after the safety analysis cutoff. Two (2%) of 111 patients given (177)Lu-Dotatate developed myelodysplastic syndrome, one of whom died 33 months after randomisation (this person was the only the only reported (177)Lu-Dotatate treatment-related death). No new cases of myelodysplastic syndrome or acute myeloid leukaemia were reported during long-term follow-up. INTERPRETATION: (177)Lu-Dotatate treatment did not significantly improve median overall survival versus high-dose long-acting octreotide. Despite final overall survival not reaching statistical significance, the 11.7 month difference in median overall survival with (177)Lu-Dotatate treatment versus high-dose long-acting octreotide alone might be considered clinically relevant. No new safety signals were reported during long-term follow-up. FUNDING: Advanced Accelerator Applications, a Novartis company.

#### 264. Genome-Wide DNA Methylation Profiling of Esophageal Squamous Cell Carcinoma from Global High-Incidence Regions Identifies Crucial Genes and Potential Cancer Markers.

Talukdar, FR, Soares Lima, SC, Khoueiry, R, Laskar, RS, Cuenin, C, Sorroche, BP, Boisson, AC, Abedi-Ardekani, B, Carreira, C, Menya, D, Dzamalala, CP, Assefa, M, Aseffa, A, Miranda-Goncalves, V, Jeronimo, C, Henrique, RM, Shakeri, R, Malekzadeh, R, Gasmelseed, N, Ellaithi, M, Gangane, N, Middleton, DRS, Le Calvez-Kelm, F, Ghantous, A, Roux, ML, Schuz, J, McCormack, V, Parker, MI, Pinto, LFR and Herceg, Z. *Cancer Res.* 2021;81(10):2612-24 [IF: 12.701]

Epigenetic mechanisms such as aberrant DNA methylation (DNAm) are known to drive esophageal squamous cell carcinoma (ESCC), yet they remain poorly understood. Here, we studied tumor-specific DNAm in ESCC cases from nine high-incidence countries of Africa, Asia, and South America. Infinium MethylationEPIC array was performed on 108 tumors and 51 normal tissues adjacent to the tumors (NAT) in the discovery phase, and targeted pyrosequencing was performed on 132 tumors and 36 NAT in the replication phase. Top genes for replication were prioritized by weighting methylation results using RNA-sequencing data from The Cancer Genome Atlas and GTEx and validated by qPCR. Methylome analysis comparing tumor and NAT identified 6,796 differentially methylated positions (DMP) and 866 differential methylated regions (DMR), with a 30% methylation ( $\Delta\beta$ ) difference. The majority of identified DMPs and DMRs were hypermethylated in tumors, particularly in promoters and gene-body regions of genes involved in transcription activation. The top three prioritized genes for replication, PAX9, SIM2, and THSD4, had similar methylation differences in the discovery and replication sets. These genes were exclusively expressed in normal esophageal tissues in GTEx and downregulated in tumors. The specificity and sensitivity of these DNAm events in discriminating tumors from NAT were assessed. Our study identified novel, robust, and crucial tumor-specific DNAm events in ESCC tumors across several high-incidence populations of the world. Methylome changes identified in this study may serve as potential targets for biomarker discovery and warrant further functional characterization. SIGNIFICANCE: This largest genome-wide DNA methylation study on ESCC from high-incidence populations of the world identifies functionally relevant and robust DNAm events that could serve as potential tumor-specific markers. GRAPHICAL ABSTRACT: <http://cancerres.aacrjournals.org/content/canres/81/10/2612/F1.large.jpg>.

**265. Diffuse large B-cell lymphoma in very elderly patients: Towards best tailored treatment - A systematic review.**

*Tavares, A and Moreira, J. Crit Rev Oncol Hematol. 2021;160:103294 [IF: 6.312]*

INTRODUCTION: Diffuse large B cell Lymphoma (DLBCL) is a potentially curative lymphoma with increasing incidence with ageing. Treatment of elderly DLBCL patients represents a particular challenge due to their comorbidities and performance status. METHODS: A search for original articles focused on the treatment of elderly DLBCL patients was performed in PubMed database and 633 were found and reviewed. Thirty-eight studies meeting our inclusion criteria were published since 2007. RESULTS: Thirteen studies were retrospective and 25 phase II/III clinical trials. Most of them investigated the efficacy of dose-adjusted R-CHOP regimen. Alternative therapeutic drugs together with geriatric assessment were also evaluated. For fit patients aged 80 and over, the strongest evidence favours R-miniCHOP regimen. CONCLUSION: A dose-adjusted R-CHOP may be the recommended treatment in elderly DLBCL patients. New tools such as the Comprehensive Geriatric Assessment provide useful guidance for treatment choice, based on comorbidities and frailty index of this group.

**266. Compassionate use of glasdegib in combination with low-dose cytarabine for relapsed, refractory acute myeloid leukemia or high-risk myelodysplastic syndrome.**

*Tavares, M, Chacim, S and Mariz, JM. Ann Hematol. 2021;100(3):837-9 [IF: 3.673]*

**267. Revisiting the clinical usefulness of C-reactive protein in the set of cancer cachexia.**

*Tavares, P, Goncalves, DM, Santos, LL and Ferreira, R. Porto Biomed J. 2021;6(1):e123 [IF: NA]*

Cancer cachexia is a highly complex multifactorial disorder that is often misdiagnosed, leading to suboptimal health outcomes. Indeed, cachexia is a concern in cancer, typifying lower response to treatment and risk of death. Thus, efforts have been made to better understand the molecular basis of this syndrome, envisioning to improve its diagnosis and management. C-reactive protein (CRP) has been reported to be consistently increased in the circulation of patients with body wasting associated to chronic diseases. However, the role of CRP in the pathogenesis of cachexia remains elusive. Several hypotheses have been advanced but most of experimental findings support an indirect effect on the activation of muscle proteolysis, mostly through its interplay with pro-inflammatory cytokines. Herein, we overview the contribution of CRP to body wasting and its putative biomarker value for the diagnosis and follow-up of the therapeutic management of cachexia.

**268. Implications of venous thromboembolism GWAS reported genetic makeup in the clinical outcome of ovarian cancer patients.**

*Tavares, V, Pinto, R, Assis, J, Coelho, S, Brandao, M, Alves, S, Pereira, D and Medeiros, R. Pharmacogenomics J. 2021;21(2):222-32 [IF: 2.533]*

Ovarian cancer (OC) represents the most lethal gynaecological neoplasia. Conversely, venous thromboembolism (VTE) and OC are intricately connected, with many haemostatic components favouring OC progression. In light of this bilateral relationship, genome-wide association studies (GWAS) have reported several single-nucleotide polymorphisms (SNPs) associated with VTE risk that could be used as predictors of OC clinical outcome for better therapeutic management strategies. Thus, the present study aimed to analyse the impact of VTE GWAS-identified SNPs on the clinical outcome of 336 epithelial ovarian cancer (EOC) patients. Polymorphism genotyping was performed using the TaqMan((R)) Allelic Discrimination methodology. Carriers with the ZFPM2 rs4734879 G allele presented a significantly higher 5-year OS, 10-year OS and disease-free survival (DFS) compared to AA genotype patients with FIGO I/II stages ( $P = 0.009$ ,  $P = 0.001$  and  $P = 0.003$ , respectively). Regarding SLC19A2 rs2038024 polymorphism, carriers with the CC genotype presented a significantly lower 5-year OS, 10-year OS and DFS compared to A allele carriers in the same FIGO subgroup ( $P < 0.001$ ,  $P = 0.004$  and  $P = 0.005$ , respectively). As for CNTN6 rs6764623 polymorphism, carriers with the CC genotype presented a significantly lower 5-year OS compared to A allele carriers with FIGO I/II stages ( $P = 0.015$ ). As for OTUD7A rs7164569, F11 rs4253417 and PROCR rs10747514, no significant impact on EOC patients' survival was observed. However, future studies are required to validate these results and uncover the biological mechanisms underlying our results.

**269. The Colon Endoscopic Bubble Scale (CEBuS): a two-phase evaluation study.**

*Taveira, F, Hassan, C, Kaminski, MF, Ponchon, T, Benamouzig, R, Bugajski, M, de Castelbajac, F, Cesaro, P, Chergui, H, Goran, L, Minelli Grazioli, L, Janicko, M, Januszewicz, W, Lamonaca, L, Lenz, J, Negreanu, L, Repici, A, Spada, C, Spadaccini, M, State, M, Szlak, J, Veseliny, E, Dinis-Ribeiro, M and Areia, M. Endoscopy. 2022;54(1):45-51 [IF: 10.093]*

BACKGROUND: To date, no scale has been validated to assess bubbles associated with bowel preparation. This study aimed to develop and assess the reliability of a novel scale - the Colon Endoscopic Bubble Scale (CEBuS). METHODS: This was a multicenter, prospective, observational study with two online evaluation phases of 45 randomly distributed still colonoscopy images (15 per scale grade). Observers assessed images twice, 2 weeks apart, using CEBuS (CEBuS-0 - no or minimal bubbles, covering < 5 % of the surface; CEBuS-1 - bubbles covering 5 %-50 %; CEBuS-2 - bubbles covering > 50 %) and reporting the clinical action (do nothing; wash with water; wash with simethicone). RESULTS: CEBuS provided high levels of agreement both in evaluation Phase 1 (4 experts) and Phase 2 (6 experts and 13 non-experts), with almost perfect intraobserver reliability: kappa 0.82 (95 % confidence interval 0.75-0.88) and 0.86 (0.85-0.88); interobserver agreement - intraclass correlation coefficient (ICC) 0.83 (0.73-0.89) and 0.90 (0.86-0.94). Previous endoscopic experience had no influence on agreement among experts vs. non-experts: kappa 0.86 (0.80-0.91) vs. 0.87 (0.84-0.89) and ICC 0.91 (0.87-0.94) vs. 0.90 (0.86-0.94), respectively. Interobserver agreement on clinical action was ICC 0.63 (0.43-0.78) in Phase 1 and 0.77 (0.68-0.84) in Phase 2. Absolute agreement on clinical action per scale grade was 85 % (82-88) for CEBuS-0, 21 % (16-26) for CEBuS-1, and 74 % (70-78) for CEBuS-2. CONCLUSION: CEBuS proved to be a reliable instrument to standardize the evaluation of colonic bubbles during colonoscopy. Assessment in daily practice is warranted.

**270. AGO2 expression levels and related genetic polymorphisms: influence in renal cell progression and aggressive phenotypes.**

*Teixeira, AL, Patrao, AS, Dias, F, Silva, C, Vieira, I, Silva, JF, Ferreira, M, Morais, A, Mauricio, J and Medeiros, R. Pharmacogenomics. 2021;22(16):1069-79 [IF: 2.533]*

Aim: Renal cell carcinoma (RCC) is the most lethal urological cancer and up to 40% of patients submitted to surgery will relapse. Thus, the study aim was to analyze the associations of AGO2 SNPs with RCC patients' prognosis, and evaluate their effect on AGO2 mRNA levels. Materials & methods: The AGO2 rs4961280, rs3928672 and rs11996715 polymorphisms and the relative quantification of AGO2 mRNA levels were analyzed by real-time PCR. Results: We observed that AGO2 rs4961280 AC + AA genotypes carriers presented a higher cancer progression risk (odds ratio= 3.13, p < 0.001), a reduced progression-free survival (log rank test, p = 0.003) and an increased risk of an early relapse (hazard ratio= 2.26, p = 0.008). In fact, these patients also presented higher circulating levels of AGO2 mRNA (p = 0.043), with the high levels being associated with more aggressive tumors. Conclusion: The AGO2 rs4961280 AA/AC genotypes are unfavorable RCC prognostic biomarkers, with the AGO2 levels being a useful RCC aggressive phenotype biomarker.

**271. Reply to Dr. Kose et al: Deep supraspinatus muscle plane block: A novel ultrasound-guided technique for the blockade of suprascapular nerve branches.**

*Teles, AS, Galluccio, F, Salazar, C and Fajardo-Perez, M. J Clin Anesth. 2021;72:110267 [IF: 9.452]*

**272. Association of Murine Double Minute 2 polymorphisms with gastric cancer: A systematic review with meta-analysis.**

*Timoteo, M, Tavares, A, Cruz, S, Campos, C, Medeiros, R and Sousa, H. Biomed Rep. 2021;15(2):69 [IF: NA]*

Gastric cancer (GC) is the 5th most common type of cancer, with the 3rd highest mortality rate worldwide in both sexes. Murine double minute 2 (MDM2) protein is the major negative regulator of p53, and genetic polymorphisms in this gene have shown to be associated with several types of cancer. In the present study, a literature search was performed using PubMed and Scopus with the following key word combinations 'gastric cancer AND polymorphism AND MDM2'. Studies were carefully revised according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to identify eligible studies that matched the inclusion criteria. Statistical analysis was performed to assess the association between the different genetic polymorphisms and GC risk, by calculating the odds ratios (OR) and the confidence

intervals (CI), with a 5% level of significance. A total of 11 manuscripts studied MDM2 polymorphisms in GC: rs937283 (n=1), rs3730485 (n=1) and rs2279744 (n=9). Both the rs937283 and rs3730485 reports showed an association with GC; however, there was only one study on each of these polymorphisms in the literature. A meta-analysis was performed for the rs2279744 polymorphism, of which studies showed a positive association between the G allele and risk of GC, either in the dominant model (OR=1.46; 95% CI 1.21-1.75; P<0.001) or recessive model (OR 1.65; 95% CI 1.45-1.87; P<0.001). In conclusion, genetic polymorphisms in MDM2 seemed to be associated with an increased risk of GC development, nevertheless, the number of studies were relatively low and the studied populations were primarily Chinese. The present meta-analysis emphasizes the need for additional studies in other populations to corroborate the association of these polymorphisms with GC.

### 273. Dissection Technique for Abdominoplasty With Scarpa Fascia Preservation: Comparative Study on Avulsion Technique Versus Diathermocoagulation.

Torres-Silva, C, Pisco, A, Valenca-Filipe, R, Rebelo, M, Peres, H, Vasconez, L and Costa-Ferreira, A. *Aesthet Surg J.* 2021;41(7):NP804-NP19 [IF: 4.283]

BACKGROUND: Many strategies have been developed to lower the high complication rate associated with a full abdominoplasty. The dissection technique may have a role to achieve this goal. OBJECTIVES: The present study compared 2 different dissection techniques to perform a full abdominoplasty with Scarpa fascia preservation: avulsion technique and electrodissection. METHODS: A retrospective observational cohort study was performed in 2 health institutions from January 2005 to January 2019. A total of 251 patients were involved: 122 patients submitted to abdominoplasty employing the avulsion technique (Group A) and 129 with diathermocoagulation (coagulation mode) (Group B). The latter was further divided into group B1 (57 patients with device settings according to surgeon's preferences) and B2 (72 patients with a specific regulation aiming at minimal tissue damage). Several variables were analyzed: population characteristics, time of hospital stay, time to drain removal, total and daily drain output, emergency department visits, readmission, reoperation, and local and systemic complications. RESULTS: The general characteristics of both groups did not statistically significantly differ except for previous abdominal surgery. The diathermocoagulation group had a significantly lower length of hospital stay and time to drain removal. Moreover, these advantages were maximized when electrocautery was conducted with a specific low-voltage setting as significant differences were found. The other outcomes were identical. CONCLUSIONS: Limiting the extension of electrodissection with the avulsion technique did not present any advantage. Utilizing diathermocoagulation (coagulation mode) during a full abdominoplasty with Scarpa fascia preservation, especially when it is aimed at minimal tissue damage, reduces patients' time with drains. LEVEL OF EVIDENCE: 3:

### 274. Thrombotic microangiopathy in oncology - a review.

Valerio, P, Barreto, JP, Ferreira, H, Chuva, T, Paiva, A and Costa, JM. *Transl Oncol.* 2021;14(7):101081 [IF: 4.243]

Thrombotic microangiopathy is a syndrome triggered by a wide spectrum of situations, some of which are specific to the Oncology setting. It is characterized by a Coombs-negative microangiopathic haemolytic anemia, thrombocytopenia and organ injury, with characteristic pathological features, resulting from platelet microvascular occlusion. TMA is rare and its cancer-related subset even more so. TMA triggered by drugs is the most common within this group, including classic chemotherapy and the latest targeted therapies. The neoplastic disease itself and hematopoietic stem-cell transplantation could also be potential triggers. Evidence-based medical guidance in the management of cancer-related TMA is scarce and the previous knowledge about primary TMA is valuable to understand the disease mechanisms and the potential treatments. Given the wide spectrum of potential causes for TMA in cancer patients, the aim of this review is to gather the vast information available. For each entity, pathophysiology, clinical features, therapeutic approaches and prognosis will be covered.

### 275. Multiple Pulmonary Nodes and Thoracic Pain: A Case Report.

Vasconcelos, S and Ferreira, AM. *Portuguese J Pediatrics.* 2021;52(3):212-5 [IF: NA]

**276. Study on Data Partition for Delimitation of Masses in Mammography.**

Viegas, L, Domingues, I and Mendes, M. *J Imaging*. 2021;7(9) [IF: NA]

Mammography is the primary medical imaging method used for routine screening and early detection of breast cancer in women. However, the process of manually inspecting, detecting, and delimiting the tumoral masses in 2D images is a very time-consuming task, subject to human errors due to fatigue. Therefore, integrated computer-aided detection systems have been proposed, based on modern computer vision and machine learning methods. In the present work, mammogram images from the publicly available Inbreast dataset are first converted to pseudo-color and then used to train and test a Mask R-CNN deep neural network. The most common approach is to start with a dataset and split the images into train and test set randomly. However, since there are often two or more images of the same case in the dataset, the way the dataset is split may have an impact on the results. Our experiments show that random partition of the data can produce unreliable training, so the dataset must be split using case-wise partition for more stable results. In experimental results, the method achieves an average true positive rate of 0.936 with 0.063 standard deviation using random partition and 0.908 with 0.002 standard deviation using case-wise partition, showing that case-wise partition must be used for more reliable results.

**277. Data Sharing Under the General Data Protection Regulation: Time to Harmonize Law and Research Ethics?**

Vlahou, A, Hallinan, D, Apweiler, R, Argiles, A, Beige, J, Benigni, A, Bischoff, R, Black, PC, Boehm, F, Ceraline, J, Chrousos, GP, Delles, C, Evenepoel, P, Fridolin, I, Glorieux, G, van Gool, AJ, Heidegger, I, Ioannidis, JPA, Jankowski, J, Jankowski, V, Jerónimo, C, Kamat, AM, Masereeuw, R, Mayer, G, Mischak, H, Ortiz, A, Remuzzi, G, Rossing, P, Schanstra, JP, Schmitz-Drager, BJ, Spasovski, G, Staessen, JA, Stamatialis, D, Stenvinkel, P, Wanner, C, Williams, SB, Zannad, F, Zoccali, C and Vanholder, R. *Hypertension*. 2021;77(4):1029-35 [IF: 10.190]

The General Data Protection Regulation (GDPR) became binding law in the European Union Member States in 2018, as a step toward harmonizing personal data protection legislation in the European Union. The Regulation governs almost all types of personal data processing, hence, also, those pertaining to biomedical research. The purpose of this article is to highlight the main practical issues related to data and biological sample sharing that biomedical researchers face regularly, and to specify how these are addressed in the context of GDPR, after consulting with ethics/legal experts. We identify areas in which clarifications of the GDPR are needed, particularly those related to consent requirements by study participants. Amendments should target the following: (1) restricting exceptions based on national laws and increasing harmonization, (2) confirming the concept of broad consent, and (3) defining a roadmap for secondary use of data. These changes will be achieved by acknowledged learned societies in the field taking the lead in preparing a document giving guidance for the optimal interpretation of the GDPR, which will be finalized following a period of commenting by a broad multistakeholder audience. In parallel, promoting engagement and education of the public in the relevant issues (such as different consent types or residual risk for re-identification), on both local/national and international levels, is considered critical for advancement. We hope that this article will open this broad discussion involving all major stakeholders, toward optimizing the GDPR and allowing a harmonized transnational research approach.

**278. Live endoscopy events (LEEs): European Society of Gastrointestinal Endoscopy Position Statement - Update 2021.**

Webster, GJ, El Menabawey, T, Arvanitakis, M, Hassan, C, van Hooft, JE, Messmann, H and Dinis-Ribeiro, M. *Endoscopy*. 2021;53(8):842-9 [IF: 10.093]

The European Society of Gastrointestinal Endoscopy (ESGE) is dedicated to improving the quality of gastrointestinal endoscopy, including through educational activities such as live endoscopy events (LEEs). The primary goal of LEEs should be to facilitate the improvement of endoscopic patient care through the acquisition of best endoscopic practice. Patients should not expect additional benefit from being treated during a LEE compared to a routine setting. There is limited available evidence on LEE safety but to date there is no indication that patients are at increased risk from participation. Pre-recorded cases with live facilitation can also be used to fulfill learning outcomes. Establishing an endoscopic curriculum with clear learning outcomes is important to structure attendees' learning, assess course outcomes, and allow

appropriate targeting of courses to learner experience. Increasingly, LEEs are streamed online and therefore the necessary measures should be taken to ensure that patients have given appropriate consent and that their anonymity has been safeguarded. ESGE recommends that an endoscopist who is not participating in the live demonstrations is named as patient advocate, and that patient safety should be prioritized throughout. In all ESGE-organized LEEs the intended learning outcomes, procedural indications and descriptions, attendee feedback, and adverse events should be recorded and submitted in a post-event report to ESGE.

**279. Correction: Myeloablative conditioning for allo-HSCT in pediatric ALL: FTBI or chemotherapy?-A multicenter EBMT-PDWP study.**

*Willasch, AM, Peters, C, Sedlacek, P, Dalle, JH, Kitra-Roussou, V, Yesilipek, A, Wachowiak, J, Lankester, A, Prete, A, Hamidieh, AA, Ifversen, M, Buechner, J, Krivan, G, Hamladji, RM, Diaz-de-Heredia, C, Skorobogatova, E, Michel, G, Locatelli, F, Bertaina, A, Veys, P, Dupont, S, Or, R, Gungor, T, Aleinikova, O, Sufliarska, S, Sundin, M, Rascon, J, Kaare, A, Nemet, D, Fagioli, F, Klingebiel, TE, Styczynski, J, Bierings, M, Nagy, K, Abecasis, M, Afanasyev, B, Ansari, M, Vettenranta, K, Alseraihy, A, Chybicka, A, Robinson, S, Bertrand, Y, Kupesiz, A, Ghavamzadeh, A, Campos, A, Pichler, H, Dalissier, A, Labopin, M, Corbacioglu, S, Balduzzi, A, Galimard, JE, Bader, P and Party, EPDW. Bone Marrow Transplant. 2021;56(10):2615 [IF: 5.483]*

**280. Chitinase 3-like-1 and fibronectin in the cargo of extracellular vesicles shed by human macrophages influence pancreatic cancer cellular response to gemcitabine.**

*Xavier, CPR, Castro, I, Caires, HR, Ferreira, D, Cavadas, B, Pereira, L, Santos, LL, Oliveira, MJ and Vasconcelos, MH. Cancer Lett. 2021;501:210-23 [IF: 8.679]*

Tumour-associated macrophages have been implicated in pancreatic ductal adenocarcinoma (PDAC) therapy response and Extracellular vesicles (EVs) shed by macrophages might have a role in this process. Here, we demonstrated that large EVs released by anti-inflammatory human macrophages decreased PDAC cellular sensitivity to gemcitabine. Using proteomic analysis, chitinase 3-like-1 (CHI3L1) and fibronectin (FN1) were identified as two of the most abundant proteins in the cargo of macrophages-derived EVs. Overexpression of CHI3L1 and FN1, using recombinant human proteins, induced PDAC cellular resistance to gemcitabine through ERK (extracellular-signal-regulated kinase) activation. Inhibition of CHI3L1 and FN1 by pentoxifylline and pirfenidone, respectively, partially reverted gemcitabine resistance. In PDAC patient samples, CHI3L1 and FN1 were expressed in the stroma, associated with the high presence of macrophages. The Cancer Genome Atlas analysis revealed an association between CHI3L1 and FN1 gene expression, overall survival of PDAC patients, gemcitabine response, and macrophage infiltration. Altogether, our data identifies CHI3L1 and FN1 as potential targets for pharmacological inhibition in PDAC. Further pre-clinical in vivo work is warranted to study the possibility of repurposing pentoxifylline and pirfenidone as adjuvant therapies for PDAC treatment.

