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Connecting Scientists and Physicians for Next Generation Cancer Management

The therapeutic management of an aggressive nodular malignant melanoma

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Abstract: Melanomas are aggressive cancers that differ from other skin tumorous lesions because of their intrinsic capability to present melanogenic enzymes along with proteins which are capable of synthetizing melanin. Nodular melanomas (NM) are the second most common type of cutaneous melanomas (40%) presenting a rapid growth rate and high metastatic potential. These types can appear in any part of the body but they usually occur on the torso and lower extremities. We present the case of a 73-year-old male patient who presented multiple progressively growing lesions on the right hypochondrium and axilla with irregular borders and colors. The histopathological report confirms the diagnosis of an ulcerated malignant nodular melanoma, Clark III, with and Breslow's index of 30 mm along with nonlocal lymph nodes. The surgical approach results in the resection of an ulcerated 13,5 x 7,5 x 1 cm piece from the right hypochondrium and a 7 x 3,5 x 3 cm piece from the right axillary region. The surgical technique of a maximum widening of the margins is considered to be the best surgical option for nodular melanomas. Although the excisions are considered to be vast, the patients' outcomes can become favorable considering the fatal evolution of NM's. One of the most important aspects of this case is represented by the age of the patient and the constant, cumulative sun damage along with the fact that he does not present mutations in the oncogene BRAF.

Keywords: Breslow's thickness; Clark level; Malignant melanoma; Metastasis; Oncologic Surgery

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Navigating the Challenges of Intrahepatic Intraductal Papillary Cholangiocarcinoma: A Case of Early Diagnosis and Management

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Abstract: Cholangiocarcinoma (CCA), the second most frequent primary liver cancer (constituting approximately 10%-15% of cases) after hepatocellular carcinoma (HCC), can be classified based on its location in intrahepatic, perihilar and distal CCA. Among these, intrahepatic CCA represents the rarest form, accounting for around 10% of cases. This malignancy exhibits an increasing global incidence and mortality rate, as a result of its typically silent presentation, leading to delayed diagnosis and difficult management. Early diagnosis represents a current challenge for physicians. Risk factors associated with intrahepatic CCA align closely with those recognized for HCC, including cirrhosis, chronic hepatitis B and C, obesity, diabetes, and alcohol consumption. Papillary tumors represent the rarest manifestation of cholangiocarcinoma. These tumors manifest as bulky masses in the lumen of biliary ducts, leading to early biliary obstruction in the course of the disease. As a result, the lesion becomes detectable in the early stages of the disease thus having greater rates of resectability and curability. The aim of this case report is to demonstrate the management of an early diagnosed intrahepatic intraductal papillary cholangiocarcinoma.

We present a 73-year-old female with a past medical history of hepatitis C, ulcerative colitis and hypertension who presented to the emergency department for weight loss and fatigue. Laboratory work revealed moderate anemia (Hb=8.2g/dl), elevated alanine transaminase (87 U/l), aspartate transaminase (161 U/l), alkaline phosphatase (164 U/l) and gamma-glutamyltransferase (151 U/l) suggesting a cholestatic pattern of liver injury. Additionally, the patient presented high tumor markers: AFP of 3.84ng/ml, CEA of 3.06 ng/ml and CA 19-9 of 108.07 U/ml. Abdominal ultrasound revealed an enlarged liver with steatosis and a neomogen, macronodular structure. In order to better define the lesion, magnetic resonance cholangiopancreatography was performed, revealing parietal thickening of the left bile duct in the proximal portion, the stenotic lesion leading to upstream dilation of the bile ducts (9mm). Due to the pattern of distribution, left hepatectomy was considered. The subsequent histopathological exam revealed intrahepatic cholangiocarcinoma with intraductal papillary proliferation. Two months after the surgery, adjuvant chemotherapy was initiated, using the combination of Gemcitabine and Capecitabine, which was well tolerated. Although intrahepatic intraductal papillary CCA has a low incidence, its clinical presentation makes it one of the easiest forms of CCA to diagnose, leading to an early stage diagnosis and efficient management compared to other forms of CCA.

Keywords: intrahepatic cholangiocarcinoma; early stage diagnosis; intraductal papillary neoplasm

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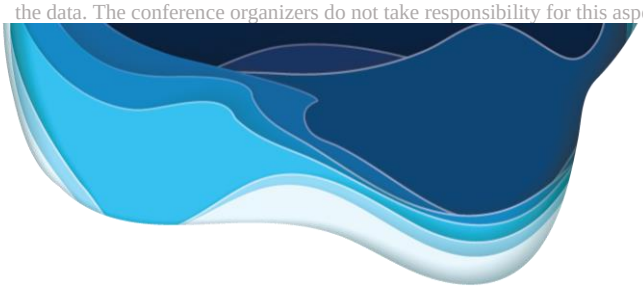

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ONCODIR - the initiative developing cutting-edge strategies for preventing colorectal cancer

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Abstract: Colorectal cancer (CRC) is the prevailing form of cancer in Europe, exhibiting an annual incidence of 450,000 cases. Approximately 230,000 individuals are projected to experience mortality. Colorectal cancer (CRC) is a significant global public health concern due to its impact on morbidity, mortality, and the effectiveness of healthcare interventions aimed at prevention and health enhancement, including associated medical expenses.
The primary objective of the ONCODIR platform is to provide a sophisticated decision-making system that is bolstered by advanced artificial intelligence technologies. This system will be meticulously built to effectively tackle specific difficulties across a range of use cases by leveraging dedicated models. The development of these models will be grounded in the principle of integrating and correlating various forms of extensive data, with a specific emphasis on conducting multidimensional analysis. Another objective of the ONCODIR framework is also to increase the transferability and replicability of health systems in the European Union and possibly in other geographical areas. The main goal of ONCODIR is to address these difficulties through the implementation of a comprehensive and interdisciplinary approach, that includes a range of co-creation activities. The achievement of the aforementioned goals will be facilitated by the utilization of various tools and methods. These tools and methodologies will serve the following purposes: the classification of citizens based on risk, the provision of integrated decision support tools for physicians, and the utilization of intelligent monitoring tools for policymakers. The aforementioned criteria will also play a role in the advancement of tailored prevention methods, efficacious interventions, and implementation plans. The achievement of this objective will be facilitated by integrating the viewpoints of citizens/patients, medical professionals, and policymakers through a participatory co-design methodology. Furthermore, the utilization of open innovation and FAIR data will be employed to augment this process, specifically concentrating on the quantification of the effects of interventions and the extraction of valuable insights. The ONCODIR project outcomes seek to address the aforementioned challenges through substantial research endeavors, with the aim of developing innovative preventive strategies for colorectal cancer that may be implemented in the healthcare sector.

Keywords: Colorectal Cancer, Innovative Strategies, Cancer Prevention

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SHIFT-HUB - The European Smart Health Innovation Hub program

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Abstract: One notable consequence of the epidemic is the expedited advancement of "digital health," which has garnered heightened attention and investment from both public and private sectors. This can be attributed to the pivotal role that digital technologies have played in combating the pandemic. The mission undertaken by SHIFT-HUB is to establish a pan-European network that collaborates to expedite the advancement of Smart Health products and services. This includes the creation and support of a Health Data and Apps platform, as well as the provision of appropriate methodologies, tools, and resources. The primary objectives of this network are to offer personalized diagnostic and care options, enhance the management and prevention of diseases, and improve overall efficiency in healthcare. The primary demographic segments within the environment are exemplified by: patients, healthcare and technology professionals. Citizens are a crucial demographic within the end-user population. This group can be further classified into patients belonging to four distinct sub-categories based on their specific pathologies, which include cancer, cardiovascular diseases, infectious diseases, and non-communicable diseases. Furthermore, the populace is actively involved in the evaluation of apps specifically created for preventative objectives; Healthcare professionals, along with public and commercial healthcare organizations, are considered end users for primary applications of Health Data & Solutions. These applications encompass enhanced and tailored diagnosis and treatment. Additionally, secondary applications including research are also utilized by these stakeholders who will possess the requisite medical knowledge and abilities to effectively design, develop, and assess these solutions by their respective areas of competence.
This collaboration aims to promote Smart Health technologies and services that can assist Europeans and patients in four major problematic groups. The goal is achieved by research, development, and innovation. A well-connected network of European "innovation intermediaries" will help technology providers and practitioners. Intermediaries including business support organizations and European Digital Innovation Hubs (EDIHs) will be crucial to developing a wide range of services and ensuring extensive coverage across Europe. The main emphasis of our research is directed towards technology providers, with a particular focus on Health Tech start-ups, small and medium-sized enterprises and mid-cap companies. These organizations are involved in the creation of hardware and software solutions that make use of many technologies utilized in the field of Smart Health. This network will provide localized assistance by facilitating connections between individuals and organizations with the appropriate skills, resources, and external services that cater to their specific needs.

Keywords: Smart Health Solution, Innovation Hub, Digital Health

Acknowledgements: This paper was supported by European Union’s Horizon Europe research and innovation program under grant agreement No.101095720 (SHIFT-HUB)

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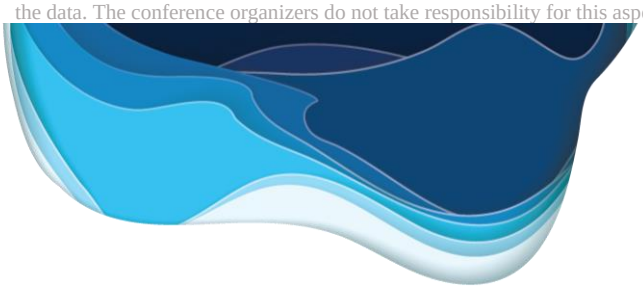

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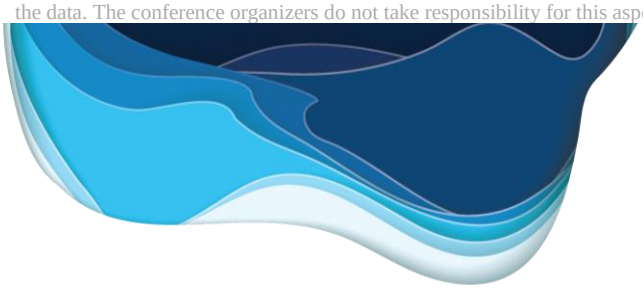

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Innovative multilevel risk factor-based tool for screening populations at risk of cancer

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Abstract: Colorectal cancer (CRC) is accountable for 12.4% of all deaths due to cancer, but it has a survival prediction of 91% for early detection. ONCOSCREEN aims to use next-generation, non-invasive, easy-to-use and cheap tools for large-scale screening of the population (4-5000 patients and clinical studies in 10 hospitals). This endeavour centres on the development of feasible policy initiatives and the implementation of risk-based screening procedures that are both innovative and cost-effective while maintaining accuracy. Additionally, the project aims to advance the creation of inventive, non-intrusive, and economically viable screening methods specifically tailored for the detection of this particular type of cancer. Among these AI tools is the multi-tiered risk evaluation, spanning lifestyle, genomic, and epigenomic factors, as well as socioeconomic status, environmental stressors, gender aspects, educational background, and urbanization inequalities both between and within EU countries. While unhealthy lifestyles are a more prominent cause in urban areas, poverty, lack of education, healthcare facilities and professionals impact rural areas more. To harness these diverse factors for personalized risk assessment, ONCOSCREEN proposes a new AI tool, ONCO-RISTE: Cancer Patients' Risk-Based Stratification Engine. ONCO-RISTE employs a semi-empirical risk stratification process, adopting various fuzzy architectures like Mamdani, Sugeno, Hierarchical Fuzzy Trees, and Adaptive Neuro-Fuzzy Inference Systems. The proposed tool will generate dynamically a risk-based calculation considering all factors, stressors, the results from faecal tests, colonoscopy adenoma/polyp classification, tissue biopsy adenoma/polyp the background of individuals and the pool of expert rules. The output of ONCO-RISTE will update dynamically an internal risk-based score and will show to individuals their risk in 5 levels from very low to very high. The objective of the ONCOSCREEN results is to fundamentally transform colorectal cancer (CRC) screening and intervention by eliminating the necessity for colonoscopies and clinical appointments. This approach intends to promote early testing and treatment among individuals in a non-invasive and cost-effective manner.

Keywords: Colorectal Cancer, AI cancer screening, Biomarkers

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Extensive drainage and intraductal radiofrequenccy ablation can improve patient outcomes in cases of inoperable perihilar cholangiocarcinoma: Interim results of the Combo-RFA trial

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Abstract: Introduction: Therapeutic options in the management if inoperable perihilar cholangiocarcinoma (pCCA) patients are very limited and include palliative chemotherapy and endoscopic drainage procedures. Recently, ERCP-guided intraductal radiofrequency ablation (RFA) has been proposed as a potential adjuvant therapy in these cases.

Study aims: We aimed to evaluate the feasibility, clinical success rates and safety profile of an endoscopic treatment protocol adding RFA to biliary stenting in inoperable pCCA patients.

Methods: We performed an interim analysis of a single center, randomized control trial of pCCA patients with ECOG 0-2 performance status and localized disease (COMBO-RFA NCT05563870)who required palliative endoscopic biliary drainage. Patients in the control arm underwent palliative stenting with plastic stents while patients in the active arm additionally received local RFA ablation. All patients were referred for palliative chemotherapy according to the current standard of care. Clinical outcomes and procedure-related adverse events (AE) rates were evaluated prospectively at 30 days and every 3 months until death.

Results: We included 20 patients (10 in the RFA arm, 10 in the control arm) between April 2022- August 2023. Patients were predominantly males (11/20), mean age was 72 years and most had complex strictures (Bismuth type IV 14/20). Median ECOG status was 1 (range 0-2) and mean bilirubin level pre-endoscopy was 16.1 mg/dl (range 1.8–36.8). At 30 days after the first procedure, 12/18 of patients had a bilirubin level that allowed chemotherapy initiation. However, only 5/18 patients underwent systemic therapy (4 in the RFA arm, 1 in the control arm), including 3 patients who received Durvalumab. Technically, adding RFA to biliary drainage was not associated with

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increased rates of procedure-related AEs (5 in the active arm vs 9 in the control arm, p=0.6). Notably, the 3 patients receiving immunotherapy have the longest overall survival in our cohort so far.

Conclusions: The preliminary results of our study show that intraductal RFA is feasible and safe in the setting of inoperable pCCA. Also, our preliminary results suggest that patients undergoing RFA were more likely to undergo systemic chemotherapy. Future studies are required to clarify the role of intraductal RFA in the management of inoperable pCCA.

Keywords: perihilar cholangiocarcinoma, radiofrequency ablation

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From Aphasia to Colon Cancer: A Case of Brain Metastasis as the Initial Presentation of Rectal Adenocarcinoma

Enache Cioc[1], Monica Adriana Nichita[1], Iolanda Goga[1], Mihaela Moraru[1], Alexandru Sasaran[2], Dan Martin[2], Andrei Giovani[2], Silviu Cristian Voinea[1,3], Alexandru Blidaru[1,3], Adina Elena Ene[1], and Daniela Luminița Zob[1]

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Abstract: Brain metastases from colorectal adenocarcinoma are uncommon and typically occur in advanced stages of the disease, when metaseses are already present in other organs. We present the case of a 78-year-old man who initially sought medical attention in October 2019 due to right hemianopsia and receptive aphasia, with brain imaging studies revealing a left temporo-parietal tumor mass. The patient underwent neurosurgical intervention, resulting in the complete ablation of the intracranial mass. Histopathological and immunohistochemical examination confirmed the tumor as a metastasis of an adenocarcinoma, likely originating from the gastrointestinal tract, although the possibility of a pulmonary adenocarcinoma could not be entirely excluded. Subsequent CT scans, upper gastrointestinal endoscopy and colonoscopy were performed, which revealed rare small bilateral pulmonary nodules and a rectal tumoral mass. A biopsy of the rectal mass confirmed the diagnosis of rectal adenocarcinoma. The patient underwent chemotherapy (XELOX regimen) which was generally well tolerated, except for transitory episodes of thrombocytopenia leading to temporary suspensions of chemotherapy administration on several occasions. After completing 10 cycles of chemotherapy, the patient underwent surgical intervention with abdominoperineal amputation of the rectum. Histopathological and immunohistochemical analysis of the excised rectal specimen revealed no evidence of residual neoplastic tissue. Besides some postoperative complications, involving an unexpected perineal evisceration and a significant median eventration, both effectively managed, the evolution of the patient was highly favorable. Long-term follow-up has shown no evidence of disease recurrence or progression of the initial pulmonary nodules, and subsequent imaging studies have been negative for new lesions. This case is noteworthy for its atypical initial presentation of rectal adenocarcinoma, mimicking a primary brain tumor, and the remarkable complete pathological response observed after chemotherapy with no signs of disease progression up to the present day. It underscores the complexity of cancer various forms of presentation and management and the importance of interdisciplinary collaboration in addressing unexpected challenges throughout the course of the disease.

Keywords: rectal adenocarcinoma, brain metastasis, xelox regimen, complete pathological response

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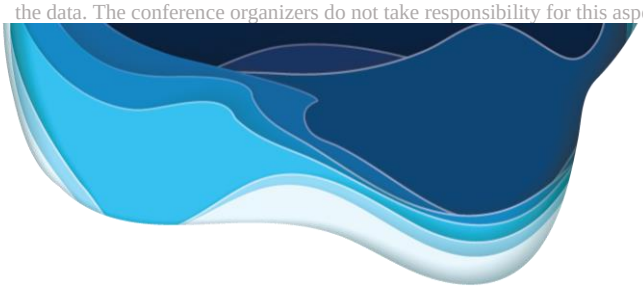

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Fulminant liver progression following total resection of primary renal Ewing's sarcoma

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Abstract: Primary Ewing sarcoma of the kidney is an extremely rare and aggressive tumor affecting young adults. Given its aggressive nature, patients typically present with advanced disease and early metastasis.

The 22-year-old patient, ECOG 1, was diagnosed in February 2021 with primary renal Ewing Sarcoma. An initial evaluation with a CT scan of the thorax abdomen and pelvis revealed the presence of a right renal mass, measuring 24.3 × 18.7 × 18.3cm, and multiple bilateral lung lesions. Tumor pathology demonstrated an extraosseous Ewing sarcoma/primitive neuroectodermal tumor. The decision was made to begin chemotherapy line 1 VAC protocol q2w with primary prophylaxis of febrile neutropenia with pegfilgrastim. Six cycles of chemotherapy were administered between July and October 2021, but complications like febrile neutropenia and grade 4 pancytopenia necessitated secondary anemia prophylaxis with darbepoetinum and the continuation of the administration at 4 weeks before reducing the total dose to 80% in the sixth cycle. The CT scan of the thorax, abdomen, and pelvis examination showed a significant reduction in lung lesions and a small dimensional improvement in renal tumor (237/170/167mm). A PET/CT scan performed in November 2021 showed residual FDG uptake in the area of the right kidney of (21/18mm), but did not demonstrate any other significant hypermetabolic areas. The multidisciplinary tumor board agreed to remove the tumor after taking into account the complete response at the level of the pulmonary lesions and the significant reduction of the primary renal tumor's metabolism. In December 2021 Complete resection (R0) of the primary tumor, with a right nephrectomy was performed. The CHT line 2 protocol IE q2w was started as a result of the CT examination in February 2022, which revealed multiple newly developed hypodense liver lesions (d max 21/23mm) without any evidence of local recurrence. A total of four cycles were administered, which were complicated by NF and grade 3 pancytopenia, which necessitated postponing chemotherapy every three weeks. The June 2022 CT evaluation revealed dimensional progression of liver lesions and local recurrence, deterioration of the general condition with ECOG PS 2, and biological evidence of hepatocytolysis and cholestasis syndrome. The CHT line 3 Gemcitabine+Docetaxel protocol was initiated, but the patient's condition deteriorated significantly, allowing only weekly Gemcitabine monotherapy for 7 weeks. The patient's general condition deteriorated with dyspnea, abdominal pain VAS 7, ascites and bilateral pleurisy, grade 4 hepatocytolysis, grade 3 thrombocytopenia, prompting referral to the palliative care service. 18 months after the diagnosis, death occurs.

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Metastatic extraosseous Ewing sarcoma in young people has a rapid progression, and the current CHT protocol is very aggressive and difficult to administer at the intensity of the recommended dose. Even if a partial response is obtained following primary CHT, radical surgical intervention with negative margins has minimal effect on tumor cell dissemination and does not improve survival.

Keywords: primary renal Ewing sarcoma; metastatic extraosseous Ewing sarcoma; impact of chemotherapy dose intense; fulminant hepatic progression;

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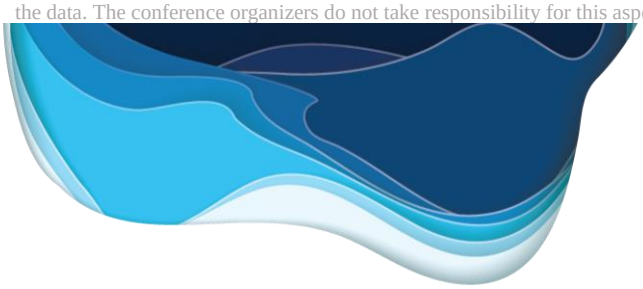

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HIF1A and lncRNAs crosstalk in cervical cancer: Unveiling the hypoxic signature

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Abstract: A common feature of solid tumors including cervical cancer is represented by low oxygen levels (hypoxia). Under hypoxic conditions a very important role in cellular response is played by a transcriptional factor namely HIF1A (Hypoxia-Inducible Factor 1 Alpha) involved in various cell processes such as angiogenesis, glycolysis, cell survival. It has been shown that HIF1A can influence the expression profile of specific lncRNAs (long non-coding RNAs), which in turn can modulate different cellular processes. Thus, exploring the interactions between HIF1A and lncRNAs in this pathology might hold great prospective for sorting out hypoxia-driven tumor progression, identifying potential therapeutic targets, and also for personalized treatment strategies. This study aims to investigate lncRNAs expression profile in a cervical cancer hypoxia model.

Materials and methods: For mimicking the hypoxic conditions CaSki cell line was used and treatment with CoCl2 was applied. Also HIF1A silencing was achieved using specific designed siRNA molecules. Afterwards, from treated/untreated cells total RNA and proteins were isolated with commercials kits and later used in qRT¬-PCR and Western blot analyses. LncRNAs expression pattern was assessed in tested samples using LncRNA Profiler qPCR Array Kit (System Biosciences). Each measurement was conducted in triplicate and the statistical analysis was computed using GraphPad Prism 6.

Results: After conducting in vitro experiments the optimal conditions for hypoxia model were established, specifically, the cells treated with 200 µM CoCl2 for 72 hours showed the most significantly elevated expression of both the HIF1A mRNA and protein levels. Whereas the best knockdown percentage (91.45%) for HIF1A silencing was observed for cells treated with 75 nM siRNA HIF1A for 48 hours. Evaluating lncRNAs profiles under these experimental conditions it has been revealed that approximatively 61 lncRNAs showed significantly aberrant expression levels in hypoxic cells (fold change>3; p-value≤0.05) while 59 displayed a significantly changed pattern of expression in HIF1A silenced cells. Moreover, through Venn diagram analysis, we identified a set of 12 lncRNAs that exhibit altered expression profiles in both experimental conditions comprising of the following: SNHG1, HAR1B, Sox2ot, KRASP1, AK023948, SNHG6, Hoxa11as, HOTAIR, GAS5-family, NEAT1 (family), Malat1, and TncRNA. Integrating the obtained results into GO analysis and KEGG pathway analysis it was shown that these lncRNAs are involved in specific cellular processes such as: cellular proliferation, growth, angiogenesis, apoptosis, cell cycle regulation, AKT signalling cell survival, chromatin remodeling, glycolysis and cell metabolism.

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Conclusion: This study findings highlight an lncRNAs hypoxic signature in cervical cancer that holds a great potential to be explored for improving disease diagnosis, prognosis, and treatment strategies.

Keywords: cervical cancer; hypoxia; lncRNAs

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Therapeutic management at a patient with metastatic pulmonary adenocarcinoma: a case report

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Abstract: Pulmonary adenocarcinomas are a type of non-small cell lung cancer (NSCLC) and they are considered the most common type of lung neoplasm. Lung adenocarcinomas are more likely to present a positive PD-L1 expression than other types of lung cancers. In the following, it will be presented a clinical case of a 69-year-old male patient diagnosed with pulmonary adenocarcinoma in March 2021. Pathology and molecular biology pointed out a PD-L1 positive > 50% and ALK, EGFR genes mutations negative. The CT examination showed a tumor mass of 32/39 mm in the right superior lobe and some calcified pulmonary micronodules. It was initiated chemotherapy with Pemetrexed in association with Cisplatin as a first-line treatment. The next CT examination revealed the presence of pulmonary. It was decided to change the therapeutic behavior and to initiate immunotherapy with Pembrolizumab in monotherapy, based on the fact that PD-L1 expression was positive. Under the new treatment line, at the following CT examination, it was not reported disease progression. In conclusion, it will be presented the clinical benefits that appeared under immunotherapy as a second-line treatment choice.

Keywords: lung adenocarcinoma; immunotherapy; PD-L1 expression

Conflict of interest: The authors declare no conflict of interest.

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High-fat diet impairs phenotype and function of Natural Killer cells in melanoma-bearing mice

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Abstract: Obesity impairs immune function and increases the risk of cancer. Recent findings highlight an impaired phenotype and functionality of natural killer (NK) cells under obese conditions. The aim of the study was the characterization of the number, subsets distribution, expression of NK cell surface receptors and *ex vivo* response to cytokine pre-activation of NK cells from melanoma-bearing mice fed a control or high-fat diet. Two groups of C56BL/6J mice were fed a normal-fat diet (NFD, 10% kcal fat) and a high-fat diet (HFD, 45% kcal fat) for 2 months. Subsequently, cutaneous melanoma was generated by subcutaneous inoculation of 0,5 x 10^6 B16F10 melanoma cells. Controls were healthy sex/age-matched mice. Two perpendicular diameters of the developed tumors were measured weekly using a caliper. After 21 days' spleens were harvested and used for assessing the flow cytometry analyses of NK cells (FACSCanto II flow cytometer with DIVA software). For *ex vivo* assay NK cells were isolated by negative selection and treated overnight with 10 ng/ml IL-12, 10 ng/ml IL-15, and 50 ng/ml IL-18. The expression of CD69, CD25, IFNγ and perforin was assessed by flow cytometry.

HFD-mice presented a significantly higher tumor volume than NFD-mice. Also, a high-fat diet impaired the phenotype and function of NK cells. Cytotoxic immune cells, NK cells were significantly decreased in HFD-mice and tumor-bearing mice. Analysis of NK cell subsets indicated a significant decrease of mature subset CD27+CD11b+ and an increase of immature NK cell subset CD27-CD11b-. The expression of activation and maturation markers CD335, CD122, CD49b, CD43, KLRG1 on NK cells was decreased in HFD-mice and mice with melanoma. Also, decrease in NK cells functionality was detected in both groups compared to the control group. Cytokine pre-activated of NK cells from group control upregulated CD69 and CD25 immunomodulatory molecules on their surface and enhanced the production of IFNγ and perforin compared with HFD or NFD mice.

The results indicate a decrease of NK cells and the mature NK cell subsets in high-fat diet mice. High-fat diet feeding resulted in decreased expression of activation and maturation markers. *Ex vivo* cytokine pre-activation of NK cells from melanoma-bearing mice displayed a decreased expression of activation markers and a reduced capacity of IFNγ and perforin production. All these data indicate an association of impaired NK cell functionality with obesity.

Keywords: NK cells; high-fat diet; melanoma

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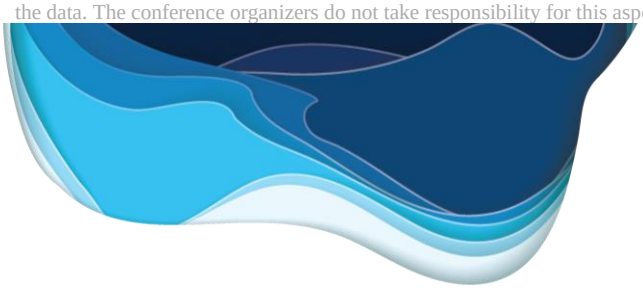

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"Navigating the complexity of metastatic squamous cell carcinoma: A multidisciplinary approach" – A Case Report

Mihaela Moraru[1], Iolanda Goga[1], Adriana Monica Nichita[1], Enache Cioc[1], Maria Andreea Ilie[1], Daniela Luminita Zob[1], Dana-Lucia Stanculeanu[1,2], Ginghina Octav[1,2], Natalia Motas[1,2], Adina Elena Ene[1], Stefania Ariana Neicu[1], Mara Mardare[1], Irina Bondoc[1], Dana Cernov[1], Adelina Silvana Gheorghe[1,2], and Elena Adriana Dumitrescu[1]

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Abstract: Cemiplimab, a promising immunotherapy targeting the PD-1 receptor, has emerged as a potential breakthrough in the treatment of this aggressive cancer. In this case, we report on a patient with squamous cell carcinoma that was localized to the presacral region and had suspicious metastases to the lung and pancreas. Initially, there was concern that the pancreatic lesion might be a second malignant neoplasm. However, histopathological examination revealed no malignant cells in the peripancreatic lymph node. Although histopathology revealed negative findings for malignancy in the lung nodules, the highly suspicious imaging features prompted the decision to intiate Cemiplimab therapy for advanced squamous cell carcinoma. After five months of treatment with Cemiplimab, there was a decrease in the suspicious lung lesions and favorable evolution of the presacral lesion.

In summary, this case report highlights the complex challenges of squamous cell carcinoma, including its metastatic potential and the complexity of diagnosis, and the subsequent response characterized by a reduction in suspicious lung lesions, stability of a previously troubling pancreatic lesion, and favorable evolution of the presacral lesion, underscores the therapeutic potential of Cemiplimab in the treatment of this aggressive cancer. This study also underscores the critical role of comprehensive clinical evaluation, including both histopathologic and radiologic assessments, in making treatment decisions.

Keywords: presacral squamous cell carcinoma, metastases, PD-1 inhibitor

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Male Breast Cancer with CHEK2 Mutation – A Case Report

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Abstract: Male breast cancer occur rarely, being responsible for less than 1% of all cancers in men. It usually affects older subjects, having a peak of incidence in the eighth decade of life. CHEK2 mutation is associated with an increased risk of cancer in general, but is particularly connected with an elevated risk of breast, colon, lung, prostate, kidney and thyroid cancer. We selected a case of a 45 years old, obese, diabetic man with gynecomastia, that presented with a 5,5/5 cm tumor mass in the central quadrant of the left breast, with skin involvement and nipple retraction. He also displayed left axillary lymphadenopathy on clinical examination. The CT scan revealed a 37/32 mm lesion and four affected lymph nodes, with no apparent distant metastasis. The core needle biopsy with histopathologic and immunohistochemical testing provided a well differentiated (G1) invasive ductal carcinoma diagnosis, with positive hormonal receptors and negative HER2. The patient underwent a chemotherapy scheme consisting of 4 cycles of Epirubicin and Cyclophosphamide every 3 weeks, followed by 8 cycles of weekly Paclitaxel and Carboplatin. Having been diagnosed with breast cancer at a much younger age than usual, he was also genetically tested and the CHEK2 mutation came out positive. The CT examination after neoadjuvant chemotherapy showed significant regression of the primary tumor mass and of the affected lymph nodes. The patient underwent left radical mastectomy with lymph node dissection. The histopathologic examination of the resected tissue revealed residual disease and six axillary lymph nodes involved. After surgery, the patient initiated hormone therapy (aromatase inhibitor and LHRH agonist) and commenced radiotherapy. He is due to begin treatment with CDK4/6 inhibitor Abemaciclib after completion of radiation therapy. The case highlights the need for better early detection of male breast cancer, as these malignancies are usually discovered in a more advanced phase than in women. Additionally, genetic testing is important to patients presenting with cancer at a younger age than expected, as it provides a means of assessing the risk of family members and of determining the possibility to acquire other forms of cancer.

Keywords: male breast cancer, CHEK2 mutation, CDK4/6 inhibitor, LHRH agonist

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Unusual evolution in low-grade uterine Leiomyosarcoma

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Abstract: 1,918,030. 1,918,030 is the estimated number of people around us that got diagnosed with cancer in 2022. 13,190, a number amounting to only 0.7% of all new cancer cases represents the estimated number of people who found out in 2022 they got a rare type of tumor from a varied group of cancers named Soft Tissue Cancer. We present the case of a 73-years old woman, one, of the 13,190 people who early in 2022 was confronted with uterine leiomyosarcoma (LMS) diagnosis. The CT scan revealed a large mass occupying the entire pelvic cavity. The elected treatment as in the majority of LMS was surgery, more precise total hysterectomy with bilateral ovaries and fallopian tubes removal along with upper colpectomy. The histopathological examination of the removed pieces indicated low-grade LMS, with the mitotic index below 10/10 HPF and necrosis sites. The examination was completed with an immunohistochemistry exam which showed Ki 67-5%. These findings combined with the patient's age suggest a slower growth rate and a less likely chance to spread to another part of the body, but after only a month and a half, the patient is admitted through the emergency department with suspicion of pelvic abscess. Upon laparotomic exploratory surgery is discovered a tumoral pelvic block consisting of the small intestine, rectosigmoid colon, anterior abdominal wall, and urinary bladder invasion. This case was brought to our attention due to its particular evolution in an elderly woman with a KI67-5%.

Keywords: Uterine cancer; Leiomyosarcoma; Surgery

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Honokiol – a novel anticancer agent in breast cancer?

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Abstract: Honokiol, large used in traditional Chinese medicine, is a polyphenolic compound extracted from the root of magnolia species. Numerous recent studies have concluded that honokiol presents an antitumor activity in various cancers such as: breast, liver, colon, gastric, ovarian, lung, skin, prostate, kidney, glioblastoma. The aim of this study is to review the therapeutic potency in breast cancer of drug delivery systems (nanoparticles, liposomes, micelles) encapsulating honokiol. It was performed a comprehensive electronic search using PubMed, MEDLINE, Web of Science, SCOPUS, Google Scholar, Cochrane library databases and were included *in vitro* and *in vivo* studies. The results of this research revealed that the developed drug delivery systems enhance the pharmacological effectiveness of honokiol in breast cancer based on the improvement of honokiol pharmacokinetic and pharmacodynamic properties. Honokiol presents a very complex biological and pharmacological profile with multiple pharmacodynamic effects (anti-inflammatory, antibacterial, antioxidative, anti-angiogenesis, hepatoprotective, cardioprotective, neuroprotective, antitumor), thus it is highlighted the high therapeutic potency of this natural compound. The available preclinical data promote the potential of honokiol to be a novel anticancer agent and the study of new honokiol formulation is further needed in order to develop new chemopreventive and chemotherapeutic strategies.

Keywords: honokiol; drug delivery systems; breast cancer;

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Early postoperative complications of total laryngectomy

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Abstract: Cancer of the larynx is the second most common malignancy of the upper aerodigestive tract. We present the case of a 68 years old man who iniatially sought medical attention at the emergency room in March 2023 due to acute respiratory failure. Laryngeal endoscopy showed an endolaryngeal tumor on the right side which caused paralysis of the right side hemi-larynx and approximately 90% narrowing of the respiratory passage. An emergency tracheostomy was performed under local anesthesia and a subsequent suspension micro-laryngoscopy was performed under general anesthesia for tumor biopsy. While waiting for the histopatological result, due to poor hygiene, the pacient presented again at the emergency room with acute respiratory failure due to blocked Tracheostomy Tube. Histopathological examination revealed invasive keratinizing squamous cell carcinoma of the larynx. Although a large variety of malignancies may occur in the larynx, 85% to 95% of laryngeal malignancies are squamous cell carcinoma (SCC), arising from the epithelial lining of the larynx. The tumor board reviewed the case and decided for surgical treatment. In August 2023 total laryngectomy with selective neck dissection was performed and three vacuum drains were placed in the anterior cervical area. Early postoperative complications are experienced by 34% of patients : the most common are pharyngocutaneous fistula, wound infection and postoperative hemorrhage. Other complications are hematoma/seroma, pharyngeal stenosis and stomal stenosis. Two days after drains removal the patient developed anterior cervical and peristomal hematoma for which exploration and drainage under sterile conditions were performed. No active bleeding was found and pressure dressings were used in order to avoid recurrence. After the hematoma was evacuated, the evolution was favorable, with no signs of hematoma recurrence until the patient was discharged, eleven days after surgery was performed. The postoperative evolution was favorable, with no signs of recurrent disease at 3 months. This case is noteworthy for its unusual timing of hematoma development, taking longer than usual for the hematoma to develop after the drains were removed. It shows that the successful management of laryngeal malignancy requires accurate diagnosis and the selection of the most appropriate treatment for the individual patient, with close post-treatment surveillance.

Keywords: acute respiratory failure, total laryngectomy, early postoperative complications, hematoma

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Analysis of cervico-vaginal microflora in women with cervical squamous carcinoma from the Republic of Moldova

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Abstract: Cervical squamous cell carcinoma (CSCC) is one of the most common types of cancer found in women in the Republic of Moldova. In 2020 there were 480 new cases and 238 deaths, this being mainly caused by infection with the Human Papilloma Virus (HPV). Cervico-vaginal flora plays a major role in the establishment and persistence of HPV. A cohort of 89 patients primarily diagnosed with CSCC was included in the study. Cervico-vaginal swabs were collected from all patients and 8 pathogens from pathogenic and conditionally pathogenic microflora were quantitatively determined: two bacterial species involved in bacterial vaginosis (*Gardnerella vaginalis* and *Atopobium vaginae*), three potentially pathogenic species associated with pelvic inflammatory disease (*Ureaplasma parvum*, *Ureaplasma urealyticum* and *Mycoplasma hominis*) and three bacterial genera associated with aerobic vaginitis (*Enterobacteriaceae*, *Staphylococcus spp*. and *Streptococcus spp*.). Analyzes were performed using the RT-PCR method. Microbial agents were analyzed in relation to the total amount of *Lactobacillus spp*. In 76/89 (85.39%) biological samples a low level of *Lactobacillus spp*. was identified and in 13/89 (14.60%) samples the level was within the normal limits. All samples with a normal level of lactobacilli also showed a normal level (or lack) of *Gardnerella vaginalis* and *Atopobium vaginae*, and only in 3/13 a pathological level of one (or two) genera of bacteria involved in vaginitis was identified. In other 1/13 samples has been determined an increased level of *Ureaplasma parvum*. In conclusion the vast majority of patients with CSCC present a low level of *Lactobacillus spp*. causing the imbalance of the cervico-vaginal microflora, either caused by the presence of cancer cells or this imbalance itself promoted the aggressiveness of other factors to transform normal cells into cancer cells.

Keywords: CSCC, cervico-vaginal microflora

Funding: The study was carried out within the State Program 2020-2023 with code 20.80009.8007.02 “Comparative study of the genomic, immunological and functional peculiarities of squamous cell carcinomas in five anatomical locations” (ANCD).

Conflict of interest: The authors declare no conflict of interest

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FANCM gene and possible implications in a familial case of breast and ovarian cancer

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Abstract: Breast cancer is one of the most frequent types of cancer. In 5-10% of cases a genetic predisposition may be identified, therefore genetic testing plays an important role in therapeutic approach and prophylaxis. We describe the case of o woman with breast cancer and familial history of breast and ovarian cancer, highlighting the particularities of the case and the difficulties faced sometimes with genetic results in the clinical management of these patients.

A woman aged 55 years old, diagnosed with breast cancer, was referred to genetic counseling. The patient has two sisters, diagnosed with breast cancer at 43 years old and respectively, ovarian cancer at 63 years old. The histology showed ER+, PR-, Her2- and Ki67 35%. According to NCCN guidelines, she was eligible for genetic testing. A panel of 52 cancer susceptibility genes were analyzed by next generation sequencing technology and both sequence variants and copy number variations (CNVs) were analyzed through dedicated software.

The analysis revealed the likely pathogenic (LP) heterozygous variant c.5101C>T in *FANCM* gene and two variants of uncertain significance (VUS), heterozygous variant c.1276+4A>G in *MSH2* gene and respectively, heterozygous variant c.1825C>T in *RNF43* gene. *FANCM* gene is involved in homologous recombination (HR) complex and it is associated with autosomal recessive Fanconi Anemia type A. Heterozygous pathogenic/likely pathogenic variants in *FANCM* gene are associated with an 1,86 increased risk for development of breast and ovarian cancer. The c.5101C>T variant is more prevalent in Finnish population, with a higher risk connotation in familial cases. It is mostly associated with ER- or TNBC. Patients carrying germline mutations in HR genes could benefit from platinum-based therapies or PARP inhibitors. Further testing of the sister with the ovarian cancer and her daughter revealed the presence of the above-mentioned variant of *FANCM* gene for both of them.

Genetic testing in this family with high risk for genetic hereditary form, revealed unexpectedly a LP variant in *FANCM* gene, which is considered low/medium risk factor for breast cancer. This gene is not currently included in the international guidelines and poses challenges regarding primary involvement in treatment and prognosis for proband, and prophylaxis options for the daughter of the proband. The collaboration of the oncologist, geneticist and surgeon is advised in order to achieve the most adequate management of the case.

Keywords: FANCM; breast cancer; hereditary;

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Detection of some TP53 and EGFR mutations in locally advanced lung cancer

Valentina Stratan[1], Veronica Balan[1,] *, Valeri Tutuianu[1,] Cristina Popa[1, 2], Victor Sitnic[1], Valeriu Bilba[1], and Sergiu Brenister[1]

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Abstract: Lung cancer (LC) is the second most common cancer worldwide. We examined lung squamous cell carcinoma (LSCC), lung adenocarcinoma (LUAD), pulmonary pleomorphic carcinoma (PPC), and lung neuroendocrine tumors (LNET). Prolonged alcohol consumption, smoking, and chronic inflammation are known to be potential factors in the development of LC. These factors may contribute to the accumulation of various gene mutations, further exacerbating the risk of LC or its prognostic. In this research, we observe the presence of distinct TP53 and EGFR mutations in LSCC compared to other types of LC. The study involved a cohort of 33 individuals primarily diagnosed with stage II and III LC investigated at the Institute of Oncology in the Republic of Moldova from 2020 to 2023. Among them, 16 were diagnosed with LSCC, 11 with LUAD, one with PPC, four with LNET, and one with mixed adeno-neuroendocrine carcinoma (MANEC). DNA extracted from fresh-frozen and formalin-fixed paraffin-embedded tumor tissue samples underwent the mutation analysis for TP53 (c.524G>A, c.818G>A, and c.817C>T) and EGFR (ex19Del, c.2573CT>AG, and c.2369C>T) genes by the castPCR method. Six individuals (18.18%, 6 out of 33) were identified as positive for at least one TP53 mutation, while only one (3.57%, one out of 28) sample tested positive for EGFR ex19Del mutation in MANEC. In particular, TP53 mutations within LSCC were identified as follows: two out of six - c.524G>A and c.818G>A, three out of six - c.818G>A, and one out of six - c.817C>T. We confirmed that all mutations were somatic by DNA testing of histologically normal tissue adjacent to the tumor or blood samples. The mutation frequencies in the TP53 and EGFR genes are 18.18% and 3.57%, indicating a higher incidence of mutations in the TP53 gene compared to the EGFR gene. Thus, LSCC exhibits a substantial occurrence (16 out of 33; 48.48%) and a high mutation accumulation rate (6 out of 7; 85.71 %).

Keywords: lung cancer, TP53, EGFR.

Funding: The study was carried out within the State Program 2020-2023 with code 20.80009.8007.02 “Comparative study of the genomic, immunological and functional peculiarities of squamous cell carcinomas in five anatomical locations” (ANCD).

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Conflict of interest: The authors declare no conflict of interest

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Occurrence rate of some TP53 gene mutations in HPV+ and HPV- head and neck squamous cell carcinoma

Valeri Tutuianu[1,*], Valentina Stratan[1], Cristina Popa[1], Victor Sitnic[1], Anastasia Monastirchii[1], Diana Cebotari[1], Corneliu Cojocaru[1]

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Abstract: Head and neck squamous cell carcinoma (HNSCC) is largely caused by alcohol and tobacco use, and human papillomavirus (HPV) infection may also be a risk factor for oropharyngeal cancer. These factors have different effects on the degree of accumulation of mutations in oncogenes and tumor suppressor genes, especially regarding the accumulation of genetic variation in the TP53 gene. The cumulative effect of these factors can increase the aggressiveness of the cancer and predict a different prognosis. Here we aimed to study the correlation between some mutations in the TP53 gene and HPV infection in people with primary diagnosis of HNSCC. A cohort of 117 subjects with HNSCC was included in the study of which 2 (2/117, 1.71%) with Hypopharynx Squamous Cell Carcinoma (HPHSC), 18 (18/117, 15.38%) with Larynx Squamous Cell Carcinoma (LXSC), 31 (31/117, 26.50%) with Oropharynx Squamous Cell Carcinoma (OPHSC) and 66 (66/117, 56.41%) with Oral Cavity Squamous Cell Carcinoma (OCSC). The TP53 gene isolated from fresh tumor tissue was tested for c.524G>A, c.818G>A and c.817C>T mutations by the castPCR method while the identification and differentiation of HPV for 12 high-risk genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59) was performed using saliva samples and the RT-PCR method. Of 117 cases tested for mutations in the TP53 gene, 32 were positive for at least one mutation (23 with a single mutation and 9 with a double mutation). The results also showed 16 (16/117, 13.68%) HPV+ cases and 101 (101/117, 86.32%) HPV- cases, of which 13 (13/16, 81.25%) HPV+ cases did not present any mutation in TP53 gene and 3 (3/16, 18.75%) HPV+ cases showed a single mutation in the TP53 gene. Double mutations were found in 3 (3/18, 16.67%) patients with LXSC and in 6 (6/66, 9.09%) patients with OCSC. All 9 cases with a double mutation in the TP53 gene were negative for tested HPV genotypes. The obtained data show that in HNSCC HPV+ cases the occurrence rate of the three *TP53* mutations tested is lower compared to HPV- cases (18.75% vs 28.71%) and the double mutations occurred only in HNSCC HPV- cases. This denotes that carcinomas induced by other etiological factors than HPV tend to have a higher rate of mutations in the TP53 tumor suppressor gene.

Keywords: HNSCC, HPV, correlation, mutation rate

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