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МАКЕДОНСКА АСОЦИЈАЦИЈА НА ГИНЕКОЛОЗИ И ОПСТЕТРИЧАРИ
MACEDONIAN ASSOCIATION OF GYNECOLOGISTS AND OBSTETRICIANS

cost EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY

Preface

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The Liquid Biopsy in Rare Gynaecological Cancers

Dr Sharon O'Toole
Trinity St James's Cancer Institute, Dublin
email: shotoole@tcd.ie

Abstract

Tissue biopsies are the gold standard for diagnosis, but the non-invasion "liquid biopsy" has been interrogated into standard of care practice for different cancers. Circulating tumour cells [CTCs] are a major component of the liquid biopsy and have significant potential as clinical biomarkers in the management, stratification, and treatment response in cancers. CTCs are essentially living tumour cells within the circulation of patients and give us a real time snapshot of how tumour cells are behaving. However, their full utility has yet to be realised in ovarian cancer due to limitations with detection and characterisation. CTCs in the circulation have been shown to exist both as individual cells and as clusters of cells that display homotypical and heterotypical phenotypes, depending on their interactions with surrounding cells. Presence of CTC clusters indicates a poor prognosis, but their utility has not been assessed in ovarian cancer or in rare gynaecological cancers. CTC clusters are the polyclonal precursor cells in metastasis and the dissection into their molecular profiles by next generation sequencing may indicate mechanisms of how an individual tumourcolonises distant sites successfully and provide insight to further patient-specific therapies. For CTCs to be fully utilised in the clinic, robust digital pathology analysis of CTCs is warranted. Through the expansion of additional CTC identification markers, machine learning and artificial intelligence may overcome these limitations around automation and reporting and result in routine CTC use in a clinical setting.

From Knowledge to Clinical Practice

Professor Riccardo A. Audisio, MD, PhD(Hon), FRCS, FEBS
EJSO – Editor in Chief
Department of Surgery
Institute of Clinical Sciences
Sahlgrenska University Hospital
Göteborg, Sweden
email: raudisio@doctors.org.uk

Abstract

The primary endpoint of Health Care is to offer all oncological patients the most appropriate cancer treatment: patient-centred care should be our mantra. Surprisingly, cancer treatment is driven by performance figures which are most frequently meaningless to our patients (time to recurrence, time to progression, etc.). Some efforts have been noticed, where clinicians and managers sat down together with patients and patient advocates, to identify their priorities, such as the health status achieved, survival, symptoms and disease control, process of recovery and health sustainability (1).

Is it possible to fairly assess the quality of medical/surgical treatments? how can we state that one treatment is effective rather than not? Clinical trials (RCTs) have been advocated in the 80's to set the standards of care; this methodology is scarcely implemented in surgical practice (2), for a number of practical reasons.

The RTC methodology is presently under scrutiny (3,4) and a sponsorship bias has been noticed as well (5). With Big-Pharma constantly keeping health care providers under pressure, exploiting the market with drugs and tools of unproven value, the role of Phase IV trials is paved and and accurate capturing of digital figures is the key. The progress of Artificial Intelligenceallowsprospective and consecutive collection of good-quality data; the value of real-time studies will soon become crucially important in guiding treatment plans.

It is suggested to consider compiling a monographic issue where epidemiological figures are merged with clinical practice, guidelines and diagnostic algorithms, in order to deliver a valid toolto expand knowledge and improve patients' care.

Pharmacological Therapies Investigated In Clinical Trials For Rare Gynaecological Cancers

Prof. Assoc. Klejda Harasani
Department of Pharmacy, Faculty of Medicine, University of Medicine Tirana
email: klejda.harasani@umed.edu.al

Abstract

The basic treatment for almost all rare gynecological cancers is surgery, however therapies including medication are also part of the standard of care, such as hormonal therapy, chemotherapy, immunotherapy and targeted therapies. The vast variability in rare gynecological cancers´ types poses a challenge to fully comprehend the trends on therapies investigated as part of clinical trials for these malignancies. Therefore, it is of utmost importance to synthesize the evidence from clinical trials and explore the type of entailed therapies.

Methods: We followed the PRISMA 2020 guidelines for systematic reviews and meta-analysis and searched two different databases: the WHO´s ICTRP (International Clinical Trials Registry Platform) and the clinicaltrials.gov databases. Articles published in Pubmed/MEDLINE reporting on results of the included clinical trials on rare gynecological cancers were also consulted. Two researchers independently screened during July 2022 for clinical trials that reported on pharmacological therapies for at least one rare gynecological cancer. The complete record of each clinical trial was reviewed and related data were extracted. We classified the treatments in the clinical trials according to the type of therapy: chemotherapy, hormonal therapy, targeted therapy, and mixed (more than one type of therapy). Drugs of targeted therapies were listed, classifying them into: 1) Overgrowth related (apoptosis induction and proliferative signaling), 2) Angiogenesis related, and 3) Immunotherapy.

A total of 213 records were included in the final review.The number of clinical trials investigating therapies for rare gynecological cancers (RGC) has steadily increased over the years, reaching 80 clinical trials initiated in the period from 2017 to 2022. Just 42,72 % of the clinical trials were specific only for rare types of gynecological cancers.Moreover, the most evident finding is the increment in trials involving targeted therapies.The most frequent type of therapy investigated in clinical trials for rare gynecological cancers was chemotherapy (89; 41,78 %), followed by targeted therapy (65; 30,52 %), and mixed therapies (49; 23,00 %), generally a combination of chemotherapy and targeted therapy. Hormonal therapy was rarely investigated (6; 2,82 %), similarly to other therapies (4; 1,88 %), namely, propranolol, radiation modifier triapine and VCN-01 virus.

There was a steady increase over the years in the overall number of clinical trials investigating pharmacological therapies for rare gynecologic cancers, particularly of those including targeted therapies such as immunotherapy (immune checkpoint inhibitors, tumour vaccines, CAR-T cells), overgrowth related and angiogenesis related targeted therapies. However, “smarter” and higher quality clinical trials are needed for these types of cancers.

Fine Needle Aspiration Cytology of the Breast and Cell Blocks: The Experience in North Macedonia

Dr. Ljube Ivkovski
Diagnostic Laboratory for Histopatology and Clinical Cytology,
Skopje, North Macedonia
email: ljubeivkovski@gmail.com

Abstract

Breast cancer is the most common cancer worldwide. Fine-needle aspiration cytology (FNAC) is an outpatient simple procedure, which gives a quick cytological diagnosis for breast lesions. Cell blocks prepared from the aspirated material of these breast lumps not only serve as useful adjunct to FNAC, but also give tissue diagnosis comparable to breast biopsies. This presentation was undertaken to present our experience with FNAC of the breast lesions and the utility of cell block technique in diagnosing various breast lesions in correlation with FNAC findings. Subsequent histopathology diagnosis was obtained and compared with cytological diagnosis wherever possible. Most of the cases were benign lesions, with fibroadenoma being the most common. Among malignant tumors, invasive mammary carcinoma of no special type was the most common type. Cell blocks were more accurate compared to FNAC in diagnosing both benign and malignant lesions. Diagnostic difficulty was encountered in certain tumors having either bland cytology or a predominant discrete pattern or a combination of extracellular mucin and papillary pattern. These lesion should be reanalyzed in correlation with histopathology, clinical findings, radiology and immunohistochemistry. FNAC serves as a rapid, economical, and reliable tool for the diagnosis of palpable breast lesions because the cytopathological examination of these lesions before operation or treatment serves as an important diagnostic modality.Cell block method is superior to FNAC in the diagnosis of both benign and malignant tumors of the breast and helps to eliminate the need for invasive breast biopsies. The use of ICH on cell blocks can help to moderate therapies with the analysis of estrogen and progesterone receptors and Her-2/neu in patients with inoperable or metastatic breast cancer.In our laboratory ICH on cell blocks has been used in over 3 000 cases as an adjunct to cytology for the last 15 years. This review will to a large extent be based on our experience.

Neuroendocrine Tumors – Rare Tumors and Rare Localisations

Dr.Celebic A[1], Dr.Miladinovic M[2], Dr. Corovic M[1].
[1] Institute of Oncology, Clinical Center of Montenegro, Podgorica, Montenegro
[2] Center for Pathology, Clinical Center of Montenegro, Podgorica, Montenegro
Email: celebic2002@yahoo.com

Abstract

Neuroendocrine tumours (NETs) are a group of heterogeneous tumours arising from neuroendocrine cells. NETs are not so common solid tumours and the incidence is estimated <5/100.000 patients. The most frequent localisations are in respiratory tract, rectum, small bowel, stomach, and pancreas, but they can also appear in thyroid, skin, urogenital system, CNS, colon, cecum, or appendix. According to literature, only up to 15% of all NETs are found in sites other than gastrointestinal tract and lungs. Among the lowest incidences are those NETs found in gynecological organs and breast.

Gynecological tract NETs are rare, biologically aggressive tumours from endocrine cells arising from the neuroectoderm, neural crest, and endoderm. Their features are high recurrence rates and poor prognosis, and therefore the treatment approach remain challenging. The primary gynecologic NETs comprise only 2% of all gynecologic malignancies, and the cervix is the most frequent site of NETs in the gynecologic tract. The ovary is the most common site for low-grade NETs and the cervix is the most common site for aggressive, poorly differentiated NETs.The updated WHO classification of gynecologic NETs is based on the Ki-67 index, mitotic activity index, and tumour features such as necrosis, and brings more uniformity in the terminology of NETs. The revised International Federation of Gynecology and Obstetrics (FIGO) Staging System remains the most accepted staging system for gynecologic NETs. Imaging plays a crucial role in the workup, staging, restaging, and follow-up of NETs, particularly by functional imaging modalities using traditional and new tracers, including 68Ga-DOTA-Somatostatin Analog-PET/CT. Management of NETs involves a multidisciplinary approach. There are no a wide consensus guidelines for either the diagnosis or management of these cases. New targeted therapies could improve the outcome for these rare malignancies, therefore a designing, organising and conducting of randomized clinical trials is mandatory for collecting solid evidence in order to make the palette of available drugs wider.

NETs of the breast includes a heterogeneous group of rare tumours, which account for <5% of all invasive breast carcinomas. Their low incidence is a main cause of a restrictive knowledge of these tumours, and are linked with case reports or small retrospective series. The diagnosis of breast NETs is based on the presence of pato-morphological features similar to gastrointestinal and respiratory NETs and neuroendocrine markers. Most recent studies suggested that breast NETs are associated with worse prognosis compared to invasive breast cancer without neuroendocrine differentiation. Thanking to its low incidence and deficiency of randomized data, there is little evidence to guide the choice of treatment, therefore breast NETs are currently treated as any invasive breast carcinoma not-otherwise specified. Most recently, attempts to molecularly define breast NETs are done, in order to provide new drivers for a more personalized treatment of this low-incidence entity.

The presentation is aimed to focus on a landscape of updated information on NETs in gynecological tract (cervix, ovary, endometrium, vagina, vulva) and the breast, including but not limited to a staging classifications, clinico-pathological characteristics, imaging, and management of these tumours.

Multimodality Treatment in Ovarian Cancer. Present and Future

Paul Kubelac, Catalin Vlad, Patriciu Achimas
The Oncology Institute "Prof. Dr. Ion Chiricuta" Cluj-Napoca, Romania
email: kubelac.paul@umfcluj.ro

Abstract

Ovarian canceris the leading cause of gynecologic cancer death. In the normal-risk population, ovarian cancer will develop in approximately 1 person in 70, at a mean age at diagnosis of 63 years.Carriers of deleterious mutations in BRCA1 or BRCA2 have a lifetime risk of up to 60%, however there are no data to support the routine use of ovarian cancer screening in the general population. Prognosis is linked to the amount of residual tumor after optimal surgical cytoreduction, with a contemporary definition of no gross residual disease. People whose disease burden and medical status is favorable should be offered primary debulking surgery while others should be offered neoadjuvant chemotherapy. In the setting of advanced disease for those who do not have a germline finding, somatic testing for BRCA andhomologous recombination deficiency (HRD) is recommended.For people with stage II or above ovarian cancer who undergo primary surgical cytoreduction, randomized phase III trials established combination platinum and taxane chemotherapy as the standard of care. With regard to maintenance therapy after initial chemotherapy, the optimal choice of treatment in all patients is not clear. Although bevacizumab is approved, PARP inhibitors are another option for maintenance treatment of advanced ovarian cancer, with the magnitude of benefit depending on BRCA or HRD status. Knowledge of germline or somatic BRCA mutations or HRD status is also relevant for optimizing treatment in the setting of recurrent disease.

Fertility Spearing Approach In “Bulky” Cervical Cancer in Young Patients- A Place Of Neoadjuvant Chemotherapy

Aljoša Mandić, MD,PhD
University of Novi Sad, Medical faculty, Oncology Institute of Vojvodina, Serbia
email: aljosa_mandic@yahoo.com

Abstract

Good oncologic and reproductive outcomes have been published in the last three decades with fertility sparring treatment in the early cervical cancer setting. Various surgical approaches have been described, ranging from vaginal and open to minimally invasive. Adequate oncologic and obstetric outcomes have been reported with all approaches. For low risk, early lesions even more conservative treatments plans can show promising results. There is still a subset of patients with a cervical cancer larger than 2 cm that have a strong desire to preserve fertility. A key goal for gynecologic oncologists is to trial fertility sparring approaches for these patients to drive a better balance of oncologic and obstetric outcomes. While NACT followed by surgical treatment is performed in some centers, we must note that there is no standard in terms of chemotherapy protocols and surgical approaches are even more variable.

An acceptable approach with NACT and fertility sparring surgery in the setting of bulky cervical cancer was identified by these three small studies. An oncologically safe approach was presented by Lanowska M et al. for patients at high risk of lymph node metastasis. They used SLN detection or complete pelvic lymphadenectomy to identify candidates for NACT and fertility sparring surgery. Developing a sentinel node detection procedure, this approach will become more acceptable. As mentioned, a further aspect that is not standardized is chemotherapy. Most protocols are double or triple combinations that are based on platinum agents. The paclitaxel/cisplatin is reported to be the most promising regiment and should be the basis for future studies. According to some authors a dose dense NACT interval has shown a better therapeutic response with no added toxicity. One further important aspect that requires consideration is ovarian function after chemotherapy. Is an examination of ovarian reserve before treatment necessary or is a normal pregnancy outcome expected? An expected normal outcome seems more likely, but further research is warranted.

In Buda A et al, systemic review, were identified 20 articles and 114 women with IB2 disease, possible candidates for NACT prior to FS surgery. Uterine conservation was achieved in 76.7% of them. Patients reached optimal pathological response to NACT in 60.9% of cases and a TIP (cisplatin, ifosfamide and paclitaxel) regime was related to the best response. Suboptimal response to NACT appeared to be an independent negative prognostic factor. Up to 9.2% of patients recurred with a median 7.4-months DFS, and 4.6% of patients died of disease. Fifty percent of women tried to conceive after treatment and NACT prior to conization appeared to be the most promising alternative to upfront radical trachelectomy in terms of obstetric outcomes. Authors concluded that NACT prior to FS surgery is an option, but the literature about this issue is still weak and FS should be carefully discussed with patients. Still some ongoing studies probably will give as some highlights in this field such as “Stage IB1 (2-4 cm) Cervical cancer treated with Neoadjuvant chemotherapy followed by fertility Sparing Surgery (CoNteSSa) study” by M. Plante.

Biobanking - The Experience in Serbia

Danica Ćujić,
University of Belgrade, Institute for the application of Nuclead Energy INEP, Belgrade, Serbia
email: danicac@inep.co.rs

Abstract

Biobanks, as collection of human biological samples, are important and valuable resource for biomedical research. Biological samples collected from donors, with accompanying demographic, clinical and pathological data enhance development and improvement of prevention, diagnostic and treatment protocols for various diseases. Biobanks are particularly important in the case of rare diseases, where the number of clinical cases is limited and results of research are not reliable enough.

In process of biomarker discovery, it is critical to perform clinical validation of potential biomarker on large representative number of high quality and well characterized patient and healthy control samples. In such cases, biobanks, as source of large collection of well characterized samples, with patient clinical, pathologic and outcome data, could impede validation process.

Shortly after COVID-19 outbreak, Institute for the Application of Nuclear Energy INEP initiated project for development of serological test for determination of antibodies against newly emerged.At the same time, sera samples from COVID patients were collected,as an important resource for ELISA test development and study of immune response in COVID-19. From May 2020 until now, more than 70 000 sera samples are collected and successively stored at INEP. Besides samples collected through INEP Laboratory, COVID -19 sample collection includes samples from several seroprevalence studies (in general population and healthcare workers), samples collected during vaccination campaign and samples taken from patients with disease that might induce immune response impairment (inflammatory bowel disease, multiple sclerosis, end stage renal disease).

As present capacity for storage was limited and not appropriate for a biobank, INEP tried to upgradethe storage capacities for the serum bank at the institute. The project of establishment of National COVID - 19 Serum Bank, that will enhance pandemic research and management, was supported by the USAID. Besides providing financial resources for biobank establishment, legal and ethical issues are also taken into account. The objective of the specimen bank is to create a national reference collection of COVID-19 positive sera samples, from individuals infected with or vaccinated against SARS-CoV-2, in order to: enhance development of novel (advanced) variants of ultrasensitive immunodiagnostic assays, reduce the need for field trials, facilitate quality control, assess analytical and clinical performances of the existing diagnostic immunoassays and establish well characterized reference materials for production of quantitative immunodiagnostic tests for COVID19 identification. Well organized serum sample biobank will also provide a service platform for COVID-19 research in the future.

Confusing Symptoms And Laboratory Tests Leading To The Diagnosis Of Mixed Germ Cell Tumor Of The Ovaries- Case Repor

Prof. Dr. Goran Dimitrov MD., PhD
University Clinic for Gynecology and Obstetrics, Medical Faculty, University Sts. Cyril and Methodius, Skopje, North Macedonia
email: gorandimi@gmail.com

Abstract

This is a case report of a 30-year-old nulligravida, finally diagnosed with a mixed germ cell ovarian tumor. In May 2019, she was admitted to the hospital with small ovarian masses, slightly elevated beta HCG, and treated conservatively for a suspected ectopic pregnancy, (with parenteral Methotrexate). After three weeks the levels of beta HCG were normalized. In November 2020, the patient was referred to the Urgent Surgical Department following an acute abdomen. They referred her to the Univ. Clinic for Gyn./Obs. with a big abdominal tumor and a possibility of its rupture (with small contents of liquid) in the pouch of Douglas. After admission, laboratory analysis showed slightly elevated beta HCG, slightly elevated Ca-125, and a ROMA index of 8% (low risk). The biochemical analysis showed very high LDH, leukocytosis, thrombocytosis, and elevated CRP. In order to preserve fertility a left adnexectomy with the tumor substrate and biopsy of the right ovary for frozen section was performed, and mixed germ tumor was diagnosed. Following the diagnosis from the frozen section, the operation was continued with total abdominal hysterectomy, right adnexectomy, and staging. The final diagnosis was mixed germ cell tumor (predominantly yolk sac, and less dysgerminoma) UICC-8/FIGO classification pT2B, pNx, pMx, L1, V1, Stage IIB. After the operation, the biochemical laboratory analyses were normalized within 15 days, and the patient was slightly better. After 15 days the patient experienced abdominal pain and pain in the spine. She was sent to the Oncology Department for further chemotherapy. In January 2021 retroperitoneal metastases in the region of the left kidney, retrovesical residual tumor, and metastases of the retroperitoneal, paraaortal left parailical lymph nodes, were found. She was started onCisplatin, Etoposide, and Bleomycin. In March 2021 the patient's condition worsened, after which she sought surgical treatmentin a foreign hospital. The patient died in April 2021.

AI Digital Pathology for Cancer Screening

Prof John O'Leary
Professor of Pathology
Trinity College Dublin, Ireland
Director of Pathology, The Coombe Women and Infants University Hospital, Dublin, Ireland, Dublin
email: OLEARYJJ@tcd.ie

Abstract

Technological advances in automation have improved approaches to cervical cancer screening and the increased focus on precision medicine has paved the way for the development of digital pathology-based approaches for whole slide imaging and artificial intelligence (AI)–based solutions, for cervical cancer screening. This revolution in cancer screening has the potential to greatly improve the sensitivity of cytology as a triage test, in the context of HPV based primary screening. The Genius Digital Diagnostics platform from Hologic is the first CE-marked digital cytology platform to combine a new artificial intelligence (AI) algorithm with advanced volumetric imaging technology to help cytotechnologists and pathologists identify pre-cancerous lesions and cancer cells in women.

This talk will give an overview of the revolutionary developmentsin cervical cancer screening, the challenges with digital cytology imaging and our first hand experience using digital cytology for cervical cancer screening.

Biomarkers and Immunotherapy in Gynecological Cancers

Tamara Jokic Visekruna
Oncology Clinic, University Clinical Centre of Republic of Srpska
email: tamara.visekruna@kc-bl.com

Abstract

Immunotherapy, with emphasis on immune checkpoint inhibitors (ICIs), has shown great success in treatment of a wide range of solid tumors.The main targets of these drugs are programmed cell death1 (PD-1), its ligand programmed death ligand 1 (PD-L1) and cytotoxic T cell lymphocyteassociated antigen4 (CTLA-4)that enable human immune system to fight cancer. This type of treatment has revolutionized clinical practice in oncology. However, its benefits remain to be seen in gynecological cancers. Although some studies have shown remarkable results, ICIs are still not a standard of care for gynecological malignancies in many countries.

Certain subtypes of endometrial cancer have shown most immunogenic potential and therefor best response to ICIs. In ovarian and cervical cancer, ICIs have had best results in combination with other agents. Despite undeniable potential of immunotherapy, not all patients have a good response to therapy. As we can expect an increase of application of ICIs, development of biomarkers as response prediction tools is necessary. Those biomarkers should later be translated into everyday clinical practice. Understanding mechanisms behind resistance to immunotherapy and combing novel therapeutics with standard treatment is crucial in improving patient outcomes.

Multi-Omics Exploration of Gynecological Cancers

Yashwanth Subbannayya
Centre of Molecular Inflammation Research (CEMIR), Department of Clinical and Molecular Medicine (IKOM), Norwegian University of Science and Technology, 7491 Trondheim, Norway
email: yashwanth.subbannayya@ntnu.no

Abstract

Gynecological cancers, which include cancers of the female reproductive tract, account for about 10% of all cancers diagnosed in women. Delineating the molecular mechanisms of these cancers can help decrease mortality and increase survival. Multi-omics approaches can provide detailed molecular landscapes of the underlying mechanisms of gynecological cancers. Multi-omics strategies can help identify biomarkers for diagnosis, screening, and prognosis and help identify potential therapeutic targets. In the current study, we talk about two examples of multi-omics exploration of gynecological cancers- one on rare ovarian cancer subtypes and the other on the application of multi-omics data to estimate cancer risk from spaceflight. Using data mining approaches, we used expression data from previously published studies to determine aberrant pathways and signaling networks in these datasets.

The Use Of The New Molecular Techniques And Their Implication On The Diagnosis, Prognosis, And Therapeutic Decisions In Gynecological Cancer.

Prof. D-r Aleksandar Petlichkovski
Institute for Immunobiology and Human Genetics, Medical Faculty in Skopje
email: aleksandar.petlichkovski@medf.ukim.edu.mk

Abstract

Major advancements in the field of molecular diagnostics and cancer therapy, combined in personalized treatment strategies, have ledto a decline in the overall rate of cancer mortality around the developed world in the last decade. In the center of these improvements in the use of molecular-guided drug regimens and success of progression-free survival is a molecular technique called next generation sequencing (NGS). The term NGS is used to describe a massive parallel sequencing technology that combine bioinformatics analysis and comparison of millions of small sequenced DNA fragments to the human reference genome. The key to advancements in the widespread clinical application of personalized cancer therapy is the faster, cheaper, and simpler sequencing of tumoral DNA.

Gene panel tests based on NGS have been developed to allow individualization to a specific malignancy They offer a number of benefits over more traditional single gene tests. Clinicians can use these tests to identify alterations in genes that are targetable at a molecular level by a range of drugs. NGS panels also help delineationof subset of patients with gene alterations associated with drug resistance within a single test. This would provide actionable information to clinicians for treatment strategy decision making. Moreover, NGS technology is particularly valuable in the identification and investigation of clinically heterogeneous inherited disorders.In gynecologicaltumors, the role of specific mutations is not as thoroughly investigated as in other tumors, despite the widespread incidence.

A number of obstacles may complicate the universal use of NGS in routine cancer care. Clinicians report a lack of clarity on evidence-based clinical guidelines. Another difficulty arises from the fact that NGS testing presents a large volume of genetic data that can be difficult to interpret. Finally, NGS testing is still expensive, and before any cancer treatment is adopted in the clinic, an economic evaluation of its costs versus benefits must be made. The cost-effectiveness of NGS testing may depend on the type of technology adopted, and clinicians often lack clear data on the clinical benefits of the new commercial and non-commercial genomic tests available.

Genetics of Breast and Gynecologic Cancers

Research Centre for Genetic Engineering and Biotechnology "Georgi D. Efremov", Macedonian Academy of Sciences and Arts, Skopje, RN Macedonia
email: dijana@manu.edu.mk

Abstract

Breast cancer is the most common cancer and the leading cause of cancer deaths among women in the world. Endometrial cancer is the most common and ovarian is the most deadly type of the gynaecologic cancers. Genetic predisposition plays an important role in all three cancers (breast, ovarian and endometrial) and has been attributed to a number of high, moderate and low-penetrance susceptibility genes.

Breast and ovarian cancer are most strongly associated with the highly penetrant BRCA1 and BRCA2 genes. Other genes, such as PALB2, TP53 (associated with Li-Fraumeni syndrome), PTEN (Cowden syndrome), CDH1 (difuse gastric and lobular breast cancer syndrome), and STK11 (Peutz-Jeghers syndrome), confer a risk to either or both of these cancers with relatively high penetrance. Lynch syndrome, an autosomal-dominant inherited cancer susceptibility syndrome, caused by a germline mutation in one of the DNA mismatch repair genes MLH1, MSH2, MSH6, PMS2, and EPCAM is the most common cause of hereditary endometrial cancer. Additional genes, such as ATM, CHEK2, BRIP1, and RAD51, are associated with breast and/or gynecologic cancers with moderate penetrance.

The presentation will summarize the current knowledge on high and moderate-penetrance genes associated with breast, ovarian and endometrial cancers, as well as the latest guidelines for the genetic testing in patients with these cancers. The pathogenic variants detected using a panel of 94 cancer genes among more the 600 cancer patients from Macedonia, the majority with breast cancer and a small number with gynecologic cancer, will also be presented.

How To Study The Role Of Non-Coding Rnas In The Pathology Of Rare Gynecological Cancers In Vitro

Asst. Prof. Dr. Petar Ozretić
Laboratory for Hereditary Cancer, Division of Molecular Medicine,
RuđerBošković Institute, Zagreb, Croatia
Email: pozretic@irb.hr

Abstract

Less than 2% of the human genome containsproteincoding genes, while the remaining, so called "junk DNA" or genomic "dark matter", encodes for non-coding RNA (ncRNA) transcripts whose role in health and disease is being extensively studied. Two of the most studied ncRNAs are microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) which regulate expression of protein codingmessenger RNAs (mRNAs)at transcriptional and post-transcriptional levels. Members of the GYNOCARE COST Action have published several papers addressing the known and potential rolesof miRNAs and lncRNAs in diagnosis, prognosis, and treatment of rare gynecological cancers. In this lecture I will give a brief overviewhow to study the role of non-coding RNAs in the pathology of rare gynecological cancers in vitro.Special emphasis will be put on steps like why it is important to precisely describe used clinical tumor samples, how to properly choosein vitro models (cancer cell lines) and healthy controls, which are molecular methods used for ncRNAs' expression profiling and validation, functional rescue assays, mRNA:ncRNA interaction studies, as well as which are useful internet databases and tools.

A Case of Autoimmune NMDA Encephalitis In A Woman With A Tubal Teratoma

Cristina Clare Gallego de Largy
Marques de Valdecilla University Hospital, Santander. Spain
email: cristinaclare.gdl@hotmail.com

Abstract

Encephalitis associated with antibodies against the anti-NMDAR (N-Methyl-D Aspartate) receptor is a neurological disease with an estimated prevalence of 2-3 cases per million inhabitants. In most cases, there is an underlying tumor, the most common being ovarian teratoma, present in 50% of cases in young women. However, tubal teratomas are rare tumors. A clinical case reported at the Marqués de Valdecilla University Hospital in Santander in 2022 of autoimmune NMDA encephalitis with a tubal teratoma is described. This is a 32-year-old woman with a large 12-cm multiseptated right adnexal cyst who was admitted in September 2021 due to pain suspecting ovarian torsion that was confirmed in the urgent surgery performed. Subsequently, she was admitted six months later due to seizures, and neurological symptoms and autoimmune NMDA encephalitis was suspected.

After 2 months in the ICU, a pelvic ultrasound was decided upon, where an image compatible with a teratoma was observed in the contralateral adnexa, and surgical intervention was decided.

Pathology shows a mature tubal teratoma.

Incidental Gonadal Germ Cell Tumors Diagnosed In Prophylactic Gonadectomy Material In Patients With Swyer Syndrome

Neli Basheska
Department of Histopathology and Clinical Cytology,
University Clinic of Radiotherapy and Oncology,
Faculty of Medicine, University Ss. Cyril and Methodius,
Skopje, Republic of N. Macedonia
email: nbaseska@gmail.com

Abstract

Background & Objective: Swyer syndrome (46,XY pure gonadal dysgenesis) is an uncommonly encountered condition characterized by bilateral streak gonads, normally developed Mullerian structures, female-appearing external genitalia, and hypergonadotropic hypogonadism in which gonadectomy is recommended upon diagnosis due to a significant risk of malignant transformation of the dysgenetic gonads. The most common neoplasm is gonadoblastoma, while in 22 to 66% of cases with gonadoblastoma an invasive germinoma (dysgerminoma/seminoma) is present, and less frequently other malignant germ cell neoplasms such as yolk sac tumour, immature teratoma, embryonal carcinoma, or choriocarcinoma. The aim of this study was to present our experience with incidentally found germ cell tumours in 3 patients with Swyer syndrome.

Method: We report the clinico-pathological characteristics of 3 cases of female phenotypic patients presenting with primary amenorrhea. Two of the patients underwent prophylactic bilateral laparoscopic gonadectomy with salpingectomy following a diagnosis of Swyer syndrome, while bilateral LPSC gonadal biopsy, followed by bilateral gonadectomy with salpingectomy, pelvic lymphadenectomy and peritoneal and omentum majus biopsy was performed in the third case. At the time of diagnosis, the patients were 17, 20 and 19-year old, respectively. The presenting features were hypergonadotropic hypogonadism and 46, XY karyotype. A hypoplastic uterus with normal-looking fallopian tubes and bilateral gonads was detected by ultrasonography and confirmed during laparoscopy. The patients with dysgerminoma underwent postoperative chemotherapy. All three patients are alive and well at 197, 168, and 123 months following surgery.

Results: The histopathological examination of the streak gonads which were completely sampled and embedded revealed the presence of bilateral focally “burnt out” gonadoblastoma in all three patients. In addition, in two patients, a coexisting dysgerminoma of 1.5 and 3.8 cm in diameter FIGO stage IC1 in the right gonad was confirmed. The sequencing of the SRY gene of the patient with bilateral gonadoblastoma without dysgerminoma overgrowth revealed a C/G substitution at the first nucleotide of codon 133, leading to Arg/Gly replacement in the SRY protein.

Conclusion: Our data suggest that patients with gonadal dysgenesis and 46, XY karyotype should be referred for bilateral gonadectomy and their operative specimens should undergo meticulous histopathological examination because of the high risk of neoplastic transformation.

“Rare Gynecological Malignancies - A Health Problem Due To Limited Oncological Therapeutic Options”

Ass.Prof. Violeta Klisarovska
University Clinic of Radiotherapy and Oncology, Skopje
email: violeta.klisarovska@medf.ukim.edu.mk

Abstract

Up to 50% of gynecological cancers can be considered rare according to the Surveillance of Rare Cancers in Europe (RARECARE) consortium definition of an incidence of less than 6 cases per 100 000 people. A quarter of all cancer deaths each year are due to rare cancers. People with rare cancers are more likely to die from their disease than people with more common cancers. These cancers usually have a poor prognosis as they are often delayed in their diagnosis and treatment due to the lack of knowledge. They are most often diagnosed in the advanced incurable stage of the disease. Although new treatments are always being developed, finding new treatments for rare cancers is very hard for many reasons. It is difficult to draw clear conclusions from research studies and clinical trials with a small non-representative population meeting the criteria for participation in clinical trials.

Given their rarity, biological and clinical data are lacking for many gynecological cancers. Current efforts are on-going to improve care of these patients, including the development of international consortia, prospective databases with biobanking, acceptance of novel clinical trial design, education of the medical field as well as improvement of patient awareness.

Rare gynecological malignancies are themselves highly specific in their clinical behavior. Their diagnostics, treatment, monitoring of patients must be adapted for them in a specific way. The current treatment experiences are mainly based on known and well-established treatments, but for localization and not according to their specific histopathology.

The biggest problems are: recurrent disease where radiotherapy has been exhausted or resistance to platinum preparations has already developed. Metastatic disease needs to be treated systemically, so there is a constant need to include new chemotherapeutics. The attempt to solve this problem is in targeted therapies, which is why immunotherapy is included, through different mechanisms of action: through inhibition of tumor pathological vascularization, blockade of certain receptors.

The conclusion is that this group of patients is without a well-developed and effective strategic treatment, which should be worked on.

Endometrial Cancer. Clinical Morphologic and Genetics Features

Tripac Irina, MD, PHD
Department of Gynaecology
Institute of Oncology of Moldova
email: i_iacovlev@yahoo.com

Abstract

Endometrial cancer (EC) is the sixth most common cancer in females. About 382,000 new cases are diagnosed each year and EC accounts for 90,000 deaths worldwide. The estimated five-year survival rate in developed countries is about 80% with primary treatment consisting of combinations of surgery, vaginal brachytherapy (VBT), external beam radiation therapy (EBRT), and adjuvant chemotherapy. Median age at uterine cancer diagnosis 62 years. The number of new endometrial carcinoma cases in Europe in 2021 was 134 578 with 41 638 deaths, and the incidence has been rising with aging and increased obesity of the population. EC is traditionally classified into 2 pathogenic types. Type I endometrial cancer is most often associated with good prognosis, while type II is associated with poor prognosis. This dualistic model does not fully capture the wide range of clinical, genetic, and molecular characteristics found in endometrial cancers. The adequacy of risk stratification systems in EC have recently been compared and challenged . There are 5 major risk stratification systems in EC, of which the modified ESMO classification was demonstrated to best discriminate for recurrence and nodal metastases in apparent early stage disease . Considering the high number of possible markers, only a few have been included in internationally recommended guidelines for risk stratification. However, none of the existing schemes were deemed highly accurate. In addition, all current systems stratify women based on pathologic data obtained after surgical staging (stage is a component of risk assignment). There is great need to obtain earlier and more biologically informative data from EC tumors that could assist in planning the optimal course of treatment for the individual. The Leiden/TransPORTEC and Vancouver/ProMisE pragmatic molecular classification systems incorporate the same integral components: identification of ECs with mismatch repair deficiency/microsatellite instability, POLE exonuclease domain mutations and aberrant p53.. Prognostic strength of molecular classification is at least equivalent to other clinicopathological features or risk stratification systems but offers the advantage of objective results. It is important to assess MSI status in endometrial cancers. ESMO consensus guidelines recommend IHC testing using antibodies against the 4 proteins listed above. In the event of indeterminate IHC findings, molecular testing with MSI PCR is recommended using one of 2 panels assessing microsatellite markers, where MSI is defined as loss of stability in ≥ 2 of 5 markers.

The prospective data of 269 patients with endometrial cancer who had undergone primary surgical treatment between 2018-2021 were included in the study. Inclusion criteria were as follows: 1) Patients were diagnosed with stages I–II endometrial cancer according to the staging system (FIGO) 2009 guidelines; 2) Patients had a complete case record, including age, body mass index, comorbidities (hypertension or diabetes), surgical procedures, pathological results (histotype, depth of myometrial invasion, cervical stromal invasion), immunohistochemical makers (Ki67), PTEN, MLH1. The exclusion

criteria were as follows: 1) The patient did not follow the standard surgical treatment; 2) Patients with other malignancies; 3) Patients who had received chemotherapy or radiotherapy before surgery; and 4) Patients without regular follow-ups.

Despite its generally favorable prognosis at primary diagnosis, recurrence of endometrial cancer remains an important clinical challenge. Recurrences were classified as locoregional, abdominal, or distant recurrences, according to the first site of recurrence. Locoregional recurrences included vaginal and pelvic recurrences (including pelvic lymph nodes and local spread to rectum and bladder); distant recurrences include lung, liver, bone, and brain metastases as well as lymph node involvement other than pelvic or paraaortic. Mixed recurrences as recurrences with multiple dissemination pathways (simultaneous locoregional, abdominal, and/or distant recurrence). In total there were 15 reccurences. 3 patients experienced local reccurence, 6 patients regional reccurence, 2 - distant reccurence, 4 patients mixed reccurence.

Ki-67, a marker of cellular proliferation, is increasingly being used in pre-surgical window studies in endometrial cancer as a primary outcome measure. Unlike in breast cancer, however, there are no guidelines standardizing its measurement and its clinical relevance as a response biomarker is undetermined.The level of the Ki-67 expression estimated in the immunohistochemical examination in 50 patients with CE in stages I-II The index more than 49 was related to deep myometrial invasion or poorly differentiated types. Acquired mismatch repair deficiency resulting in microsatellite instability (MSI) is a diagnostic phenotype for a multitude of cancer types MSI is of clinical relevance. The group of MMRd accounts for 23–36% of EC while only 2% of all EC are associated with Lynch syndrome. MLH1 promoter methylation was detected in 50 patients with EC in stages I-II. The proportion of patients under 50 years of age at EC onset was significantly higher. Endometrioid type carcinoma accounted for more than 80% in each group. High rate of MLH1 promoter methylation is observed in patients with EC from high risk group. The proportion of G1 and G2 was significantly lower than that of the other groups and the proportion of G3 G4 was significally higher in patients from high risk group. We identified promoter methylation MLH1 in 2 patients with well differentiated adenocarcinoma from low risk group.

Research based on clinical-morphological and molecular-genetic studies revealed new pathogenetic mechanisms and predictors of EC exacerbation, such as the presence of the c.389G>A (p.R130Q) PTEN gene, promoter methylation MLH1, the proliferation marker Ki-67, which allowed the development of a mathematical model for predicting the evolution of the disease in EC patients from different risk groups over a 3-year period.

Integrative Omics Strategies for Rare Gynecological Diseases

Sureyya Ozcan [1,2]
[1]-Department of Chemistry, METU, Ankara, Turkiye
2-Cancer Systems Laboratory (CanSyL), METU, Ankara, Turkiye
email: sozcan@metu.edu.tr

Abstract

The definition of rare tumors is an annual incidence of six or fewer per 100,000 population but in clinical practice they are not so rare – more than 50% of them are classified as rare. This group of tumors create a lot of problems both for the medical teams and patients. The lack of knowledge about them very often leads to delay in diagnosis and treatment.

In this presentation are introduced some cases of rare tumors from clinical practice and are discussed the problems that the medical team has to resolve.

Keywords: rare gynecological tumors; vulval leiomyosarcoma; vaginal myoma; vaginal leiomyosarcoma; primary vaginal Non-Hodgkin's Lymphoma; metastatic vaginal tumors.

Fertility Issues in Cancer Survivors

Vera Dimitrievska, PhD
University of American College, Skopje, North Macedonia
email: vdimitrievska@gmail.com

Abstract

As part of the European B²-InF project, with the main aim to explore young adults' knowledge, perceptions and concerns about infertility and Assisted Reproduction Technology (ART), and to contrast it with the information provided by ART providers in 8 countries (Albania, Belgium, Spain, Italy, Kosovo, Northern Macedonia, Slovenia, Switzerland), we interviewed 98 non-parent people aged between 18 and 30 (10 to 15 per country) about family, parenthood, infertility and ART. In addition, we examined the websites of 33 medical centres (3 to 5 centres per country). The objective is to describe and analyse, from a gender perspective, the social representations that these different centres make visible on their websites, through the texts and images posted.

It is very important that fertility issues are taken into consideration at when dealing with young female cancer patients. Cancer in a female's reproductive system, especially before or around puberty, together with its treatment, can have an adverse effect on fertility. Three themes emerged from the analysis of the interviews: 1. Parenthood and (in)fertility; 2. Young people's perception on ART; 3. Information and publicity of ART. Parenthood was described as a relationship beyond biological ties and infertility identified as a social tabooThe interviews reveal a representation of intensive parenthood, and in particular of intensive motherhood, which would impose major sacrifices on women. Pre-treatment of cancer patients particularly for young women should be diverse. The practice includes cryopreservation of ovarian tissue, oocytes, and possibly embryos, ovarian transposition, and fertility-sparing surgery. For women who are infertile post-treatment, options include the use of donor gametes or embryos, adoption and surrogacy.

Surveillance of Rare Female Genital Tumours In Europe: An Update of Frequency And Outcome

Gemma Gatta
Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
email: gemma.gatta@istitutotumori.mi.it

Abstract

According to the available definition for rare cancer, we identify rare malignancies of the female genital tract.

In Europe, ovarian and cervix cancers are rare with an incidence rates below 6 per 100,000/year, which is the threshold to define rare cancer. Epithelial tumour of vagina and vulva, sarcoma of uterus, rare epithelial cancer of corpus uteri, trophoblastic tumours of placenta and epithelial tumour of fallopian tube are other gynaecological rare cancers.

This contribution will present the principles for the definition of rare cancers, number and rates of new diagnosis (incidence) and 5-year survival for gynaecological rare cancers (GrC).

We select data from the RARECAREnet search tool [1] for both incidence and survival. The rare entities defined combining topography and morphology ICD-O codes were identified through a consensus process of oncologists, surgeons, genetists, epidemiologists and patients association representatives. The experts were mainly from the ESMO faculty [2]. All the material, cases incidence from the EUROCARE project and methods for the estimation of indicators of frequency and outcome were described in the RARECAREnet website. The latter is freely available [1]. The period of analysis is 2000-2007.

Some tables and figures, as given by the search tool, show incidence rates (per 100,000/year) and survival (%) by the GrC. Summarizing: among all the GrC, epithelial of ovary and cervix uteri rates showed the highest annual incidence rates (>5-<6), intermediate for vulva and vagina (2) and lowest (incidence rates < 0.8) for all the other GrC; as for all the epithelial cancers, incidence rates increased with the increasing of age; rates during the study period increased for rare corpus uteri and decreased for cervix uteri and epithelial and non epithelial ovarian cancers, incidence was stable for the other rare malignancies. Five-year survival was highest (>80%) for the trophoblastic tumour of placenta and non epithelial tumour of ovary and lowest (<50%) for the rare epithelial tumours of corpus uteri and of ovary; progress of 5-year survival was reported for cervix and vulva and vagina cancers. Survival, according with the recent EUROCARE project report (data not published and with some more registries included with respect to the previous report) showed slightly improved outcome for rare of corpus uteri and the majority of epithelial ovarian cancers, compared with survival figures derived from the RARECAREnet search tool (2000-2007).

As for all rare cancers, outcome of GrC benefits of centralization of diagnosis and treatment. For these tumours a study [3] showed a large number of hospitals involved, not an optimal organisation with a recognised network. Furthermore, geographical disparities of outcome across European countries was reported for GrC [1]. While disparities of survival mainly depend of access to the best available treatment and timely and correct diagnosis, incidence of these cancers can be reduced because risk factors are almost known and for cervical cancer an affective screening is available.

Surveillance of Rare Female Genital Tumours In Europe: An Update of Frequency And Outcome

Gemma Gatta
Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
email: gemma.gatta@istitutotumori.mi.it

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International Perspectives of Rare Gynecological Cancers

Prof. Dr. Gligor Tofoski
University Clinic for Gynecology and Obstetrics, Medical Faculty, University Sts. Cyril and Methodius, Skopje, North Macedonia
email: gtofoski@yahoo.com

Abstract

Today we are witnesses of an epidemiological transition which has occurred during the second half of the 20th century and is still going on in this century. This transition in which the dominance of infectious diseases is superseded by noncommunicable diseases, has made cancer and cardiovascular diseases the leading causes of premature death. Current situation regarding rare cancers is not similar to the common malignancies. Rare cancers are not so rare. The European Reference Networks (ERN) consider a disease rare when <6/100,000 persons per year are affected. Rare cancers account for about 22% of all cancers diagnosed worldwide, more than any of the single common cancers alone. Despite efforts mainly in some European nations, a few improvements have been observed in the management of rare cancers. Rare gynecological cancers account for more than 50% of all the gynecological cancers, with approximately 80,000 new cases per year in Europe, involving more than 30 different histologic diagnoses, with a very limited number of patients in each diagnostic category. The group of rare tumors is becoming larger as molecular classification further subdivides common tumors. The WHO Classification of Female Genital Tumors in the 5th edition of the WHO classification of tumors from 2020, is revised based on histomorphological and molecular pathology data. Some examples of rare gynecologic cancers include, but are not limited to: cervical adenocarcinoma, papillary serous tumors of the endometrium, clear cell cancers of the gynecologic tract, carcinosarcomas, gynecologic sarcomas, tumors of the vulva and vagina, sex cord tumors, small cell tumors of the gynecologic tract, germ cell tumors, gestational trophoblastic tumors.

Studying the molecular basis of rare gynecologic cancers is the path to development of new diagnostic, prognostic and treatment strategies. Molecular and genetic studies have also led to the discovery of new targets and the development of targeted agents, including monoclonal antibodies, small molecules and check-point inhibitors.

Coordination of clinical trials and expert opinions are necessary for drawing conclusions which will guide future cancer research. Especially important is the involvement of pharmaceutical industries in the process in order to develop cost-effective new diagnostic modalities and treatments. Moreover, ethics in clinical trials of cancers must be a top priority. Ethical principles should be followed, and the best results be achieved because each one of us theoretically may be a part of this group of patients.