Annals of Research in Oncology
Vol. 4(3), 161-173, 2024

MEETING REPORT

FROM BENCH TO BEDSIDE: HIGHLIGHTS FROM THE INTERNATIONAL DIALOGUE ON OVARIAN CANCER

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Doi: 10.48286/aro.2024.94

Key words: *ovarian cancer; multidisciplinary approach; chemoresistance; progranulins; radiotherapy.*

Received: July 31, 2024/**Accepted**: Oct 10, 2024
Published: Sept 23, 2024

This report covers the "***International Dialogue on Ovarian Cancer: From Bench to Bedside***" held live on May 22, 2024, at Temple University and the University of Messina. The meeting aimed to foster discussion between primary and clinical research, providing a state-of-the-art overview and guiding future steps in ovarian cancer research.

BURDEN OF OVARIAN CANCER THROUGH THE YEARS

Ovarian cancer is the third most common gynecological cancer with an incidence rate of 10.3 per 100,000 and a mortality rate of 6.2 per 100,000 from 2016 to 2020. Its high lethality is evident from a mortality-to-incidence ratio of 0.6. Lifetime risk is 1.1%, increasing significantly

for BRCA1 and BRCA2 mutation carriers. Survival rates vary by stage: localized ovarian cancer has a 92.4% survival rate, while distant/metastatic disease, which is the most common one, drops to 31.5% (1). Late diagnosis often leads to poorer outcomes. From 1930 to 2021, breast and uterine cancer mortality decreased due to effective screenings (2, 3). Ovarian cancer mortality initially rose due to an aging population but later declined with better disease management. Despite the absence of early diagnosis methods and vaccines, advancements in treatment have contributed to this reduction. Different histotypes, such as epithelial, sex cord-stromal, and germline types, require distinct management strategies, with epithelial ovarian cancer being the most common and diverse in subtypes (3-9). Radical surgery is still the preferable choice, but therapies have evolved, targeting molecular underpinnings of ovarian cancer. Platinum-based chemotherapy and PARP (poly-ADP ribose polymerase) inhibitors are crucial, but resistance development necessitates new treatments targeting hormone receptors, mesothelin, folate receptors, and programmed cell death 1 (PD-1). Radiotherapy remains crucial for managing metastasis. The role of the tumor microenvironment is under investigation. Efforts to reduce mortality have transformed ovarian cancer into a chronic condition, managed by cycles of surgery, chemotherapy, and adjuvant treatment (10-13). Each cycle induces molecular changes, leading to chemoresistance, requiring multidisciplinary management in specialized centers (14). The cost of reducing ovarian cancer mortality includes significant impacts on patient quality of life and financial resources. Patients face functional impairments from diagnosis through relapse management. Financial burdens stem from surgical complications, advanced imaging, and other high-resource interventions (15-20). Addressing ovarian cancer's challenges requires tackling the absence of a clear pathogenic agent, lack of early diagnosis strategies, and the disease's dynamic heterogeneity (14). Multiomics and artificial intelligence (AI) offer potential solutions in the learning process, enabling personalized treatment approaches. Developing patient-derived organoids and integrating multidisciplinary teams are essential steps towards continued progress.

DNA REPAIR MECHANISMS: THEIR ROLE IN CANCER DEVELOPMENT AND CHEMORESISTANCE

DNA damage is one of the leading causes of cancer development, increasing genome instability as a hallmark of cancer. Many DNA repair pathways have evolved to preserve genome stability, and many proteins involved in these processes are mutated in cancer, underlying the relevance of these pathways for cancer development and progression (21, 22). Principal cancer therapies, such as radiation or chemotherapy, aim to induce DNA damage, causing cell death in both cancerous and healthy cells, thus increasing off-target effects (23). The advent of next-generation sequencing has ushered in the era of personalized medicine through genome analysis. In particular, the use of PARP1 inhibitors in breast and ovarian cancers mutated in BRCA1/BRCA2 genes has opened the synthetic lethal era of cancer treatment, leading to a selective effect on mutated cells without off-target effects on healthy cells (24). However, PARP1 inhibition leads to the development of resistance mechanisms, reducing the effectiveness of drug treatments (25). In this context, the identification of novel DNA repair

proteins within synthetic lethality could be crucial to mitigating emerging resistance mechanisms (26). Furthermore, it is important to study the possible connections between the DNA damage response and other cellular pathways, such as the induction of DNA/RNA hybrids generated upon DNA damage and the activation of the adaptive immune response. This could open new possible connections between immunotherapy and DNA repair in the context of cancer treatment (27, 28).

PROGRANULINS: A NEW TARGET FOR ONCOLOGICAL TREATMENT

Progranulin is emerging as a critical growth factor with diverse roles in both normal physiology and cancer. Initially recognized for its involvement in embryogenesis and adult tissue homeostasis, progranulin deficiencies are linked to neurological disorders like frontotemporal dementia. However, its upregulation is a hallmark in various cancers, including ovarian, brain, multiple myeloma, and epithelial cancers such as liver, breast, and bladder (29, 30). In cancer, progranulin fosters tumor growth by enhancing cell proliferation, migration, invasion, and chemotherapy resistance (31, 32). It also significantly impacts the tumor microenvironment by modulating cancer-associated fibroblasts and immune surveillance (33). Despite its known oncogenic roles, the detailed molecular mechanisms behind progranulin's function in cancer remain largely unexplored (34). Recent studies have highlighted progranulin's ability to interact with multiple receptor tyrosine kinases (RTKs), such as EphA2 in bladder cancer, suggesting a complex, context-dependent function (35). For example, in malignant mesothelioma, progranulin regulates migration, invasion, adhesion, and tumor formation through a signaling network involving RTKs like EGFR and RYK, a Wnt pathway co-receptor (36). Exploring progranulin's role in ovarian cancer could unveil new diagnostic and prognostic biomarkers and therapeutic targets. The interaction between cancer cells and their microenvironment is crucial, and progranulin exemplifies this intricate relationship. By understanding and targeting progranulin-related pathways, we can potentially develop more effective treatments for ovarian cancer, highlighting the importance of studying cancer cell-microenvironment interactions.

MODULATION OF GENE EXPRESSION AND ITS APPLICATION

Modulating gene expression is a powerful tool scientists use to explore gene functions. Key methods include gene knockdown and knockout. Knockdown reduces gene expression but does not eliminate it, often using RNA interference (RNAi) (37). RNAi leverages the cell's defense mechanism against viruses, in which double-stranded RNA attracts the enzyme DICER (38). DICER cuts the RNA into small interfering RNAs (siRNAs), which guide the RNA-induced silencing complex (RISC) to degrade target mRNA. Techniques such as lipofection or electroporation transiently transfect cells with siRNA, while short hairpin RNA (shRNA) integrated via plasmids or lentiviral infection ensures long-term knockdown. Gene knockout, however, uses CRISPR-Cas9 technology to completely silence genes (39). CRISPR-Cas9 acts as molecular scissors, creating double-stranded breaks (DSBs) in DNA. The cell's repair mechanisms, often error-prone, lead to permanent gene inactivation. High-throughput screening with siRNA or CRISPR libraries allows researchers to rapidly investigate thousands of genes, identifying new drug targets or resistance mechanisms. These gene-silencing techniques have propelled therapeutic advancements (40, 41). The first siRNA-based therapy, Patisiran, was FDA-approved in 2018 for hereditary transthyretin amyloidosis (hATTR) (42). By 2023, six siRNA therapies were approved for various rare metabolic disorders. In December 2023, the FDA approved CASGEVY®, the first CRISPR/Cas9-based therapy for sickle cell disease, marking a significant milestone in genome editing (43). These advanced techniques are crucial not only for understanding biological processes but also for developing innovative treatments. The ability to modulate gene expression through knockdown and knockout is transforming genetic research and therapy, offering new ways to combat diseases and improve health outcomes.

THE ROLE OF CDKs

The hallmarks of cancer first published by Douglas Hanahan and Robert Weinberg in 2000 highlighting mechanisms by which normal cells become

cancerous (44) have been updated over the years; however, two critical traits, sustained proliferative signaling and evasion of growth suppression, have remained. They are closely associated with cyclin-dependent kinases (CDKs) (45, 46). CDKs, when dysregulated through overexpression, silencing, or other mutations, lead to uncontrolled cell proliferation and genomic instability which points to the importance of CDKs as a possible novel targeted strategy. CDKs are serine/threonine kinases that regulate cell cycle progression by partnering with specific cyclins and they control transitions among the various cell cycle phases. These transitions ensure accurate cell division and growth. Interestingly, some CDKs do not only have a cell cycle regulatory role but also regulate other cellular processes such as DNA damage and repair, transcription, senescence, invasion, metabolism and immune response, regulation of protein ubiquitination and stability (47). Within various cancers, CDK expression has been studied and it has been found that CDKs can either act as oncogenes or tumor suppressor. Many clinical trials have been conducted to investigate the effects of targeting these kinases. Of particular importance in the cancer field are D-cyclins activating CDK4 and CDK6 in the G1 phase. Small molecule CDK4/6 inhibitors have been approved by the FDA, palbociclib, ribociclib and abemaciclib, which have shown impressive results for patients with hormone receptor-positive (HR+) and HER-negative breast cancer (BC), extending median progression-free survival and prolonged median overall survival (48). Due to these results, FDA-approved CDK4/6 inhibitors show potential in treating other malignancies, especially ovarian cancer. As with several targeted therapies, tumors eventually develop resistance and resume cell proliferation despite CDK4/6 inhibition. New combination treatments, involving CDK4/6 inhibitors plus inhibition of other pathways such as with immunotherapies, chemotherapy (platinum, PARPi), and other targeted therapies are being conducted to achieve synergistic effects and improve patient outcomes (49).

DRUG DEVELOPMENT FROM NATURE

Nature is an ideal source for anticancer drug development due to the unique chemical structures produced by various organisms over millions of years for self-protection (50-52). The U.S. National Cancer Institute (NCI) has a research program focused on discovering new natural compounds for cancer therapy, involving phases from the establishment of a Natural Products Repository to clinical translation. Successful molecules undergo high-throughput screening, chemical characterization, bioassay development, and preclinical studies before clinical trials (53). Among the drugs developed from natural compounds, Trabectedin, derived from *Ecteinascidia turbinata*, is used for soft tissue sarcomas and ovarian cancer. Irinotecan, Topotecan, and Camptothecin (CPT) are DNA topoisomerase I inhibitors used against ovarian, cervical, and lung cancers. However, CPT's effectiveness can be limited by cancer cells' ability to repair DNA damage through homologous recombination (HR) (54, 55). In 2023, Barone *et al.* discovered that a hydrophilic extract from a DHO tomato genotype effectively combats cancer cell lines by modulating the DNA damage response (DDR) triggered by CPT treatment. The extract showed significant cytotoxic effects on cervix adenocarcinoma and triple-negative breast adenocarcinoma cell lines when combined with CPT. The DHO extract appeared to redirect DNA repair induced by CPT from gene conversion to single-strand annealing, a mutagenic and error-prone mechanism, preventing efficient DNA repair by cancer cells and enhancing CPT efficacy. These findings suggest a potent molecule in the DHO extract that could augment cancer therapy (55). Combining natural substances such as the DHO extract with conventional chemotherapeutics could synergistically lower CPT doses and minimize side effects. Future research will focus on a single extract component, testing food chain by-products on tumor cells, characterizing their composition through NMR and HPLC, and assessing anti-tumor capabilities through cell viability and migration assays. If promising, the molecule's molecular pathway will be investigated to understand its biological activity and potential for cancer therapy (53).

CORE PRINCIPLES OF RADIOLOGIC DIAGNOSIS AND STAGING IN OVARIAN CANCER

The primary goals of preoperative imaging for ovarian neoplasms are to predict whether the mass is benign, borderline, or malignant and evaluate for metastatic disease. Ultrasound (US) is the

first-line imaging modality due to its widespread availability, low cost, excellent spatial resolution, and ability to depict flow within solid tissue using color Doppler. The Ovarian-Adnexal Reporting and Data System (O-RADS) US risk stratification tool categorizes adnexal masses into higher risk categories (56). Indicators of higher risk include larger size, multilocular masses, papillary projections, irregular inner walls or septa, and solid components with flow (56). When US results are indeterminate, magnetic resonance imaging (MRI) is used for further characterization. The O-RADS MRI classification ensures correct risk stratification of ovarian masses based on high-resolution multiplanar T1 and T2 diffusion-weighted sequences and dynamic contrast-enhanced studies (57). This classification produces five scores that define the probability of malignancy (57). Although staging laparotomy and histopathological examination are the gold standards for staging in women suspected of having ovarian carcinoma, contrast-enhanced computed tomography (CT) is the necessary noninvasive method for preoperative staging and detection of nodal and peritoneal deposits. CT can calculate the peritoneal cancer index (PCI), which combines the distribution of peritoneal metastases (PMs) in 13 abdominopelvic regions with tumor size, providing a measurement of peritoneal carcinomatosis volume and a valuable prognostic index (58). However, CT has limitations, such as reduced sensitivity for detecting small PMs (<5 mm) and those in specific anatomical locations (mesentery and bowel serosa), especially in the absence of ascites (58). MRI offers better detection of subcentimetric PMs in certain anatomical areas, including the bowel serosal surface, pelvis, right hypochondrium, and mesentery. Nevertheless, MRI's usefulness is limited to selected cases due to lower spatial resolution, longer examination times, motion artifacts, lower availability, higher cost, and the need for experience in image acquisition and interpretation. Despite these limitations, Multidetector computed tomography (MDCT) remains the preferred choice for evaluating suspected recurrence and surgical complications (59).

KEY INDICATIONS FROM NUCLEAR MEDICINE

Ovarian cancer staging is crucial for prognosis (60). The role of [18F]Fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) in initial detection is widely debated (61). Despite some studies indicating its high sensitivity and specificity, FDG PET/CT struggles to distinguish benign from borderline tumors and cannot replace surgical staging (62). However, it is valuable for detecting distant metastases and lesions that may contraindicate primary cytoreduction (63). Sentinel lymph node (SLN) mapping is not standard for ovarian cancer due to its transperitoneal spread (61). While current clinical trials are exploring its role in early-stage ovarian cancer, comprehensive lymphadenectomy remains the gold standard (64). CT and MRI are traditional methods for monitoring treatment response. FDG PET/CT offers earlier detection of metabolic changes, potentially identifying responders versus non-responders sooner. However, more research is needed to establish its role in treatment monitoring. FDG PET/CT is effective in detecting recurrent ovarian cancer, especially in patients with rising CA-125 levels but negative or inconclusive CT/MRI findings (65, 66). Studies show it has a high sensitivity (91%) and diagnostic accuracy (AUC 0.95). NCCN and ESMO-ESGO guidelines recommend FDG PET/CT for suspected recurrence, particularly with rising tumor markers and negative findings on other imaging modalities (67). FDG PET/MRI combines anatomical and metabolic imaging, offering detailed staging and detecting peritoneal carcinomatosis. Although limited by cost and availability, it reduces radiation exposure and provides superior anatomical details (68). Emerging data show that new PET radiopharmaceuticals highlights promise. Radiolabeled Fibroblast Activation Protein Inhibitor (FAPI) offers high tumor-to-background ratios, potentially improving staging and follow-up (69). Pentixafor targets CXCR4, a marker associated with advanced disease and poor prognosis. Theranostics combines imaging and therapy, providing targeted treatments (70). In ovarian cancer, FAPI variants and HER2-targeted radioimmunotherapy are under investigation. These novel approaches require rigorous clinical trials to establish their efficacy and safety (71).

CUTTING EDGE DECISION: SURGICAL INDICATIONS

Surgery plays a pivotal role in the management of ovarian cancer due to the necessity of histological

diagnosis via tissue biopsy, the complete removal of all macroscopically visible disease and to stage the patient accurately for prognostic and treatment purposes (13). Surgery is stratified based on the stage of the disease stage: early-stage ovarian cancer (Stage I/IIA) versus advanced stages (IIB-IV). In early stages of disease fertility sparing surgery (which provides a surgical removal of the disease by maintaining a woman's possibility to perform a pregnancy without the removal of the uterus) can be offered to premenopausal fertile women in stage IA to IC grade 1, stage IA grade 2 and in conventional histological subtypes. In stage IC grade 2, stage IA clear cell it can be offered in selective cases with an adequate counseling with the patient. In these cases, laparoscopic surgery is preferred due to its lower morbidity compared to laparotomy. Comprehensive surgical staging for early disease includes peritoneal cytology, total hysterectomy with bilateral salpingo-oophorectomy, and random abdominal biopsies. Additionally, omentectomy, appendectomy (for mucinous subtypes), and systematic pelvic and aortic lymphadenectomy are performed. For advanced stages (IIB-IV), primary cytoreductive surgery aims for complete removal of all visible disease, ideally achieving no residual tumor. Radical cytoreduction is crucial since superior survival outcomes are associated with minimal residual disease. Advanced surgical techniques may involve bowel resection, diaphragmatic stripping, splenectomy, and resection of metastases in collaboration with other surgical specialties. Exploratory laparoscopy is crucial for assessing the predictive index value (PIV) according to the Fagotti score, which ranges from 0 to 14, as it helps predict the feasibility of achieving optimal cytoreduction. Scores above 8 typically indicate the need for neoadjuvant chemotherapy (NACT) rather than immediate surgery. While the PIV according to Fagotti is primarily used to assess the feasibility of surgery before it is undertaken, laparoscopy also allows for the assessment of the Peritoneal Cancer Index (PCI), which indicates peritoneal involvement, known as tumor load. In this case, 13 abdominal regions are summed to calculate the total PCI score. The maximum possible score is 39, indicating widespread peritoneal involvement. Laparoscopy not only allows for a histological diagnosis but also facilitates the acquisition of molecular characteristics of the tumor, which may be useful for targeted neoadjuvant chemotherapy. The future perspective for ovarian cancer treatment is personalized care, beginning with diagnostic laparoscopy to evaluate the PIV according to the Fagotti score and to assess tumor load using the PCI. The concept of tumor load refers not only to the extent and localization of the disease but also to the surgical feasibility and effort required to achieve complete resection: for instance, an extensive disease in the pelvis might still allow for complete resection (RT0), while extensive disease involving the peritoneal surface of the left hypochondrium, including the stomach, may be surgically unapproachable. If the PIV score is lower than 8, primary debulking surgery can be performed. If the PIV is 8 to 14, which also suggests high intraoperative risk, and in cases of chemosensitive tumors (high grade, BRCA mutated), the patient can undergo NACT with targeted treatment. For non-chemosensitive tumors (mucinous, BRCA wild type, LGSOC), the decision can be made between primary debulking surgery or NACT, with adequate counseling (3 to 6 cycles followed by surgery). Finally, in cases of unresectable disease, which represents less than 5%, patients should directly undergo NACT. The role of surgery in the natural history of ovarian cancer is as follows: first, upfront debulking surgery or NACT (3 to 6 cycles) followed by interval debulking surgery, then, if necessary, adjuvant chemotherapy and, in particular cases, secondary or tertiary cytoreduction. Many studies have shown that in cases of relapsed ovarian cancer, secondary cytoreduction, if residual tumor is zero (RT0), can increase survival by up to 15.9 months. We are now moving away from generalized guidelines, where primary debulking surgery was often preferred over neoadjuvant chemotherapy, or laparoscopy over laparotomy, to more tailored approaches where PDS, NACT, LPS, and LPT are all viable treatment options that must be carefully chosen for each patient. The integration of advanced diagnostic and surgical techniques promises further improvements in survival and quality of life for ovarian cancer patients (72-74).

INSIGHTS INTO ONCOLOGIC APPROACHES FOR OVARIAN CANCER

Epithelial ovarian cancer (EOC) therapy involves medical oncology in neoadjuvant, adjuvant, and advanced settings. Early-stage ovarian cancer

therapy benefits from adjuvant platinum-based chemotherapy (ChT), significantly prolonging overall survival (OS) and progression-free survival (PFS) as shown in the ACTION and ICON1 trials. Standard adjuvant therapy consists of six cycles of carboplatin plus paclitaxel. Histology impacts treatment, with serous carcinoma benefiting more from extended adjuvant therapy compared to non-serous tumors. Adjuvant ChT is not recommended for patients with low-grade serous and endometrioid carcinoma stage IA or expansile mucinous stage IA-IB (74-77). In advanced EOC (stage III-IV), the goal of surgery is complete or optimal cytoreduction. Primary cytoreductive surgery (PCS) followed by systemic treatment remains the gold standard when feasible. While surgery is typically recommended after three to four cycles of neoadjuvant chemotherapy (NACT) for responding patients, the optimal number of cycles is not definitive. Studies have shown that patients receiving more than four cycles often have worse survival outcomes, potentially due to underlying health conditions or advanced age. However, these findings require cautious interpretation, as the poor outcomes may be influenced by these biases. Patients needing six or more cycles might be biologically different, requiring more cycles to achieve the same favorable outcomes as those with fewer cycles. Recent observational studies suggest that interval debulking surgery (IDS) can be delayed to six or more cycles of NACT without negatively impacting long-term survival, provided that complete cytoreduction (CC0) is achieved. Therefore, surgical timing should be tailored to optimize outcomes rather than focusing solely on minimizing NACT cycles (74). Standard ChT in this setting involves six cycles of paclitaxel plus carboplatin every three weeks (75, 76). Adding bevacizumab, an anti-VEGF antibody, to first-line therapy and as maintenance, improved median PFS in trials GOG-218 and ICON7, with a greater benefit in OS for high-risk populations (stage III with residual tumor >1 cm or stage IV) (79, 80). About 50% of high-grade serous carcinomas show homologous recombination deficiency (HRD). HRD-positive tumors, irrespective of BRCA1/2 mutation, respond well to PARP inhibitors (PARPi) as maintenance therapy post-first-line ChT, offering significant benefits to patients with BRCA1/2-mutated or HRD-positive tumors (75, 76). Up to 70% of patients with stage III-IV high-grade ovarian cancer relapse within three years. Recurrent disease therapy includes platinum-based regimens, with the treatment-free interval (TFIp) influencing platinum sensitivity. Combinations like carboplatin-pegylated liposomal doxorubicin (PLD) are preferred due to their safety profile. Bevacizumab is approved for use with platinum-based therapies as maintenance for patients with a TFIp >6 months. Three PARPi (olaparib, niraparib, rucaparib) are also approved for maintenance therapy in responders to platinum rechallenge (75, 76). Future perspectives involve precision medicine, targeting molecular pathways and immunotherapies like pembrolizumab and dostarlimab for dMMR or high TMB ovarian cancer (75, 76).

THE ROLE OF RADIOTHERAPY IN THE MANAGEMENT OF OVARIAN CANCER

Ovarian cancer treatment has seen evolving roles for radiotherapy, with renewed interest in combining it with targeted therapies for metastatic disease. Historically, whole abdominal radiotherapy (WAR) was the standard adjuvant treatment until the 1970s, aimed at reducing peritoneal and abdominal recurrence (81). Its use declined due to significant gastrointestinal toxicity, including chronic enteritis and bowel stenosis (82, 83). Dembo *et al*. identified patient subgroups who could benefit from WAR based on prognostic factors such as age, tumor grade, and peritoneal cytology (84). Despite these insights, high toxicity rates often led to treatment discontinuation (85).

Radiotherapy is now predominantly used for metastatic ovarian cancer (MOC), especially in oligometastatic disease, defined by a limited number of metastatic lesions (81-85). Stereotactic body radiotherapy (SBRT) has shown promising results in this setting. Studies such as the SABR-COMET trial demonstrated improved overall survival when SBRT was added to standard treatments. Macchia *et al*. further confirmed the efficacy and safety of SBRT in metastatic persistent and recurrent ovarian cancer (86). CT-guided high-dose-rate interstitial brachytherapy ablation (CT-HDR-IBTA) is another emerging technique, showing effectiveness and low toxicity in treating abdominal and pelvic metastases. Combining radiotherapy with PARP inhibitors (PARPi) like olaparib enhances radiosensitivity, particularly in BRCA1-deficient tumors, by inhibiting DNA repair (87).

Adjuvant low-dose whole abdominal irradiation (WAI) is being reconsidered for its potential to enhance chemosensitivity, especially with agents like docetaxel. The Gynecologic Oncology Group (GOG) conducted studies indicating that low-dose WAI could improve progression-free survival in recurrent ovarian cancer (88). Moreover, low-dose radiotherapy (LDRT) has been shown to stimulate T-cell infiltration, enhancing the immune response and potentially improving outcomes when combined with immunotherapy (89). Novel techniques like oxygen-guided radiotherapy and lattice radiotherapy are also being explored, aiming to treat hypoxic tumor areas with high radiation doses and improve the efficacy of immunotherapy (90). These advancements highlight the evolving role of radiotherapy in managing ovarian cancer, emphasizing its potential when used in combination with other therapeutic modalities.

CONCLUSIONS

Ovarian cancer is heterogeneous and complex due to its biology and behavior within individual patients. The more data we gather from various omics, the better we can delineate this complexity. However, with more data comes the challenge of translating these findings into clinical practice, as much of the evidence needs validation from primary research to the clinical setting. The question remains: are we now able to predict ovarian cancer behavior in a single patient? We need to pave the road to that goal. Today's challenge requires a transdisciplinary approach that includes not only physicians but also informatics engineers, data analysts, and primary researchers.

ACKNOWLEDGMENTS

Sincere thanks are extended to Associate Professor Vincenzo Carnevale from the Department of Biology at the College of Science and Technology. His masterful lecture on artificial intelligence applied to medical science opened new perspectives for many clinicians and researchers attending the congress. His expertise and vision significantly enriched the discussions and inspired new avenues of thought and research.

Profound gratitude is also extended to Stephen J. Williams, Ph.D., from Temple University, Sbarro Health Research Organization, for his exemplary role as the moderator of the congress. His adept moderation and insightful contributions significantly enhanced the quality and success of the event. His dedication to ensuring a smooth and engaging experience for all participants was instrumental. His invaluable support and professionalism were pivotal to the success of the congress.

COMPLIANCE WITH ETHICAL STANDARDS

Fundings

There were no institutional or private fundings for this article.

Conflict of interests

The Authors have declared no conflict of interests.

Availability of data and materials

The data underlying this article are available in the article.

Authors' contributions

All Authors made substantial contributions to the reporting of the congress. AG, AE, and CM organized the congress and coordinated the overall event. SRB and CM documented and summarized the sessions, ensuring accurate and comprehensive coverage. The gynecological contributions were reported by AE and CM, while the primary research focus was managed by AM, LA, MC, MD, and SRB. The radiological aspects were conducted by AB, and the radiotherapy components were handled by SPe, SPa and MS. The oncological parts were covered by NS and FO, CM and SRB drafted the initial report manuscript, with all authors participating in the review and revision process. PC was responsible for project administration and logistics. All Authors have read and approved the final manuscript.

Ethical approval

N/A.

Publication ethics

Plagiarism

Authors declare no potentially overlapping publications with the content of this manuscript and all original studies are cited as appropriate.

Data falsification and fabrication
All the data correspond to the real.

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