Gynecologic cancers form a huge burden of morbidity and mortality around the world. Data available from various centers worldwide indicate vast regional variations in incidence, common sites of occurrence, age and stage of presentation. Cancers of cervix, ovary, uterus, vagina, and vulva as a group, are referred to as gynecologic cancers. Each gynecologic cancer is unique, with different signs, symptoms and risk factors. In the developed world, most gynecological cancers are endometrial or ovarian, whereas cervical cancer is more common in the developing world and is the leading cause of gynecological cancers deaths worldwide.

It is estimated that, worldwide, cervical cancer accounts for 487,300 new cases and 269,500 deaths; uterine corpus cancer for 233,300 new cases and 61,400 deaths; ovarian cancer for 230,000 new cases and 140,100 deaths; cancers of the vagina, vulva, placenta, and ill-defined sites together constitute 74,900 cases. Less developed countries account for more than 80% of the cervical cancer cases, whereas almost 60% of uterine corpus cases occur in the developed world.

Management algorithms for most gynecological cancers follow a path of surgery followed by radiation, chemotherapy, or a combination of both therapies. However, patients with post-therapy persistent or recurrent disease have limited treatment options, often as a result of a complex mix of patients, tumor and treatment factors. For some time there has been indirect evidence that women have more favourable outcomes if they are treated by specialist gynecological oncologists in cancer centres.

Chemotherapy is playing an ever increasing role in the treatment of patients with the common gynecologic malignancies, including ovarian, cervical and endometrial cancers. Although changes to the scheduling and administration of chemotherapy have improved outcomes to a degree, a therapeutic ceiling is being reached with this approach, resulting in a number of trials investigating the efficacy of targeted therapies alongside standard treatment algorithms. Furthermore, there is an urge to develop subtype-specific studies in an attempt to improve outcomes which currently remain poor.

In developing countries like India, a significant proportion of patients are unable to access and avail complete preventive, diagnostic and therapeutic means due to lack of organized screening, awareness, inadequate healthcare services and financing. To reduce the current burden of gynecological cancer in low- and medium-resource countries, attention should be focused on formulation and translation of appropriate cancer control policies and investments in human resource development, awareness creation and healthcare infrastructure.

The present issue of the Cancer News highlights the newer advances in the field of endometrial cancer and features the regular articles, such as Special Feature, Guest Article, Perspective and In Focus. We are grateful to Dr U D Bafna, Professor and Head, Department of Gynecologic Oncology, Kidwai Memorial Institute of Oncology, Bengaluru for the "Guest Article"; Dr Veena P, Associate Professor, Dept of Obstetrics and Gynecology, JIPMER, Puducherry for the Purview, Dr Ashutosh Mukherji, Associate Professor, Dept of Radiotherapy, Regional Cancer Centre, JIPMER, Puducherry for the "Perspective", and Dr Jyoti Bajpai and Dr Subhadeep Bose; Dept of Medical Oncology, Tata Memorial Hospital, Mumbai for the "In Focus".

Suggestions / comments from the readers are welcome.

Dr D C Doval
GYNECOLOGIC ONCOLOGY: CHANGING SCENARIO, CHANGING NEEDS

Gynecological malignancy consists of those cancers that originate from the ovary, cervix, endometrium, vulva or vagina. They affect 2.2% of the female population by the age of 65 years of age. In developed countries, this is the second most common cause of cancer deaths in women after breast cancer[1]. In the developing world, cervical cancer remains the commonest cause of gynecological cancer deaths.

Treatment for gynecological cancers is almost always multimodal. This requires co-ordination of surgery with chemotherapy and radiotherapy. In 1999, the Calman-Hine published their report in the NHS Executive-Improving Outcomes in Gynecological Cancer[2]. The report specified ample indirect evidence that women have favorable outcomes if they are treated by specialist gynecological oncologists in dedicated cancer centers. Hence, gynecological cancers were one of the first cancer sites to have centralization of care.

Much later, a Cochrane Review by Yin Ling Woo and colleagues, published in the March 2012 issue of The Cochrane Library, evaluated the effect of centralization of cancer care for women with gynecological malignancies[3]. The review identified five studies, covering 62,987 women with gynecological cancer, and concluded that women with gynecological cancers might have improved outcomes if treated in specialist centers. The findings were stronger for women with ovarian cancer than for the other gynecological cancers, as several of the studies examined ovarian cancer only. A meta-analysis of data from three of the studies (covering over 9000 women) concluded that women with ovarian cancer who received care in hospitals with a gynecological oncologist on site had improved survival compared with those treated in non-specialist hospitals; hazard ratio (HR) of death was 0.90 [95% confidence interval (CI) 0.82 to 0.99]. The importance of developing gynecologic oncology as a specialized field could reflect of not only in the quality of the treatment to patients but also in the field of clinical research and advances.

**Bevacizumab in Gynecological Cancers**

Over the last several years, major changes have been seen in each aspect of gynecologic oncology, including clinical research and management protocols. Treatment of gynecological cancers has took a big leap in 2014 with the introduction of bevacizumab (BEV, Avastin), in gynecological cancers. A recombinant drug, humanized anti-vascular endothelial growth factor (anti-VEGF) monoclonal antibody, which had already been approved for three tumor types, was accorded approval for the treatment of advanced cervical cancer also in November 2014. Study demonstrated a substantial overall survival (OS) benefit of BEV in recurrent or metastatic cervical cancer, that were considered difficult to cure[4]. Later in the year, another milestone was achieved, when this magic drug was approved for the treatment of platinum-resistant ovarian cancer as well. More and more researches with immunotherapies for metastatic cervical carcinomas, including human papillomavirus (HPV) targeted-tumor infiltrating lymphocytes, have been carried out with promising results[5,6]. Additional validation, however, is required in the near future regarding the survival benefit of these drugs in cervical cancer.

**Screening of Cervical Cancer**

Cervical carcinoma being a very common cancer in India and other developing countries and a leading cause of cancer deaths, its prevention through screening is of paramount significance. PAP smear as a screening method introduced in the 1950s, resulted in 60% and more decrease in deaths from cervical cancer. Although the Papanicolaou (PAP) smear test has been used since long in national cancer screening programs and has proved its efficacy in reducing the cervical cancer incidence, it is many times either unaffordable or unapproachable in developing countries. Hence, there is an urgent need to develop a low-cost screening test for the early detection of precancerous lesions and of cancers of the uterine cervix. Visual inspection with acetic acid (VIA) is among those with promising future. Evidence suggests the feasibility and efficacy of VIA for preventing cervical cancer in countries like India[7]. Over the last few years, the HPV-based screening tests have been of particular interest among oncologists. Several randomized controlled trials have compared HPV-based screening and cytology-based screening tests. These trials showed HPV-based screening at 5-year intervals offered better protection against invasive cervical cancer than cytology alone at 3-year intervals. Eventually, based on the results of the ATHENA trial[8] that suggested that the HPV test was more sensitive and efficient for cervical cancer screening than cytology, the HPV test, the Cobas HPV...
test (Roche Molecular Systems, Pleasanton, CA, USA) received FDA approval in April 2014 as the primary screening tool for cervical cancer in women aged 25 and older.

**Endometrial Carcinoma**

Following a report by The Cancer Genome Atlas (TCGA) research network regarding integrated genomic analyses of high-grade serous ovarian cancers, TCGA published the integrated genomic analyses of endometrial carcinoma in 2013 [9]. Whereas early-stage endometrioid cancers are often treated with adjuvant RT, serous tumors are treated with chemotherapy. However, clinicians sometimes encounter tumors that are likely to recur within one year even after staging surgery and adjuvant RT. To improve the poor prognosis associated with aggressive histologic subtypes, including high-grade endometrioid and serous tumors, researchers attempted to provide key molecular insights into tumor classification that might affect postoperative adjuvant treatment. The findings suggested that clinicians should consider treating high copy number altered endometrioid tumors with chemotherapy rather than adjuvant RT.

A Phase II trial of vaginal cuff brachytherapy (VCB) followed by chemotherapy in early endometrial cancer patients with high or intermediate risk factors had shown encouraging results. Based on this study, the GOG 249 (10) conducted a randomized Phase III trial of pelvic radiation therapy (RT) versus (VCB), followed by paclitaxel-carboplatin chemotherapy (VCB / C) in patients who were high risk and had early stage endometrial cancer. But this study showed similar RFS and tolerability for both study groups.

**Ovarian Carcinoma**

Like cancer cervix, which is the commonest cause of death in the developing world, epithelial ovarian cancer (EOC) is the most common cause of death from gynecological cancer in the developed world. The current standard treatment of these patients consists of maximum surgical cytoreduction and systemic chemotherapy. Tendency to disseminate into the peritoneal cavity is one of the most distinctive features of EOC. Local recurrence is the rule and the disease remains confined to the peritoneum and intra-abdominal viscera. This makes it an ideal target for loco-regional therapy.

Improved long-term results have been observed in highly selected patients using cytoreductive surgery (CRS), along with intra-operative hyperthermic intraperitoneal chemotherapy (HIPEC). Optimal cytoreduction of advanced ovarian cancer is currently the most important prognostic factor and a target to achieve. However, even after a complete resection, the appearance of local recurrences during the later period is very common due to the presence of microscopic residual disease. HIPEC is a useful therapeutic measure to achieve a higher degree of debulking and thereby to eliminate the residual microscopic component responsible for recurrences. There is much less indirect evidence for a potential benefit of HIPEC for less advanced stages (I - II) and for earlier time-points in the treatment of ovarian cancer (upfront, interval and consolidation). CRS and HIPEC offers a significant survival benefit in patients with recurrent EOC. This observation applies to both platinum-sensitive and platinum-resistant disease.

The CHORUS trial reinforced the non-inferior treatment efficacy and reduced postoperative morbidity and mortality with NACT, compared with primary surgery (PS). The results were consistent with the results of the previous EORTC trial and endorsed the evidence that NACT could be considered as an alternative to PS for newly diagnosed advanced EOC.

Poly (ADP-ribose) polymerase (PARP) inhibitors are among the most exciting new classes of agents in the management and treatment of ovarian cancer. Olaparib, the lead oral PARP inhibitor, acquired approval by the US Food and Drug Administration (FDA) for the treatment of recurrent germline BRCA-mutant ovarian cancer in patients who have received at least three prior lines of chemotherapy and have failed [11].

These new class of PARP inhibitors target a cancer cell’s inability to repair DNA that is seen in cells that have BRCA mutations. Germline BRCA mutations have been identified in up to 17% of women with ovarian cancer and are associated with the high-grade serous histologic subtype, though other histology can harbour BRCA mutations as well as mutations in other DNA repair genes. Currently, most accepted guidelines have recommended that all patients with ovarian cancer, regardless of histology, should undergo genetic testing for the detection of high-risk inherited gene mutations.

Apart from this, PARP inhibitors are being investigated in combination with other agents, including antiangiogenics. The combination of olaparib and cediranib, an oral inhibitor of vascular endothelial growth factor receptor 2, was first tested in a Phase I study of patients with
recurrent epithelial ovarian or triple-negative breast cancer [12]. The anti-cancer activity observed in the study encouraged another randomized Phase II study. In this study, drug combination was compared with single-agent olaparib in patients with platinum-sensitive recurrent ovarian cancer.

The explosion of clinical trials following this study, investigating PARP inhibitors in the treatment of hereditary ovarian cancer has resulted in significantly improving progression-free survival of recurrent ovarian carcinoma patients.

**IMRT and IGRT**

Radiation treatment, both external beam and brachytherapy are an integral part of gynecological cancer treatments, both cervical and endometrial carcinomas. In the field of radiation too, newer technologies like IMRT, IGRT have made their mark.

Accurate targeting of tumors with maximal sparing of normal tissues has been the goal of radiotherapy practice. Over the past two decades, the ability to achieve this goal has improved immensely through advances in imaging technology, specifically the computerized tomography (CT), magnetic resonance imaging (MRI), positron-emission tomography (PET) and fusion PET/CT [13]. Targeted planning has made it possible for physicians to concentrate the doses to the target areas and thereby protect the normal organs from the effects of radiation, reducing toxicity and increasing chances of cure. Several studies, including one by AIIMS, India, have suggested no significant differences in DFS (79.4% vs. 60%, p=0.651) and OS (76% vs. 85.7%, p=0.645) observed between the two groups, IMRT and the conventional radiation. However, patients in the IMRT group were less likely to develop grade e”2 acute GI toxicity (31.8% vs. 63.6%, p=0.034) and chronic GI toxicity (13.6% vs. 50%, p=0.011) relative to those in the conventional RT group [14]. Given the large tissue volume and a relatively low dose (45 to 55 Gy) of the adjuvant RT for endometrial cancer, the potential toxicity benefits of IMRT for uterine cancer might be less prominent than those of pelvic RT for cervical cancer, wherein the total delivered RT dose is often much higher (>80 Gy).

Image based brachytherapy treatments with the help of modern imaging techniques (CT, MRI) to visualize the tumor, the applicators and the organs at risk and prescribe the doses accurately to pre-defined volumes and with dose–volume constraints, are being used at many centers to improve the treatment quality and hence the outcome [15]. Although there are concerns about the cost, the effectiveness and the utility of these researches and new modalities of treatment, it cannot be denied that these scientific and technologic advances have brought us to a stage where we can improve healthcare access and responses across the entire cross-section of patients facing gynecologic malignancies even in a low resource country like India.

**Indian Scenario**

In India and other developing countries, however the concept of centralized specialist care in oncology is still in the nascent stage. Although India is as developed as any other country in the world in terms of advanced technology and experienced oncologists for cancer treatment, these facilities are concentrated in some selected cities. Cancer detection and treatment facilities lag far behind in rural India where 70 percent of the population resides.

Provision of financially sustainable cancer care remains a formidable challenge in the treatment of cancer worldwide, more so in low resource countries. Addressing socio-economic, cultural, and ethical issues affecting gynecologic cancer care will aid in ensuring development of easier and more acceptable models of cancer care in resource-limited countries. “Unrestrained and uncritical adoption of new technologies without commensuration of cost benefit analyses remains the rule in the technology deprived and gullible communities where any form of technology is rapturous once found.” It is imperative to understand that policy makers on healthcare in developing countries emphasize the optimal use of scarce resources based on evidence-based practices.

Health education and population-based screening is cheaper and more effective in the management of most gynecologic cancers. Health education should be institutionalized using mass media and other culturally acceptable means of community mobilization. Systematic, available, and affordable cancer screening should be incorporated into basic healthcare. Healthcare practitioners need to accept limited life expectancy in patients with advanced cancers. They should know when and be readily willing to switch to palliative care where necessary. A strong collaboration between gynecologists, palliative care physicians, and general surgeons is essential for optimal gynecologic cancer care. In addition, research in developed countries should emphasize feasibility treatment plans, provision of affordable chemotherapeutic drugs, surveillance of cancer survivors, family therapy, and the vital role of counsellors and social welfare practitioners in the care of cancer.
References


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**Guest Article**

**Transcending from Chemotherapy to Targeted Therapy in Frontline and Recurrent Management of Epithelial Ovarian Carcinoma**

**Introduction**

Epithelial ovarian cancer (EOC) remains the most lethal gynecologic malignancy. During the last two decades, there has been only marginal improvement in 5-year overall survival. Epithelial ovarian cancer is a diverse and genomically complex disease. Genomic characterization of different histologies into type I EOC, such as low-grade serous, mucinous, clear cell and endometrioid, and type II EOC, such as high grade serous adenocarcinomas and carcinosarcomas have revealed heterogeneity in leveraged pathways for proliferation and invasion. Despite all subtypes exhibiting striking heterogeneity, their systemic management has remained largely identical.

Although changes to the scheduling and administration of chemotherapy have improved outcomes to a degree, a therapeutic ceiling is being reached with this approach, resulting in a number of trials investigating the efficacy of targeted therapies alongside standard treatment algorithms. Furthermore, there is an urge to develop subtype-specific studies in an attempt to improve outcomes, which currently remain poor.

**Evolution of Frontline Chemotherapy in Epithelial Ovarian Cancer in the Last Three Decades**

**Cyclophosphamide vs Paclitaxel:** With the publication of the results of the Gynecologic Oncology Group (GOG) protocol 111 in 1996, intravenous paclitaxel replaced intravenous cyclophosphamide in the adjuvant treatment of advanced-stage ovarian cancer. PFS and median overall survival were significantly longer (P<0.001) in the cisplatin–paclitaxel group (38 months versus 24 months).

**Cisplatin vs Carboplatin:** Two randomized Phase III trials led to the replacement of cisplatin with carboplatin when combined with paclitaxel. This regimen is widely accepted around the world as one of the current standards in treating ovarian cancer.
Dose-Dense Paclitaxel: A single study in Japan (JGOG 3016) has suggested that intravenous paclitaxel given weekly at 80 mg/m² combined with standard doses and schedules of carboplatin can allow dose intensification resulting in prolonged PFS and overall survival. The trial included 631 women with stages II to IV EOC, and the results showed impressive improvements in PFS and OS among patients in the experimental arm [PFS: 28.2 versus 17.5 months; OS: 100.5 versus 62.2 months]. As for safety, hematologic toxicity was the most common reason for treatment discontinuation and was significantly more frequent among patients assigned to dose-dense treatments (60% versus 43%, \( P = 0.03 \)).

The MITO-7 was an European trial involving 810 patients with stages IC to IV EOC. This trial was designed to compare a conventional tri-weekly scheduling system with a weekly regimen of carboplatin (an AUC of 2 mg/mL per minute) and paclitaxel (60 mg/m²), which were administered for 6 cycles and 18 consecutive weeks, respectively. The MITO-7 results were significantly different from the Japanese data, which found that weekly treatments were not associated with improved outcomes between the control and experimental arms [PFS: 17.3 versus 18.3 months; estimated 2-year survival rate: 78.9% versus 77.3%]; the quality of life reports and toxicity rates showed a better tolerability profile for the weekly scheduling. It should be noted that the scheduling used in the MITO-7 was quite different from that adopted in the JGOG 3016, as paclitaxel was given at a lower dose (60 mg/m² versus 80 mg/m²) and carboplatin was administered at an AUC of 2 mg/mL per minute every week in combination with paclitaxel.

Intraperitoneal Chemotherapy

The administration of intraperitoneal chemotherapy has also generated much controversy. By giving chemotherapy via the peritoneum, a pharmacological advantage is created but randomized trials have shown this approach to be toxic and direct comparisons of equivalent doses and schedules of agents administered intravenously to intraperitoneally have been scarce. The study that has generated the most disagreement is GOG 172. This study showed that intraperitoneal therapy increased overall survival from 49.7 months to 65.6 months compared to intravenous therapy (\( P = 0.03 \)) in patients with small-volume residual disease (<1 cm) following surgery. The intraperitoneal arm of GOG 172 also incorporated a higher dose of cisplatin and weekly treatments, thus, contaminating the results. A well-designed study of intraperitoneal therapy (NCT00951496) has completed enrolment and should report soon.

Targeted Therapy in Epithelial Ovarian Cancers

Although changes to both chemotherapy schedules and routes of administration are associated with improved survival, it appears that a therapeutic ceiling with these drugs has been reached. EOC still lags behind a number of common solid malignancies in terms of the sluggish incremental extension in OS during the last 20 years.

Anti Angiogenic Therapy

Bevacizumab with Frontline Conventional Chemotherapy: Bevacizumab, a monoclonal antibody that binds to the vascular endothelial growth factor (VEGF)-receptor ligand VEGF-A, has been most extensively investigated in clinical research.

The GOG-218 and International Collaborative Ovarian Neoplasm group (ICON7) trials evaluated the addition of bevacizumab to carboplatin/paclitaxel in first-line therapy.

ICON7 found that the greatest benefit of adding bevacizumab was seen in a higher-risk population with stage III–IV disease and residual disease greater than 1 cm. In this population, PFS at 42 months was 14.5 months with standard therapy alone and 18.1 months with bevacizumab added, with respective median OS of 28.8 and 36.6 months.

On the basis of these trials, the European Society for Medical Oncology’s clinical practice guidelines suggest bevacizumab in addition to chemotherapy in patients with poor prognostic features, such as stage IV or suboptimally debulked disease.

Bevacizumab in Relapsed Ovarian Cancer

In relapsed disease, both the OCEANS (Ovarian Cancer Study Comparing Efficacy and Safety of Chemotherapy and Anti-Angiogenic Therapy in Platinum-Sensitive Recurrent Disease) and AURELIA (Avastin Use in Platinum-Resistant Epithelial Ovarian Cancer) trials have evaluated the addition of bevacizumab to chemotherapy and demonstrated an improvement in PFS.

In AURELIA, in patients with relapsed platinum-resistant ovarian cancer, median PFS was 3.4 months with chemotherapy alone versus 6.7 months with the
addition of bevacizumab. Median OS was 13.3 months with chemotherapy alone versus 16.6 months with bevacizumab plus chemotherapy, which did not reach statistical significance, but 40% of patients receiving chemotherapy crossed over to single-agent bevacizumab on progression, compromising the OS data.

In the OCEANS trial, the addition of bevacizumab to carboplatin / gemcitabine in patients with relapsed platinum-sensitive ovarian cancer also improved PFS, with PFS of 12.4 months in the chemotherapy plus bevacizumab group versus 8.4 months in the chemotherapy plus placebo group. The preliminary analysis did not demonstrate an OS difference, at 33.3 and 35.2 months for the bevacizumab and placebo groups, respectively. The large crossover in these trials also significantly affected the interpretation of OS data.

Nintedanib

Nintedanib was the first triple angiokinase inhibitor developed with the principle of impeding tumor angiogenesis at multiple levels through targeting VEGF, fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF).

A double-blind Phase III study in the first-line setting compared nintedanib combined with either carboplatin/paclitaxel or placebo and confirmed significantly prolonged PFS with the nintedanib / chemotherapy group (18.3 versus 16.6 months).

Trebananib

Trebananib developed to block Ang-1 / Ang-2 and Tie-2 binding (angiopoietin signaling axis) has garnered some interesting results in a series of consecutive TRINOVA Phase III studies for patients with primary or relapsed EOC. The first of these trials (TRINOVA-1; n=919) focused on the combination of paclitaxel with either trebananib or placebo with the trebananib-containing group associated with significant extension in PFS.

Pazopanib

Pazopanib is a multifunctional tyrosine kinase inhibitor that principally targets VEGFR (VEGFR-1, VEGFR-2, VEGFR-3), platelet derived growth factor receptor (PDGFR) (PDGFRα and PDGFRβ), fibroblast growth factor receptor (FGFR), and c-kit. Additional targets include colony-stimulating factor 1, lymphocyte-specific tyrosine kinase, and interleukin (IL)-2-inducible T-cell kinase.

Although a plethora of studies are ongoing for recurrent/resistant EOC, there has been some recent excitement generated from a Phase III study investigating pazopanib as a maintenance therapy in the first-line setting (AGO-OVAR 16, a Phase III randomized, placebo-controlled trial of pazopanib versus placebo as maintenance after first-line treatment for stages II–IV EOC). Interestingly, maintenance pazopanib significantly prolonged median PFS compared with placebo by 5.6 months (17.9 versus 12.3 months, respectively). Inevitably, this was slightly offset by grade 3/4 toxicities, with hypertension (30.8%), neutropenia (9.9%), hepatotoxicity (9.4%), and diarrhea (8.2%) being the most frequently encountered. OS advantages are yet to be seen.

Cediranib

Cediranib (oral anti-VEGFR-1, VEGFR-2, VEGFR-3, and c-kit) also serves as an effective therapeutic strategy with some favorable results generated from both Phase II and III studies.

The Phase III ICON6 trial equally randomized to standard chemotherapy, concurrent chemotherapy and cediranib, or concurrent therapy followed by maintenance cediranib. With restricted mean survival times the concurrent maintenance group conferred significant superiority over standard treatment in terms of both PFS (12.6 versus 9.4 months) and OS (20.3 versus 17.6 months).

Sunitinib and Sorafenib, multi-tyrosine kinase inhibitors, have shown disappointing results in small trials.

PARP Inhibitors

Female carriers of germline mutations in BRCA1 and BRCA2 are at high risk of developing ovarian cancer, with lifetime risks of nearly 40% and 11%, respectively. Mutation in BRCA1 or BRCA2 is seen in 10%–20% of ovarian cancers, and defects in other homologous recombination pathway genes in another 6%.

However, in the most common form of malignant epithelial ovarian cancer, HGSC, defects in homologous recombination occur in up to 50% of cases, including germline or somatic loss-of-function mutations of BRCA1 or BRCA2, epigenetic silencing of BRCA1. These patients generally exhibit better outcomes compared with patients with sporadic ovarian cancer, including improved platinum sensitivity and overall survival.
Olaparib has also been investigated as maintenance monotherapy for platinum-sensitive relapsed HGSC. In a randomized placebo-controlled Phase II trial, olaparib demonstrated a significant improvement in PFS of 8.4 months compared with 4.8 months with placebo.

**Targeting Type I Ovarian Cancer**

**Low-Grade Serous Ovarian Carcinoma:** Low-grade serous carcinoma (LGSC) of the ovary, although generally having a more indolent course, has notably extremely poor response rates to chemotherapy. The LGSC group is frequently characterized by driver mutations in the MAPK pathway, which has created a surge of interest in small molecules targeting this pathway.

The MEK inhibitors have been trialed in this population with some success. The GOG Phase II trial of selumetinib (a MEK 1/2 inhibitor) in 52 patients with recurrent LGSC reported a response rate of 15% and 65% of patients with stable disease.

**Ovarian Clear Cell Carcinoma:** Ovarian clear cell cancer (OCCC) patients also experience disappointing responses to chemotherapy, whether it is standard carboplatin/paclitaxel or alternative regimens, such as irinotecan/cisplatin.

From a genomic perspective, up to 50% of OCCCs are characterized by somatic inactivating mutations in ARID1A and more than 30% of cases consist of activating mutations in PI3K (PIK3CA). Although a small Phase II study is currently investigating the addition of temsirolimus (mTOR inhibitor), there is paucity of trials confirming the efficacy of targeting the PI3K signaling pathway in OCCC.

**Mucinous Ovarian Carcinoma:** In parallel with LGSC and clear cell subtypes, mucinous ovarian carcinomas are also more resistant to carboplatin/paclitaxel than HGSC. As these tumors have more biological similarities to colorectal tumors, the GOG0241 study was conceived to assess the appropriateness of applying standard regimens in this disease to mucinous ovarian carcinomas. But this Phase III study was suspended because of poor patient accrual.

**Endometrioid Ovarian Carcinoma:** Endometriosis is associated with endometrioid ovarian carcinomas, which also exhibit distinct pathways of tumorigenesis. Endometrioid ovarian carcinomas have been found to harbor a range of mutations in cell signaling pathways, including activating mutations in CTNNB1 and PIK3CA (approximately 20% mutation rate), in addition to PTEN (~20%). Given this, it is possible that the mTOR inhibitors (Temsirolimus) may have efficacy in this population and are being studied.

**Conclusions**

In comparison to the significant advances in survival witnessed in other malignancies with targeted therapies, the progress in case of EOC has been relatively sluggish. Bevacizumab appears promising in poor prognosis advanced EOC with macroscopic residual disease. Nintedanib and trebananib have shown improvement in PFS in Phase III trials. Pazopinib, cediranib and the PARP inhibitor olaparib appear promising as maintenance therapies following combination chemotherapy in advanced EOC. In advanced Type I EOC, the results so far have not been encouraging.

**References**


(Dr U D Bafna, Professor and Head, Dept of Gynecologic Oncology, Kidwai Memorial Institute of Oncology, Bengaluru)
Introduction

Diagnosis of cancer in a young patient can be a devastating situation. Cancers by themselves, and the treatments used to cure them have profoundly negative effects on the fertility of young patients. Major diagnostic and therapeutic advances have greatly improved survival rates of cancer patients over the past years. One of the major sequelaes of cytotoxic chemotherapy and/or radiotherapy in young girls and women is premature ovarian failure which depends on age and follicular reserve of the patient, and the type and dose of the drugs used. Even though majority of young cancer survivors are interested in parenthood, very few access fertility preservation techniques prior to treatment. While cancer elsewhere in the body affects reproductive system mainly due to the effects of therapies, cancer of reproductive organs is a difficult situation due to the complexity involved. Several strategies aimed at the preservation of fertility have been developed in these groups of patients; gonadal protection or fertility-sparing approaches use both medical and surgical strategies.

Medical Strategies

Hormone Suppression: Both GnRH agonists (GnRHas) and antagonists (which function with identical end-results) have been used in gonadal protection during cytotoxic chemotherapy. GnRHas simulate a pre-pubertal hormonal milieu, and through this mechanism, and/or possibly others, might minimize the gonadotoxic effect of chemotherapy and increase the chances of spontaneous ovulations (1). It is essential to remember that treatment with GnRHas should begin at least one week before the beginning of chemotherapy as the initial flare-up effect causes undesirable ovarian stimulation. The application should continue in the form of depot-injections during the whole duration of chemotherapy, so that the down-regulating effect remains for at least two weeks after the chemotherapy. Although this therapy is found to have significant protective effect on post-chemotherapy ovulation and resumption of menses, subsequent pregnancy rates have been inconsistent (2). An interesting downside of GnRHas was hypothesized by Emons et al (3), who noted that a variety of cells, including those of the breast, ovary and endometrium express GnRH receptors and the direct effects of GnRHas on human cancer cells are not sufficiently understood. These receptors mediate several effects, such as inhibition of proliferation, induction of cell-cycle arrest, and inhibition of apoptosis, induced by cytotoxic drugs. So they reported that GnRH, a therapy concomitant with cytotoxic chemotherapy, might actually reduce the efficacy of chemotherapy.

Progestins and Endometrial Cancer

Endometrial cancer in a young nulliparous woman desirous of pregnancy is a difficult situation for the treating gynecologic oncologist. Standard management would involve removal of the uterus and ovaries which will obviously preclude any hope of pregnancy. Fortunately this is not a common scenario; less than 10% of endometrial cancers occur in women less than 40 years. Fertility sparing options using conservative treatment is possible only in well-differentiated early endometrial cancer in the absence of any myometrial invasion or adnexal disease seen on imaging. These options include treatment with hormones with different routes of administration based on hormone sensitivity of these tumors. Hormones include progestogens, antiestrogens, GnRHas, and aromatase inhibitors, while the most widely used are progestogens, especially high dose medroxy progesterone acetate (600 mg/day orally) and megestrol acetate (160-320 mg/day orally). Endometrial sampling 3 monthly has to be done to assess the response to treatment. Side-effects of such high dose progestins include thrombus formation, mood alterations, headaches, weight gain and breast pain and/or tenderness. To circumvent these side effects due to systemic high dose of progestins, the progesterone-releasing IUD is used to generate a localized effect within the endometrium. Response to treatment has been high (rates of 73%–81%), but not absolute. Recurrence rates are also appreciable (18%–40% with follow-up times up to 358 months)(4). Assisted reproductive technologies may be necessary for conception in these women after achieving complete remission (4). The biggest concern with conservative management of endometrial carcinoma is disease progression while on treatment or after initial response to medical treatment. Women opting for conservative management should be aware that hormonal therapy is not the standard form of management and regular follow-up is essential. Potential adverse oncologic outcome should be considered before deciding for conservative treatment.
Surgical Strategies

Ovarian Transposition and Gonadal Shielding:
Irradiation to the ovaries can be quite damaging, and successful ovarian protection in this circumstance has been achieved through ovarian transposition. In this technique, the ovaries are transposed, laparoscopically or in a laparotomy, to a location outside of the field of radiation. This procedure not only has the advantage of sparing fertility, but also of maintaining ovarian function and evading premature menopause. The procedure precludes spontaneous pregnancy, requiring ART.

Cervical Cancer

Although 40% of all cases of invasive cervical cancer in the United States are diagnosed in women younger than 45 years of age, the scenario in India is not the same. In our country, women complete their family quite early and the need for fertility preservation in treatment of cervical cancer is not that frequent. Standard treatment of invasive cancer in early stages includes radical hysterectomy and pelvic radiotherapy, both of which are incompatible with normal fertility. Cervical conization, simple trachelectomy (cervicectomy) and radical trachelectomy (resection of parametrial tissue with cervix) are being used in women with early stage disease (5). Radical trachelectomy combined with pelvic lymphadenectomy, open or laparoscopic has been proposed by Dargent et al. as a conservative treatment for cervical cancer in stage 1A or 1B tumors (less than 2 cm) (5). It is a must to assess the pelvis for the extent of disease and perform pelvic lymphadenectomy before proceeding with radical trachelectomy. They suggest that the vaginal approach limits the parametrial resection to tissue in the medial half of the broad ligament, restricting radical vaginal trachelectomy to those women with tumors less than 2 cm and with invasion of less than 10 mm. Because the abdominal radical trachelectomy procedure appears to be equivalent to the traditional radical procedure, this limitation may not be applicable to abdominal trachelectomies. Successful pregnancies after abdominal radical trachelectomy procedure have been reported. In a study of 236 women reported to have undergone radical vaginal trachelectomy, 63 live born babies have been reported (6). Although there were no recurrences in patients treated with abdominal radical trachelectomy, concerns about long term adverse events limit the possibility of recommendation of this technique for general use. Adverse effects of the treatment include cervical stenosis, dysmenorrhea, infertility, hematometra, hematosalpinx, or endometriosis. Obstetric adverse events like second trimester miscarriages and preterm births have led to propose a more conservative treatment, the simple trachelectomy for very early lesions.

Ovarian Cancer

In the case of ovarian neoplasms, certain factors like tumor histologic subtype, stage, extent of disease, pre-existing ovarian reserve, and willingness of the patient decide the possibility of fertility-sparing treatment. But it is extremely important to remember that we are handling a potentially recurrent disease and the patient should be counselled accordingly regarding the need for strict follow-up.

The most suited ovarian tumors for fertility-sparing surgery are non-epithelial malignant ovarian tumors, particularly germ-cell tumors. Germ-cell tumors are routinely managed by conservative surgery; unilateral salpingo-oophorectomy, but it has to be emphasized about the need for adequate staging. Cure rates are quite high (90%–95%), and despite the usual need for post-operative chemotherapy, resumption of menstruation occurs in at least 80% of patients (7).

Even though epithelial tumors occur at a later age, borderline ovarian tumors, neoplasms of contro-versial biologic potential and clinical significance, occur at a younger age and deserve a special mention. More than 30% of borderline tumors of the ovary affect women under 40 years of age. They share a risk profile similar to that of malignant ovarian tumors, but are associated with a much better prognosis. Surgical staging followed by conservative surgery may be considered among young women who wish to preserve fertility in borderline cases. Although recurrence rates for early borderline tumors have been reported to be similar to or slightly higher than those for traditional surgical management, survival rates are not compromised as recurrences are well-treated with repeat and definitive surgical management (8).

A small proportion of invasive epithelial cancer occurs in women younger than 35 years of age. Conservative treatment can be considered for young women who desire to preserve their fertility and have stage 1A well differentiated disease. Unilateral salpingo-oophorectomy along with adequate surgical staging is considered an appropriate therapy in these women. The results of unilateral salpingo-oophorectomies have been compared with hysterectomies and bilateral salpingo-oophorectomies, and five-year survival rates are found to be similar in both groups (33).
Other Fertility Preservation Strategies

Advances in medicine and technology have led to increasing survival rates in patients affected by oncological diseases. This is paralleled by advances in reproductive medicine, leading to the development and increasing use of various fertility preservation techniques. For children, adolescents, women without partners, or women wishing to retain their ability for paternity selection at the time of fertilization, oocyte cryopreservation is the only fertility-sparing option. Embryo cryopreservation is a widely used method of fertility preservation and has been available to cancer patients for years. Cryopreservation and transplantation of ovarian tissue seems to be the most promising way of future fertility (10). As of now, the only established method for fertility preservation in female cancer patients is in vitro fertilization and embryo cryopreservation.

Conclusion

Various medical and surgical strategies have been developed to preserve fertility in young women afflicted with cancers, especially gynecological cancers (Table 1). GnRHas produce a pre-pubertal hormonal milieu reducing the gonadotoxic effect of chemotherapy. Progestins play an important role in the conservative management of early stage well differentiated endometrial cancer. Radical tracheectomy and more recently even simple tracheectomy have been used with promising results for early stage cervical cancer. Conservative surgery with adequate surgical staging can be used in germ-cell ovarian tumors, borderline epithelial ovarian tumors and early invasive cancers. In all these women, it is extremely important to emphasize on the need for strict follow-up. Ovarian transposition, gonadal shielding, oocyte cryopreservation and embryo cryopreservation are being used in women with cancers before embarking on definitive treatment. Ovarian tissue cryopreservation and transplantation after cytotoxic chemotherapy are found to be a promising options in future.

References


(Dr Veena P, Associate Professor, Dept of Obstetrics and Gynecology, JIPMER, Puducherry)
PERSPECTIVE

DEFINING THE ROLE OF RADIOTHERAPY IN CARCINOMA VULVA

Background

Cancers of the vulva and especially squamous cell carcinomas, a dominant type, are not a common occurrence[1]. They account for less than 5% of all gynecological cancers with a peak incidence in the late 6th or early 7th decade of life [1]. The disease spreads by both local extension and lympho-vascular embolization. Studies, such as those by Kelley et al [2] on incidence of metastatic disease in patients with 1 mm or less invasion; or by Cherry & Glucksman [3] on en bloc tumor resections and biopsies, found very low incidence of lymphatic tumor emboli. This led to a sub-classification of stage I disease, wherein nodal dissection could be safely omitted. Since the last 60-70 years, radical vulvectomy and inguino-femoral node dissection has been the standard treatment for squamous cell carcinomas of the vulva [4]. Lymph-node involvement represents the most important prognostic factor for recurrence and survival [5]. The 5-year disease-specific survival in patients with negative inguino-femoral lymph nodes is 70-93% but in node positive disease, it is 25–41%. Lymphatic metastases from lateralized lesions do not cross over without ipsilateral metastatic disease while spread from midline lesions can be identified in either or both groins. Pelvic lymph-node dissection has been routinely performed in patients with a node positive groin dissection, but in recent years there has been a shift towards less morbid surgery with an increasing role of adjuvant irradiation and now recently even preoperative irradiation or chemo-radiation.

Discussion: Irradiation in Vulvar Cancers

In general there is a broad consensus that radiotherapy in the adjuvant or sometimes even definitive setting may need to be given in specific risk groups to account for risk of local and regional recurrence, and to improve outcomes in patients with advanced disease. Patients with nodal disease, whether in intermediate stage group or advanced stage group require adjuvant radiotherapy as they would otherwise have a significantly impaired prognosis [6]. It has been seen that 20–30% of patients presenting with inguino-femoral nodal disease also have involved pelvic lymph nodes and this risk increases proportionally with the number of involved groin nodes. Other indicators of poor prognosis include two or more nodes, extracapsular spread and large size of the metastases (> 10 mm). In fact a recent analysis reported that compared to node negative patients, even a single positive node led to impaired prognosis. Based on findings of meta-analyses, the recommendations of both FIGO and UK based Royal College of Obstetrics and Gynecologists (RCOG), have been put forward (Table 1). In the next sections, we shall discuss the role of irradiation in the different settings of vulvar cancer.

Adjuvant Irradiation / Chemo-Radiation for Nodal Disease or Nodal Boost: A substantial clinical benefit of adjuvant radiotherapy has been clearly described by the landmark GOG 37 Trial [6], especially for patients with two or more lymph-node metastases. A subset analysis of the GOG trial indicated a survival advantage for patients with palpable groin nodes or having more than one pathologically positive groin node. These results have provided level-1 evidence on the use of postoperative radiotherapy for this patient population. The role of radiation in patients with a single intra-capsular metastasis remains controversial [7]. Also role of surgery with pelvic lymphadenectomy in the case of inguino-femoral nodal disease has been debated as the only available randomized trial has reported that pelvic radiotherapy is superior to surgery regarding overall survival [6]. Recommended dose for adjuvant nodal irradiation is 45-50 Gy by conventional techniques. There is, however, not much literature on the role of chemo-radiation in adjuvant setting. Han and colleagues compared survival rates in patients who received chemo-radiation or radiation alone as primary treatment or in an adjuvant setting. They forced that while the survival rates were better in the group receiving chemo-radiation, though the difference was not statistically significant [8]. Thus after the GOG 37 trial results, pelvic radiation therapy and irradiation of the involved groin have become the standard of care for patients with positive groin dissections.

Adjuvant Irradiation / Chemo-Radiation for Perineum: Current recommendations based on GOG studies for postoperative radiation treatment of the perineum include close or positive margins, depth of invasion more than 5 mm, lympho-vascular invasion, or an infiltrative pattern of growth. Studies such as those by Heaps et al [9] on resection margins (higher risk below 8mm); GOG Protocol 36 [10] on tumor size and LVSI
larger than 4 cm and lympho-vascular invasion associated with 21% risk of local recurrence compared to 9% without) have been useful in framing indications. Advanced lesions (T3, T4) have been found to benefit more from doses higher than 60 Gy with improvement in local control from 62% to 80% [11]. Re-excision may not be sufficient in view of the negative prognostic implications of many risk factors, and therefore in cases with close margins along with factors such as depth of invasion >5 mm and/or positive lympho-vascular space invasion, adjuvant radiation should be considered.

**Elective Irradiation / Chemo-Radiation for Groin Nodes:** The standard treatment of vulvar cancer with a clinically negative groin has been radical vulvectomy or wide local tumor excision with bilateral inguino-femoral node dissection. However, as mentioned before in cases where the groin is clinically negative, less than 20% patients are expected to have pathologically proven nodal disease and would have, therefore, unnecessarily undergone nodal dissection and its attendant morbidities. A reasonable alternative could be elective groin irradiation. An early report from the University of Florida treated patients with N0-1 nodes with elective bilateral groin irradiation to 45 Gy in 5 weeks and observed no groin failures or treatment complications. After the decision of adjuvant radiotherapy from the GOG 37 trial and in view of the high morbidity associated with radical inguinal node dissection; the GOG compared in an RCT (GOG 88), radical vulvectomy and elective inguinal node radiotherapy with standard superficial and deep inguinal node dissection [12]. This trial was, however, stopped after the interim analysis revealed an unacceptably higher rate of nodal failure and death in the radiotherapy arm. Subsequent analysis of the radiotherapy arm showed

**Table 1: FIGO/RCOG Recommendations for Radiation Therapy / Chemotherapy in Vulvar Cancers**

<table>
<thead>
<tr>
<th>Clinical Situation</th>
<th>RCOG Recommendation</th>
<th>FIGO Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early stage disease</td>
<td>Surgery is primary modality with sentinel nodal dissection considered adequate to assess nodal disease (Category B)</td>
<td>Surgery considered complete therapy. Role of lymph node dissection debatable. Sentinel node dissection considered adequate to decide on further nodal dissection (Category B)</td>
</tr>
<tr>
<td>Stage III disease with groin nodes</td>
<td>Surgery is the cornerstone of therapy for the groin nodes in women with vulval cancer (Category A) Individual women who cannot be optimised to surgery can be treated with primary radiotherapy</td>
<td>Surgery primary modality of therapy. Nodal dissection may be limited to inguino-femoral dissection. Pelvic lymphadenectomy is associated with increased morbidity (Level 1)</td>
</tr>
<tr>
<td>Adjuvant RT to inguino-femoral nodes</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Adjuvant RT to perineum</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Elective RT to inguino-femoral nodes</td>
<td>-</td>
<td>Elective irradiation of groin nodes not recommended outside trial protocol and only in low risk cases with adequate CT based treatment planning. This may be useful and less morbid substitute for bilateral groin dissection in low risk patients but cannot be strongly advocated at this time without further prospective evaluation</td>
</tr>
<tr>
<td>Definitive chemo-RT</td>
<td>Individual women who cannot be optimized to surgery can be treated with primary radiotherapy</td>
<td>Reported in many single institution series with high response rates. Role vis-à-vis pre-operative chemo-RT is still debatable. Those patients not fit for surgery can also be considered for radical RT (Level 2b)</td>
</tr>
<tr>
<td>Pre-operative chemo-RT</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Recurrent disease</td>
<td>Primary and recurrent vulval cancer does respond to chemotherapy but responses are variable and toxicity may be a problem in this population of patients (Category C)</td>
<td>Better prognosis even in recurrent disease include smaller primary recurrence (5 cm or less), size of the groin recurrence (2 cm or less), lack of perineal skin involvement, lack of tissue necrosis, and higher radiation doses. Aggressive treatment of recurrent vulvar cancer only for patients with localized disease and reasonable performance status</td>
</tr>
<tr>
<td>Palliative radiotherapy</td>
<td>-</td>
<td>For advanced local disease, metastatic spread, or significant co-morbidities in patients to palliate symptoms such as bleeding, ulceration, necrosis, pain, and malodourous discharge</td>
</tr>
</tbody>
</table>
that there was an under dosing of the nodal bed because of the single anterior field used and dose prescribed to a depth of 3 cm, whereas pelvic CT imaging shows that average depth of femoral nodes was about 6 cm. This could be the reason for the high failure rates [13]. In fact in the GOG trial 37, radiotherapy was delivered by AP-PA portals and was able to adequately cover the deep inguinal nodes [6]. Thus presently elective irradiation of groin nodes is not recommended outside a trial protocol and that also only in low risk cases and with adequate CT based treatment planning to completely cover the nodal bed. This approach may be useful and a less morbid substitute for bilateral groin dissection in low risk patients but there is no recommendation for routine clinical use without further prospective evaluation.

**Neoadjuvant Chemo-Radiotherapy:** 5-FU or cisplatin alone or in combination with or without mitomycin-C has been most commonly used in vulvar cancer. A GOG study in patients with advanced vulvar cancer examined outcomes of preoperative chemo-radiotherapy (4,760 cGy with concurrent 5-FU) in reducing extent of surgery [14]. Nearly half the patients completing treatment (46.5%) had no visible vulvar disease at the time of planned surgery, and only 2.8% had residual unresectable disease. Similar series have been reported from University of California and Loma Linda University. This approach would be desirable for midline tumors in which excising any residual disease could still affect clitoral or sphincter function, despite tumor regression.

**Definitive Chemo-Radiation:** The use of definitive chemo-radiation has been reported in many single institution series with high response rates even in large sized tumors [15]. It is still debatable whether definitive chemo-radiation is better than preoperative chemoradiation and surgery mainly because of the paucity of large randomized trials in this setting and because of the low incidence of vulvar cancers and as most indications come from observational trials. There is now encouraging evidence for definitive chemoradiation to allow organ preservation in place of extensive mutilating surgery for locally advanced vulvar cancer [14]. Elderly patients or those medically unfit for radical surgery can also be successfully treated with radiation therapy alone. Several sizable series from the United States and Europe have noted long term survival rates of between 20% and 45% in advanced cases.

**Radiation for Recurrent Disease:** Treatment in recurrent cases is difficult because of previous surgery/irradiation. These cases can be salvaged occasionally with external beam radiation, sometimes in combination with radiation implants. Failure in the groin is almost never salvaged whereas perineal failures can be successfully managed depending on the extent of disease. Factors indicating better prognosis even in recurrent disease include smaller primary recurrence (5 cm or less), size of the groin recurrence (2 cm or less), lack of perineal skin involvement, lack of tissue necrosis, and higher radiation doses. Aggressive treatment of recurrent vulvar cancer should only be reserved for patients with localized disease and with a reasonable performance status.

**Palliative Radiotherapy:** It is indicated for advanced local disease, metastatic spread, or significant co-morbidities in patients to palliate symptoms such as bleeding, ulceration, necrosis, pain, and malodorous discharge. Palliative regimens, such as 2,500 cGy in 10 fractions are usually recommended.

**Techniques and Sequelae of Irradiation:** Treatment volume usually depends on management of the nodal bed. When treating the vulva alone, an appositional perineal field is used with the patient in the lithotomy position. The beam energy used should cover the required depth. If the tumor cannot be adequately encompassed, an anterior-posterior photon field is used with the patient in the frog-leg position to minimize dose to the inner thighs. A bolus is used to ensure full dose to the mucosa and skin where indicated. In preoperative radiation treatment, portals include the groin, perineum, and low pelvic lymph-nodes, while in the adjuvant setting, anterior-posterior fields are used to cover both the vulvar and nodal bed in one treatment portal. In cases where this could result in irradiation of significant normal perineal tissue, a central shield is placed in the anterior-posterior fields and a direct perineal field used to treat the vulva. When electrons are used for the perineal field, care needs to be taken as overlap of divergent beams can create hot spots, a critical area being the medial divergence of the anterior/posterior photon beam into the perineal field.

The total dose for definitive vulvar irradiation should be 6200 to 6400 cGy, with the dose tailored to the size of the primary. When treating with definitive chemoradiation, fraction sizes of 180 cGy are used which could
be reduced to 160 to 170 cGy with twice daily treatments if vulva is also included in the field with concurrent chemotherapy on days 1 - 4 in weeks 1, 3 and 6 of irradiation. In the pre-operative or adjuvant setting, a dose of 4000 to 5000 cGy with a fraction size of 180 to 200 cGy is used. When high-risk features are present, such as extracapsular extension or positive margins, dose escalation to 60 Gy or the addition of concurrent chemotherapy may be considered. Acute reactions, such as erythema, full-moist desquamation, and associated perineal discomfort, are expected during radiation and usually resolve 3 weeks after treatment completion. With concurrent 5-FU, myelo-suppression, mucositis, rash, and hand-foot syndrome can occur. Potential late toxicities include vulvar fibrosis, atrophy, telangiectasia, ulceration and necrosis.

**Brachytherapy:** Interstitial implantation may be a treatment option for patients with locally advanced or recurrent vulvar disease or in medically inoperable patients [16]. It is especially useful for lesions near the clitoris or urethra where surgery would definitely result in loss of organ function. The potential morbidities include fistula formation and ulceration due to non-uniform dose distribution and hot spots. CT planning prevents this by proper anatomical assessment of needle placement as well as dosimetric analysis.

**Future Perspectives:** An evolving body of literature is pointing towards greater acceptability of preoperative chemo-radiation to reduce morbidity. The question whether surgery could be altogether avoided by giving radical chemo-radiation needs to be studied in the following contexts: comparison with pre-op chemo-radiation, previous bad experience with GOG 88 trial which, however, was due to incorrect radiotherapy delivery rather than non-effectiveness of radiotherapy. Availability of newer radiotherapy techniques, such as IMRT, would enable single field treatment of primary and nodes while enabling gross disease dose escalation through simultaneous integrated boost. Additionally, optimization of dose delivery with treatment planning software and improved imaging should permit individualized radiation therapy. Addition of newer molecules such as erlotinib and their role with irradiation, is also being studied.

**Conclusion**

Clinical management of patients with vulvar cancer is challenging and highly dependent on the tumor stage. The extent of surgical resection and the indication for adjuvant treatment have to be balanced with psychosocial aspects. In early stage disease (FIGO I–II), therapy involves surgical resection of the primary tumor and staging of the groin lymph-nodes. In intermediate-stage vulvar cancer (FIGO III), radical lymphadenectomy and adjuvant therapy, such as radiation or chemo-radiation, have to be included in the treatment protocol. Radiation, often with concurrent chemotherapy, is now becoming an integral part of disease management through attempts to minimize surgical morbidity and improve treatment outcomes. For locally advanced or metastatic vulvar cancer (FIGO IV), neoadjuvant or definitive chemo-radiation is now being considered. Newer radiotherapy techniques can help in dose escalation and normal tissue sparing.

**References**


**NEW TECHNOLOGIES**

**Early Detection of Ovarian Cancer**

Scientists at Medical University of Vienna, Austria have developed a “three-way” catheter which may be a potential tool in early detection of ovarian cancer. The catheter prevents irrigation liquid / lavage of the uterine cavity from draining into the abdominal cavity and can be harvested virtually painlessly. The researchers have established an approach for lavage of the uterine cavity to detect shed cancer cells. The lavage was used to obtain samples from patients and was further examined for the presence of somatic mutations using massively parallel sequencing (next-generation sequencing) and in a subset, singleplex analysis. Identification of specific mutations in 80% of cases could be observed, thereby revealing the presence of tumor cells in the irrigation fluid. This study proved that tumor cells from ovarian neoplasms are shed and can be collected via lavage of the uterine cavity and examined for the early diagnosis. This is an important development, since ovarian cancer has virtually no symptoms and is only discovered quite late in around three-quarter of all cases.

*(Journal of Clinical Oncology, Nov 2015)*

**New Cervical Brachytherapy Technique**

According to researchers at University of Iowa Hospitals and Clinics, USA, a new technique of brachytherapy, using a shield rotating in a corkscREW pattern inside a tube-shaped intrauterine applicator, could improve treatment outcomes by increasing radiation dose to tumors and decreasing toxicity. The existing cervical brachytherapy technique involves depositing doses of radiation directly in tumors using the sources that deliver radiation uniformly around the source. Hence, the ability to personalize treatment gets limited due to the incapability to deliver a desired tumor dose because of limitations imposed by nearby healthy tissues. However, the new technique improves upon the existing technology by fitting a rotation shield to the source catheter that delivers radiation to the tumor. This shield rotates around the radiation source following grooves in the inner wall of the applicator that are shaped like a series of corkscrews. This new method would allow physicians to provide patients personalized radiation therapy by choosing different grooves to guide treatment and rotating the shield to block the radiation from reaching healthy tissues.

*(Medical Physics, Nov 2015)*
**GLOBE SCAN**

**Mutation Spectrum of Endometrial Carcinomas**

Somatic POLE mutations have been found in a subset of endometrioid ECs, particularly in FIGO Grade 3 tumors while POLD1 mutations are reportedly rare in ECs. While it has been suggested that POLE mutation confers good prognosis, the data remains conflicting. Our study aims to determine the mutation spectrum of somatic and germline POLE and POLD1 gene mutations in South East Asian (SEA) women with FIGO Grade 3 endometrioid ECs. Forty-seven patients diagnosed with FIGO Grade 3 endometrioid EC, diagnosed between 2009 and 2013, were included. Next generation sequencing (NGS), using formalin fixed embedded (FFPE) tissue was utilized to sequence tumor and matched normal tissue. Pathogenic POLE (somatic or germline) and POLD1 (germline) mutations were detected in 29.7% (14/47) and 4.3% (2/47) patients, respectively. Three pathogenic germline mutations, one POLE and two POLD1, were novel. Pathogenic germline and somatic POLE and POLD1 mutations were associated with 100% recurrence-free survival. In contrast, among the wild-type POLE and POLD1 patients, 25% (8/32) had recurrence with 15.6% (5/32) subsequently dying of the disease. Somatic POLE-mutated tumors were more commonly associated with microsatellite stable (MSS) ECs (83% vs 49%; p=0.04) and peritumoral lymphocytic infiltration (75% vs 42%; p=0.05). All tumors with tumoral infiltrating lymphocytes exhibited peritumoral lymphocytic infiltrate but not vice versa. Mutations in POLE and POLD1 in SEA women with Grade 3 endometrioid ECs are associated with improved recurrence-free survival. (Singapore: Gynecol Oncol, Dec 31 2015)

**Recurrent Ovarian Cancer**

Ovarian cancer is the 5th most common cancer found in women in the UK. The stage of the disease at diagnosis is the single most important determinant of ovarian cancer survival, as many patients only present with advanced disease. Treatment of ovarian cancer involves a combination of ‘upfront’ primary surgery followed by chemotherapy. Not all patients can continue with platinum combination therapies due to loss of activity or toxicity-related issues, including hypersensitivity, neurotoxicity, alopecia and ototoxicity. Therefore, the choice of second-line chemotherapy must take into account factors, such as platinum-free treatment interval (PFI), patient’s performance status, current symptoms, history of and likely future toxicities while on chemotherapy, dosing schedule requirement, and cost of treatment. A consensus in 2010 established four distinct subgroups within the ROC patient population based on the PFI: (platinum sensitive <12 months; partially platinum sensitive 6-12 months; platinum resistant <6 months, and refractory disease, 4 weeks). Within patients with platinum sensitive disease, those with partially platinum sensitive disease remain the most clinically challenging to manage effectively. Non-platinum based combination therapies, in particular trabectedin with pegylated liposomal doxorubicin (PLD), offers new options together with a significant survival advantage relative to PLD alone for these patients. (UK: EJC Suppl, Dec 2014)

**Assisted Reproductive Techniques**

The trend toward late childbearing has made fertility preservation a major issue for women who face gynecological cancer. New techniques in assisted reproductive medicine enable conception after primary treatment of these cancers. Here, the authors aimed to review the efficacy and safety of assisted reproductive techniques (ART) after fertility-preserving treatment of gynecological cancers. The authors conducted a systematic literature review of both prospective and retrospective studies in the PubMed, EMBASE, CENTRAL and SciSearch databases. In the retrieved studies, they evaluated live births, clinical pregnancies, overall survival and disease-free survival. They identified many prospective and retrospective studies on this topic, but no relevant randomized clinical trials. Fertility-sparing treatments with safe oncological outcomes are feasible in endometrial, cervical and ovarian cancer cases. After cancer treatment, ART seem safe and show variable obstetrical outcomes. Hence, after fertility-preserving treatment for gynecological cancers, ART can enable pregnancy to be achieved with apparent oncological safety. The success of such procedures should directly impact clinical practice and management of those patients who require fertility-sparing treatment. (Spain: Hum Reprod Update, Jan 12 2016)
EMERGING ROLE OF SYSTEMIC THERAPIES IN CARCINOMA ENDOMETRIUM

Introduction

Endometrial cancer is the most common gynecological malignancy in high income countries, with a 2 – 3% lifetime risk of developing the disease [1]. The incidence of endometrial cancer cases is very low in India, the highest being observed in Bangalore (ASR 4.2 per 100,000), while in Mumbai it is around 2.8 per 100,000 [2]. More than 90% of cases of endometrial cancer occur in women >50 years of age, with a median age at diagnosis of 63 years. However, 4% of women with endometrial cancer are younger than 40 years old, many of whom still wish to retain their fertility. The majority of endometrial cancers are diagnosed early (80% in stage I), with five-year survival rates of over 95%. However, five-year survival rates are much lower if there is regional spread or distant disease (68% and 17%, respectively) [3]. The median age at diagnosis is 61 years, with 20% diagnosed before menopause, including 5% who develop the disease before the age of 40 [3].

Chronic unopposed estrogenic stimulation is considered to be the main underlying risk factor. The most common presentation is per vaginal bleeding, and in two-thirds of cases it is diagnosed at an early stage, whilst in the remaining it presents with metastasis to lungs, liver, bone. The most common histology subtype is endometrioid adenocarcinoma, followed by serous and clear cell varieties. The purpose of this document is to review the risks and benefits of current treatment options and optimize treatment for women with endometrial cancer.

Staging of Endometrial Cancer

The staging of endometrial cancer is largely surgical, which was last updated in 2009 by the Cancer Committee of the International Federation of Gynaecology and Obstetrics (FIGO) [4] (Table 1).

Prognostic Variables in Endometrial Cancer

Although stage of disease is the most significant prognostic variable [4] there are a number of other factors which correlate with outcome within the same stage of disease. The factors which portend a poorer outcome are summarized in Table 2.

Treatment Paradigm in Carcinoma Endometrium

The cornerstone of treatment for endometrial cancer is total hysterectomy and bilateral salpingo-oophorectomy + peritoneal assessment + some form of regional lymph node assessment. Adjuvant treatment is required based on stage, grade, and range from vaginal brachytherapy to pelvic irradiation with an aim to reduce vaginal and pelvic recurrences. In advanced stage disease, surgery is performed only if negative margins are feasible, otherwise the treatment is palliative in intent with some form of systemic hormonal or chemotherapy. Table 3 summarizes the NCCN 2015 guidelines and the ESMO-EGO-ESTRO consensus guideline statement of 2015 on endometrial cancer [10, 11].

Treatment of Advanced Stage Endometrial Cancer

Need of Systemic Therapy: Patients with advanced stage endometrial cancer (defined as bulky FIGO stage

Table 1: FIGO 2009 Staging of Endometrial Cancer

<table>
<thead>
<tr>
<th>STAGE I</th>
<th>Tumour confined to the corpus uteri</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>No or less than half myometrial invasion</td>
</tr>
<tr>
<td>IB</td>
<td>Invasion equal to or more than half of the myometrium</td>
</tr>
<tr>
<td>STAGE II</td>
<td>Tumour invades the cervical stroma, but does not extend beyond the uterus</td>
</tr>
<tr>
<td>STAGE III</td>
<td>Local and / or regional spread of the tumour</td>
</tr>
<tr>
<td>IIIA</td>
<td>Tumour invades the serosa of the corpus uteri and / or adnexa</td>
</tr>
<tr>
<td>IIIB</td>
<td>Vaginal and / or parametrial involvement</td>
</tr>
<tr>
<td>IIIC</td>
<td>Metastasis to pelvic and or para-aortic lymph nodes</td>
</tr>
<tr>
<td>IIIC1</td>
<td>Positive pelvic nodes</td>
</tr>
<tr>
<td>IIIC2</td>
<td>Positive para-aortic lymph nodes with or without positive pelvic lymph nodes</td>
</tr>
<tr>
<td>STAGE IV</td>
<td>Tumour invades bladder and / or bowel mucosa, and / or distant metastases</td>
</tr>
<tr>
<td>IVA</td>
<td>Tumour invasion of bladder and / or bowel mucosa</td>
</tr>
<tr>
<td>IVB</td>
<td>Distant metastases, including intra-abdominal metastases and / or inguinal lymph nodes</td>
</tr>
</tbody>
</table>
III A – IV) or recurrent disease form a heterogeneous group that may present with local bulky disease, nodal disease, or distant metastases [4]. Surgical cytoreduction should only be considered when there are chances of achieving removal of all macroscopic residual disease. Patients with metastatic disease, even if resected to microscopic residual disease, have a high risk of recurrence, and warrant some form of adjuvant treatment [11, 12]. Radiation therapy reduces local recurrences; however, failures outside the radiation field are common. These aforesaid reasons support the need for systemic therapy in advanced stage endometrial cancer either as an adjuvant or salvage approach [11, 13].

**Options for Systemic Therapy:** The majority of patients with advanced or recurrent cancer will require some form of systemic therapy during the course of their disease. Systemic therapy consists mainly of hormonal therapy or cytotoxic chemotherapy. The choice between the types of systemic therapy depends on the histopathological characteristics of the tumor and clinical features of the individual patient [11,13]. Hormonal therapy is usually reserved for tumors with grade 1 or 2

### Table 2: Prognostic Variables in Endometrial Cancer

<table>
<thead>
<tr>
<th>Variable</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age [5]</strong></td>
<td>5 yr OS (early stage disease)</td>
</tr>
<tr>
<td>&lt; 40 y</td>
<td>96.3%</td>
</tr>
<tr>
<td>51-60 y</td>
<td>87.3%</td>
</tr>
<tr>
<td>61-70 y</td>
<td>78%</td>
</tr>
<tr>
<td>71-80 y</td>
<td>70.7%</td>
</tr>
<tr>
<td>&gt; 80 y</td>
<td>53.6%</td>
</tr>
<tr>
<td><strong>Histological type [6]</strong></td>
<td>Cancer related deaths</td>
</tr>
<tr>
<td>Serous (10%)</td>
<td>39%</td>
</tr>
<tr>
<td>Clear cell (3%)</td>
<td>8%</td>
</tr>
<tr>
<td><strong>Histological grade and myometrial invasion [7]</strong></td>
<td>Chance of pelvic nodal involvement</td>
</tr>
<tr>
<td>Grade 1, &lt; 1/3 myometrial invasion</td>
<td>3%</td>
</tr>
<tr>
<td>Grade 3, &gt; 1/3 myometrial invasion</td>
<td>34%</td>
</tr>
<tr>
<td><strong>Lymphovascular space invasion [8]</strong></td>
<td>Relative risk of death</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Hormonal receptor status [9]</strong></td>
<td>PR more stronger predictor of survival than ER</td>
</tr>
</tbody>
</table>

### Table 3: Treatment Paradigm for Endometrial Cancer

1. **NCCN 2015 GUIDELINES [10]**

<table>
<thead>
<tr>
<th>Stage</th>
<th>NCCN v2.2016</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STAGE I A</strong></td>
<td></td>
</tr>
<tr>
<td>Grade 1 without ARF</td>
<td>Observation</td>
</tr>
<tr>
<td>Grade 1 with ARF</td>
<td>Observation or VBT</td>
</tr>
<tr>
<td>Grade 2 or 3 without ARF</td>
<td>Observation or VBT</td>
</tr>
<tr>
<td>Grade 2 or 3 with ARF</td>
<td>Observation or VBT and/or pelvic RT</td>
</tr>
<tr>
<td>STAGE IB</td>
<td></td>
</tr>
<tr>
<td>Grade 1 without ARF</td>
<td>Observe</td>
</tr>
<tr>
<td>Grade 1 with ARF</td>
<td>Observe or VBT</td>
</tr>
<tr>
<td>Grade 2 without ARF</td>
<td>Observe or VBT</td>
</tr>
<tr>
<td>Grade 2 with ARF</td>
<td>Observe or VBT and/or Pelvic RT</td>
</tr>
<tr>
<td>Grade 3 without ARF</td>
<td>Observe or VBT and/or Pelvic RT</td>
</tr>
<tr>
<td>Grade 3 with ARF</td>
<td>Observe or VBT and/or Pelvic RT +/- CT</td>
</tr>
<tr>
<td><strong>STAGE II</strong></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>VBT and/or pelvic RT</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Pelvic RT and VBT</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Pelvic RT +/- CT and VBT</td>
</tr>
<tr>
<td><strong>STAGE III A</strong></td>
<td>CT +/- Pelvic RT or pelvic RT +/- VBT</td>
</tr>
<tr>
<td><strong>STAGE III B – III C</strong></td>
<td>CT and/or tumour directed RT</td>
</tr>
<tr>
<td><strong>STAGE IV A – IV B</strong></td>
<td>CT +/- RT</td>
</tr>
</tbody>
</table>

**ARF -** Adverse risk factors (age, positive LVS, tumor size, lower uterine/cervical involvement); **VBT -** vaginal brachytherapy, **RT -** radiation therapy, **CT -** chemotherapy
endometrioid histology, positive ER/PR status, and in absence of rapidly progressing disease [11]. Chemotherapy, on the other hand, is preferred as an upfront systemic modality in patients with visceral involvement or rapidly progressive disease, where a rapid response is required [11,13].

**Evolution of Systemic Chemotherapy:** Endometrial cancer is a relatively chemo-sensitive disease, with anthracyclines, platins and taxanes shown to be the most active agents [11,13].

Historically, doxorubicin showed response rates (RR) in the range of 20–30% in multiple Phase 2 and 3 trials [13], and similar response rates were obtained with single agent cisplatin and carboplatin [14,15]. Two large randomized studies showed the combination of cisplatin and doxorubicin to be superior in terms of response rate (41-43% vs 17–25%), but no overall survival (OS) benefit could be demonstrated and there was an increase in nausea/vomiting and grade 3-4 myelotoxicity [16,17].

In a GOG trial [18], conducted in patients with measurable FIGO III–IV endometrial cancer, the addition of paclitaxel to cisplatin and doxorubicin was associated with a higher RR and PFS (Progression Free Survival) than cisplatin and doxorubicin alone (objective response rate [ORR]: 57% vs 34%, respectively; P < 0.01; median PFS: 8.3 vs 5.3 months, respectively; P < 0.01), and a small but significant improvement in OS (median 15.3 vs 12.3 months, respectively, P = 0.037). However, toxicity, especially peripheral neuropathy, was significantly higher (grade 2–3: 39% vs 5%, 40% vs 14%, respectively).

### Table 4: Selected Trials of Chemotherapy in Advanced Endometrial Cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Regimen</th>
<th>Sample size (n)</th>
<th>Response Rate (%)</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aapro 2003 [16]</td>
<td>Dox 60 mg/m² q 4 w Dox 60 mg/m² + CDDP 50 mg/m² q 4 w</td>
<td>87</td>
<td>17</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Dox 60 mg/m² q 3 w Dox 60 mg/m² + CDDP 50 mg/m² q 3 w</td>
<td>90</td>
<td>17</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Thigpen 2004 [17]</td>
<td>Dox 60 mg/m² q 4 w Dox 60 mg/m² + CDDP 50 mg/m² q 4 w</td>
<td>150</td>
<td>25</td>
<td>5.2</td>
<td>9.0</td>
</tr>
<tr>
<td>Fleming 2004 [18]</td>
<td>Dox 60 mg/m² + CDDP 50 mg/m² q 3 w Dox 50 mg/m² + Paclitaxel 160 mg/m² q 3 w + GCSF</td>
<td>129</td>
<td>34</td>
<td>5.3</td>
<td>12.3</td>
</tr>
<tr>
<td></td>
<td>Dox 50 mg/m² + Paclitaxel 50 mg/m² + Paclitaxel 160 mg/m² q 3 w + GCSF</td>
<td>134</td>
<td>34</td>
<td>5.7</td>
<td>15.3</td>
</tr>
<tr>
<td>Miller 2012 [19]</td>
<td>Paclitaxel 175 mg/m² + carboplatin AUC 6 q 3w Dox 50 mg/m² + CDDP 50 mg/m² + Paclitaxel 160 mg/m² q 3 w + GCSF</td>
<td>663</td>
<td>51</td>
<td>14</td>
<td>36.5</td>
</tr>
<tr>
<td></td>
<td>Dox 50 mg/m² + CDDP 50 mg/m² + Paclitaxel 160 mg/m² q 3 w + GCSF</td>
<td>532</td>
<td>51</td>
<td>14</td>
<td>40.3</td>
</tr>
</tbody>
</table>

Dox - Doxorubicin; CDDP - Cisplatin; GCSF - Granulocyte colony stimulating factor
respectively). For this reason, it has not been widely adopted as a standard of care.

Finally, Miller et al. (GOG 209) [19] conducted a randomized, non-inferiority trial that compared the combination of paclitaxel 160 mg/m², cisplatin 60 mg/m² and doxorubicin 50 mg/m² (TAP) with paclitaxel 175 mg/m² and carboplatin AUC 6 (TC), both administered every 3 weeks. A total of 1305 patients were included in this trial. Preliminary data (not yet fully published) indicate a similar response rate (51.3% vs 51.2%) and PFS (median 13.5 vs 13.3 months). The median OS (primary study endpoint) was 40.3 months for TAP and 36.5 months for TC, which met the criteria of non-inferiority. TC had a more favorable toxicity profile than TAP in this trial, with fewer patients discontinuing due to toxicity (12% vs 18%). In addition, TC can be administered in the outpatient setting whereas TAP is given inpatient in most countries. This part may be important in terms of logistical, financial and quality of life considerations in the palliative setting [19].

The options for second line chemotherapy are quite limited. Women with a prolonged disease free interval can be retreated with taxanes/platin combination with response rates ranging from 25 – 65% [20], otherwise agents like topotecan, liposomal doxorubicin, ixabepilone and gemcitabine have been used in the second line setting, with dismal response rates [21].

The selected randomized trials depicting the evolution of systemic chemotherapy are summarized in Table 4.

Hormonal Therapy: Hormonal therapy is the preferred frontline systemic therapy for patients with hormone receptor positive grade 1 or 2 tumors in the absence of rapidly progressive disease as it provides excellent risk/benefit ratio and convenient toxicity profile. The progestogens, medroxyprogesterone acetate (MPA) or megestrol acetate (MA) are generally recommended. The reported response rates are in the range of 15–20%. Features that predict a better response are hormone receptor expression, low-grade histology, and a long disease-free interval [11,20,21].

The GOG [20] randomized 299 patients with advanced or recurrent endometrial cancer to receive either 200 mg/d or 1,000 mg/day of oral MPA. Among 145 patients receiving the low-dose regimen, there were 25 complete (17%) and 11 partial (8%) responses, for an overall response rate of 25%. For the 154 patients receiving the high-dose regimen, there were 14 complete (9%) and 10 partial (6%) responses, for an overall response rate of 15%. Median survival durations were 11.1 months and 7 months, respectively, for the low-dose and high-dose regimens. It was concluded that 200 mg/d of MPA was a reasonable initial approach to the treatment of advanced or recurrent endometrial cancer, particularly for patients whose tumors were well differentiated or PR-positive. Patients with poorly differentiated or PR-negative tumors had only an 8–9% response rate [20]. If an objective response is obtained, the progestogen should be continued indefinitely. Side effects from progestins include weight gain, edema, thrombophlebitis, tremor, headache and hypertension [20].

The nonsteroidal antiestrogen tamoxifen has been used to treat patients with recurrent endometrial cancer. Responses are usually seen in patients who have previously responded to progestins, but an occasional response may occur in a patient who is unresponsive to them. Tamoxifen is administered orally at a dose of 20 mg daily or twice daily, and is continued for as long as the

Table 5: Selected Trials of Hormonal Therapy in Advanced Endometrial Cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Regimen</th>
<th>Prior Chemotherapy</th>
<th>N</th>
<th>Response Rates(%)</th>
<th>Median OS (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thigpen</td>
<td>MPA 200 mg/day</td>
<td>No</td>
<td>145</td>
<td>25</td>
<td>11.1</td>
</tr>
<tr>
<td></td>
<td>MPA 1000 mg/day</td>
<td></td>
<td>154</td>
<td>15</td>
<td>7.0</td>
</tr>
<tr>
<td>Whitney</td>
<td>MPA 200 mg/day q wk. and</td>
<td>No</td>
<td>61</td>
<td>33</td>
<td>13</td>
</tr>
<tr>
<td>2004 [24]</td>
<td>TAM 40 mg daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fiorica</td>
<td>MGA 160 mg/day x 3wk</td>
<td>No</td>
<td>61</td>
<td>27</td>
<td>14</td>
</tr>
<tr>
<td>2004 [25]</td>
<td>followed by TAM 40 mg/ day x 3 wk.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thigpen</td>
<td>TAM 40 mg /day</td>
<td>No</td>
<td>68</td>
<td>10</td>
<td>8.8</td>
</tr>
<tr>
<td>2001 [26]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ma 2004</td>
<td>Letrozole 2.5 mg/day</td>
<td>Adjuvant only</td>
<td>28</td>
<td>9.4</td>
<td>n/a</td>
</tr>
<tr>
<td>[27]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MPA - Medroxyprogesterone acetate; MGA - Megestrol acetate, TAM - Tamoxifen
disease is responding [21,23]. In a review of the literature, Moore et al reported a pooled response rate of 22% for single-agent tamoxifen [21]. Sequentially alternating MPA and tamoxifen lead to promising response rates of around 30%. However, progression-free survival was short (3 months), as with single-agent progestins [23,24].

In postmenopausal women, the principal source of estrogen is through the conversion of androstenedione by aromatase in peripheral adipose tissue. Aromatase is also elevated in endometrial cancer stroma and locally produced estrogen may act in a paracrine fashion to stimulate cancer growth. The response rates to aromatase inhibitors in recurrent and metastatic endometrial cancer have been only about 10% [25]. Ongoing trials combining mTOR inhibitors plus MA/tamoxifen (based on the premise that inhibiting PI3K/Akt pathway reverses progestin resistance) have reported dismal response rates (14%) but unacceptably high response rates [26]. Selected randomized trials of hormonal therapy in advanced endometrial cancer are summarized in Table 5.

**Molecular Targeted Therapy:** As described before, endometrioid and serous histologies form the bulk of aggressive endometrial cancers. Molecular genetic alterations involved in the development of endometrioid cancers differ from those of serous cancers. In endometrioid cancers, microsatellite instability (MSI) and mutations in PTEN, PIK3CA, and beta catenin genes are the most common form of molecular abnormalities, whereas in serous cancers alterations in p53, STK15, p16, E-cadherin and C-erb B2 are more common [29].

The benefit of standard cytotoxic chemotherapy and hormonal therapies is at best modest; hence several targeted therapies are undergoing clinical evaluation for use in advanced endometrial cancer. Angiogenesis inhibitors, mTOR inhibitors and PI3K kinase inhibitors are the most promising amongst these which have been tried in pretreated patients with endometrial cancer [29-34]. The response rates achieved with molecular agents are summarized in Table 6.

Recent trials are focusing on combining targeted agents with first line chemotherapy. GOG - 86P is a 3-arm trial which compared the addition of bevacizumab, temsirolimus or ixabepilone to first line TC in 349 patients with advanced or recurrent endometrial cancer. No differences in PFS were seen when the three arms were compared with historical data for TC from GOG 209, but bevacizumab appeared superior when the median OS results were compared with these historical control data (34.0 vs 22.7 months; p < 0.039) [35].

The value of adjuvant systemic therapy in patients with high-risk early-stage endometrioid endometrial cancer is still controversial.

Susu mu et al [36] (JGOG 2033) compared whole-pelvic radiation with three or more cycles of cyclophosphamide, doxorubicin, and cisplatin (CAP) chemotherapy in 385 patients with stages IC to IIIC endometrioid adenocarcinoma (“intermediate risk”; 60% stage IC, 15% grade 3). At a median follow-up of 5 years, there were no significant differences in progression-free (pelvic radiation 83.5% vs CAP 81.8%) or overall survival (85.3% vs 86.7%). In a subgroup analysis of “high to intermediate risk” cases (stage IC; stage IC grade 3; stage II or stage IIIA), a survival benefit for CAP was suggested [36]. Maggi et al [37] conducted a randomized controlled trial in 345 high-risk endometrial cancer patients to compare five cycles of cisplatin, doxorubicin and cyclophosphamide with external pelvic radiation. In a multivariate analysis, the investigators reported no difference between therapies in terms of progression-free or overall survival [37].

Hogberg et al [38] presented the results of a EORTC trial (EORTC 55991) of radiation alone versus adjuvant chemotherapy before or after radiation in 382 patients with stage I, II, IIIA (positive peritoneal cytology only).

<p>| Table 6: Single Agent Trials of Novel Agents in Chemotherapy Pretreated Endometrial Cancer |</p>
<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiangiogenic agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab [30]</td>
<td>15 mg/kg iv q3w</td>
<td>13.5%</td>
</tr>
<tr>
<td>Sunitinib [31]</td>
<td>50 mg/d po 4 wk on, 2 wk off</td>
<td>15%</td>
</tr>
<tr>
<td>mTOR inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temsirolimus [32]</td>
<td>25 mg iv q 1 wk</td>
<td>4–14%</td>
</tr>
<tr>
<td>Anti EGFR agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trastuzumab [33]</td>
<td>2 mg/kg iv q 1 wk</td>
<td>0%</td>
</tr>
<tr>
<td>Erlotinib [34]</td>
<td>150 mg po daily</td>
<td>12.5%</td>
</tr>
</tbody>
</table>
or IIIC disease who had high-risk factors for recurrence (one or more of deep myometrial invasion, nondiploid DNA, or serous, clear cell, grade 3, anaplastic histology). Chemotherapy was not standardized and included doxorubicin and platinum (AP); paclitaxel, doxorubicin, and platinum (TAP); paclitaxel and platinum (TP); or paclitaxel, cisplatin, and epirubicin. The study suggested an improvement in progression-free survival with chemotherapy (7%) improvement at 5 years, p=0.03, but survival data were too early to draw any conclusions [38].

All studies showed that the use of chemotherapy lowered the risk of distant metastasis, but did not improve OS in the overall study population. Protocols JGOG 2033 and EORTC 55991 demonstrated an improvement in OS with the use of chemotherapy in the higher risk subgroup defined as either stage II-IIIa or stage IC, grade 3 and/or age >70 (73.6% vs. 89.7%, p=0.006 in JGOG 2033; 75% vs 82%, p=0.046 in EORTC 55991).

A limitation of these studies precluding generalization of results to all patients with early stage disease is that patients with stage III disease or incompletely surgically staged patients were eligible for inclusion and represented 25%-40% of the study population in those trials [36-38].

Two major trials (PORTEC 3 and GOG 249) are ongoing which aims to answer the use of systemic therapy in early endometrial cancer as an adjuvant treatment. PORTEC-3 randomized patients with high risk early disease (stage I-II, grade 3) and patients with locally advanced disease (stage IIIA-IIIC) to Pelvic RT vs. concurrent cisplatin and Pelvic RT followed by carboplatin and paclitaxel; GOG 249 randomized early stage high/intermediate risk patients to Pelvic RT vs. Vaginal brachytherapy followed by three cycles of carboplatin and paclitaxel. Results of these studies are being eagerly awaited for.

Outlook

The role of systemic therapy in carcinoma endometrium is evolving. The role of systemic therapy in the treatment of early endometrial cancer is yet to be defined clearly, and probably the benefit is restricted to high risk cases. In advanced disease, outcomes have improved over time with the use of optimal regimens and scheduling, but response rates are still low. Recent comprehensive molecular characterisations of primary tumors have identified drugs targeting the PI3K / PTEN / AKT / mTOR pathway and FGFR2 as promising for further studies also reflected currently in Phase I and Phase 2 trials in endometrial carcinoma that are in progress.

Improved ability to intelligently deliver biomarkers driven target systemic therapies in well selected patient populations in clinical practice will increase the likelihood of benefits in near future.

References


CANCER NEWS FEBRUARY 2016

SPECTRUM

CAN SBRT REPLACE BRACHYTHERAPY BOOST IN CARCINOMA CERVIX

Cervical cancer is not only the leading cancer amongst women in India but also widely prevalent around the world with more than 500,000 cases detected worldwide in 2014 (1). Most of the women in our country present with locally advanced carcinoma cervix, for which the standard treatment is external beam radiotherapy followed by brachytherapy boost. It is a well known fact that addition of brachytherapy boost to external beam RT, increases the local control and improves the OS (2,3,4). In some few patients, for various reasons like uterine malformations, bulky residual disease after external radiotherapy, severe vaginal stenosis, contraindications to anesthesia or patient choice, brachytherapy may not be possible. It is in these cases that an alternative is sought to deliver the full dose of radiation.

Another factor that compels us to think about SBRT / IMRT boost for carcinoma cervix, is the advancement in technology, which enables to deliver a high precision radiation in comparison to the numerous uncertainties associated with brachytherapy (BT). Regardless of the BT technique, implementing and delivering an appropriate BT plan is plagued by several challenges. Even if the applicators geometry is reproduced at each treatment, significant variations in inter- and intra-fraction delivery are common. It is also well known that brachytherapy is a treatment modality where the skill of the physician is paramount and can alter the results of treatment, like improper ovoid placement reduces both local control (LC) and DFS and insufficient cavity packing reduces disease-free survival (DFS) (5,6).

A recent publication by Sarah Kilic, Bernadette Cracchio & Omar Mahmoud reviewed the data available on the non-brachytherapy alternatives in carcinoma cervix (7). They found very limited data to support the use of SBRT and IMRT as boost therapies. Most of the reports in the literature were retrospective studies, with only 3 studies being prospective but these studies also had significant heterogeneity. These studies are heterogeneous in treatment plan (delivery technique and dose fractionation) and follow-up time, include small patient populations, and often address other gynecologic malignancies in addition to cervical cancer.

In most of the studies, the pelvic planning target volume (PTV) received photon beams to 45-50.4 Gy in 1.8 to 2 Gy per fraction. However, the studies were inconsistent in their reporting of dosimetric information for normal tissue and precluded a dose-toxicity analysis. In majority of these studies, the rationale for employing a BT alternative was either patient refusal of BT or anatomical constraints preventing proper BT delivery.

The study by Matsuura et al used hyper-fractionated schedule for boost; a small conformal boost volume (1.2 to 1.6 Gy per fraction) was initiated concomitant with pelvic irradiation, and continued after the fifth week twice daily with at least 6 hours between fractions. They did not use image guided radiotherapy. Two-year local control was 85.7%, with the highest toxicity being grade 2 rectal bleeding, affecting only 2 out of 7 patients (8).

Three studies employed similar conformal radiotherapy techniques. Two-year local control was reported as 79% by Barraclough et al, (9) 83% by Chan et al (10) and 60% by Park et al (11). Park et al used real-time tracking of gold fiducial markers implanted in the cervix and observed no grade 3 or higher late toxicities. Therefore, although this study delivered a higher total dose and a higher dose per fraction than the two aforementioned studies, Park et al observed lower toxicity rates, likely due to the use of image guidance. In contrast, late grade 3 urinary and late grade 3 rectal toxicities were 2% in Barraclough et al and 17% in Chan et al, despite delivering lower total dose with lower biologic effective dose (BED), implying the importance of image guidance for accurate EBRT delivery.

Some recent studies employed SBRT for boost delivery, each delivered 16 to 30 Gy to the cervix in 2 to 6 Gy per fraction. The follow-up time was short (6 to 36 months). Three of the four studies demonstrated encouraging results, with minimal late toxicity and local control rates of 78% (Hsieh et al), 100% (Marnitz et al), and 100% (Haas et al) (12,13,14). Marnitz et al and Haas et al used the CyberKnife (CK) system to track gold fiducials implanted in the cervix for precise SBRT boost delivery. This may explain the studies’ high rate of local control (both 100%) compared to Hsieh et al (78%). However, the findings of Hsieh et al may also be accounted for a longer overall treatment time (79 days) and the inclusion of patients with advanced disease.

Paradoxically, Kubicek et al observed high rectal toxicity despite using multiple measures to ensure
accuracy: CTV definition by MRI and a 0.5 cm PTV to CTV expansion, in addition to CK tracking of cervical fiducials (15). However, caution is needed due to a small patient population (only 4 patients with cervical squamous cell carcinoma), short follow-up time (median 4 months), and heterogeneity of treatment plans.

Most of the data regarding non-brachytherapy boost has emerged from USA, where a simultaneous decrease in the usage of brachytherapy has been reported as per SEER data analysis (16). A critical review of this decrease in the usage of brachytherapy has been attributed to several explanations such as decreasing brachytherapy training and expertise, failure of clinicians who lacked the ability or resources: to administer brachytherapy to refer patients to centers with greater expertise and inappropriate applications of EBRT. It has been estimated that 50% of facilities treat <3 cervical patients per year in USA. With such a small volume, it is not possible to maintain routine procedure and to adequately accommodate with new developments in the field. The adverse consequence of low patient numbers is clearly demonstrated by the fact that patients treated in small-volume centers are less likely to receive brachytherapy (17).

There are many challenges to overcome in order to accurately deliver boost to cervix using SBRT or IMRT techniques, such as target motion and internal target volume dilemma, dosimetry and radiobiological considerations. There are many unanswered questions and inadequately addressed issues. Therefore, large prospective studies to definitively establish or invalidate non-BT alternatives for treating cervical cancer radiotherapy are urgently needed.

References

(Dr Jaskaran Singh Sethi, Sr Consultant & Coordinator, Dept of Radiation Oncology, Cancer Therapy Centre-JOSPL, Fortis Hospital, Noida)
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- Dr. Wing-Chung (John) Chan
- Dr. Bharat N Nathwani
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- Dr. Jay Mehta
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- Dr. Anurag Mehta

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