Recent Advances in Gynaecological Oncology

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1 Introduction

In 2020, there were 19.3 million new cancer cases and 9.9 million deaths due to cancer worldwide [1]. Total female cancer reported in 2020 was approximately 9.2 million new cases and about 4.4 million deaths, with breast and cervix cancers being the two leading female cancers [1]. Awareness, prevention, equitable distribution of resources, early diagnosis, and affordable treatment are the prime strategies needed to combat cancer. There has been significant progress in the surgical and medical management of gynaecologic malignancies in the past several years, backed by landmark clinical trials. As a result, there is increasing emphasis on tailored, less morbid but equally efficacious treatment and chronic maintenance therapy. This chapter focuses on integrating various evidence-based updates that helped us to understand and better our current practice in gynaecological oncology.

2 Cervical Cancer

Worldwide, cancer of the cervix is the fourth most common cancer in females and the second most common cancer in India after breast cancer [1, 2]. China and India contribute more than a third of the global cervical cancer burden [3]. Globally, about 604,127 new cases and 341,831 deaths due to cancer cervix were reported in 2020 [1]. India recorded 123,907 new cases and 77,348 deaths due to cervical cancer.

2.1 Prevention and Screening

The World Health Organization's strategic plan of "90/70/90" targets by 2030 includes 90% of girls covered with an HPV vaccination by age 15, 70% of women screened using a high-performance test by age 35 and again by age 45, and 90% of women identified with preinvasive and invasive cervical cancer adequately managed [4]. Elimination of cervical cancer is defined as an incidence of fewer than 4 cases per 100,000 women [5]. Scaled-up vaccination, screening, and pre-cancer treatment are essential elements of management strategy, especially in low-resource countries. The recom-

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mended starting age for screening is 25 years with a primary HPV test (Cobas or Onclarity HPV test) every 5 years. However, co-testing with pap smear and HPV DNA test remains an essential modality until the wide availability of primary HPV tests [6]. WHO recommends HPV DNA-based study as the preferred cervical cancer primary screening modality compared to visual inspection with acetic acid or cytology [7]. The Federation of Obstetric and Gynaecologic Societies of India (FOGSI) concurs with the recommendation but advises visual inspection with acetic acid in low-resource settings till affordable HPV tests are available [8]. Another FDA-approved new method, namely dual stain testing (p16 and Ki-67) in the liquid-based cytology (LBC) sample, has emerged to predict pre-cancerous lesions in HPV-positive patients more accurately [9].

Previously the protective role of HPV vaccination against preinvasive cancers has been proven in multiple RCTs. The human papillomavirus (HPV) vaccine's protective effect against invasive cervical cancers is documented. A Swedish study reported an incidence of cervical cancer of 47 cases per 100,000 persons among vaccinated women and 94 cases per 100,000 persons among unvaccinated. The protective effect was more significant among women who were vaccinated before the age of 17 [10]. Another study by Jacqueline et al. reported a decline in the rates of both cervical squamous carcinoma and adenocarcinoma since the introduction of HPV vaccination in the U.S. [11] Recently, vaccination armament has been augmented with the introduction of second-generation nonavalent HPV vaccine with an efficacy of around 96% [12]. In the future, HPV vaccination in national immunization schedule and single-dose HPV vaccine would be the best cost-effective way to overcome cancer cervix.

2.2 Human Papillomavirus-Negative Cervical Cancer and Classification of Adenocarcinoma

Approximately 5.5–11% of all cervical cancers are HPV-negative [13]. The truly HPV-negative cervical cancers are almost all cervical adenocarcinomas, most likely caused by mutations of PI3K-AKT [13]. The median age of patients with HPV-associated adenocarcinoma (HPVA) was 42 years, compared to 55 years for patients with non-HPV-associated adenocarcinoma (NHPVA) [14]. The median size of HPVA was 21 mm, compared to 38 mm in NHPVA [14]. They are often diagnosed at an advanced FIGO stage and have a poor prognosis [13]. Based on this, a new classification of endocervical adenocarcinoma was suggested [14]. Those with easily identified apical mitotic figures and apoptotic bodies were considered HPV-associated adenocarcinoma and further subcategorized based on cytoplasmic features. Tumours with no easily identifiable apical mitotic activity and apoptotic bodies were classified as non-HPV-associated adenocarcinoma. A new 3-tier pattern-based system to classify endocervical adenocarcinoma into patterns A, B, and C is suggested [15]. Pattern A tumours are characterized by well-demarcated glands frequently forming clusters or groups with relative lobular architecture and carries good prognosis. Systematic lymphadenectomy can be avoided in this subset of endocervical adenocarcinoma. Pattern B tumours demonstrated localized destructive stromal invasion along with tumour cells within the stroma. Pattern B is associated with intermediate prognosis. Pattern C showed diffusely infiltrative glands along with extensive desmoplastic response and definitely justifies an aggressive surgical staging.

2.3 FIGO 2018 Staging

The new revised FIGO 2018 staging considers technological developments, tumour size, and poor prognosis of nodal metastases in case of cervical cancer [16]. The lateral extent of the disease is not considered anymore in stage 1A. Stage 1B is further subdivided based on tumour size into Stage 1B1 ≥5 mm depth to <2 cm, 1B2 ≥2 cm to <4 cm, and 1B3 as ≥4 cm. A newer stage IIIC is introduced for positive pelvic and paraaortic nodes either on pathology or radiology irrespective of the tumour size, C1 being positive pelvic

nodes only and C2 being paraaortic nodes. FIGO no more recommends any specific modality for imaging but allows the choice on imaging to be based on resource settings and patient affordability. In case of nonavailability of the imaging, FIGO 2009 clinical staging can be used to stage the disease. Many unanswered questions remain, such as measurement of tumour size, the definition of parametrial involvement, ovarian metastases, and lower uterine segment extension [17].

2.4 Minimal Access Surgery

The landmark LACC trial, a prospective multicenter RCT, included stage IA1 with LVSI, IA2, or IB1. The patients were randomly assigned to undergo minimally invasive surgery (laparoscopy or robot-assisted surgery) or conventional open surgery [18]. The study was prematurely stopped and showed that MIS was inferior to open surgery with a low DFS at 4.5 years (86.0% in MIS and 96.5% in the open). The 3-year overall survival was 93.8% vs. 99.0%, with HR for death from any cause being 6.00. The trial was criticized for missing information like tumour size, parametrial size, and involvement, which were essential predictors for recurrence. Similar findings were reported in an epidemiological study [19]. The recommended approach for radical hysterectomy is open and abdominal, according to NCCN and European guidelines [20, 21]. Majority of patients (92%) enrolled in the LACC trial had stage IB1 tumours. In an analysis of NCDB of patients with stage IA disease, there was no difference in survival based on the route of hysterectomy with 4-year survival rates of 97.7% for open and 98.6% for MIS hysterectomy [22].

2.5 Nodal Assessment

The presence of lymph node metastases is an important prognostic factor for survival in cervical cancer. Sentinel lymph node (SLN) appears feasible in cervical cancer due to systematic lymphatic drainage of the cervix and ease of administration of the dye. It has been increasingly used in the management of early cervical cancer. In a prospective French study (Senticol), the use of dual dye yielded a detection rate of 97.8% with a sensitivity of 92%, with a negative predictive value of 98.2% [23]. Sentix, a multicenter prospective observational trial, evaluated sentinel lymph node (SLN) biopsy without pelvic lymph node dissection in patients with early-stage cervical cancer. Though the bilateral detection rate was 91%, the frozen section failed to detect 54% of positive lymph nodes (pN1), including 28% of cases with macrometastases and 90% with micrometastases [24]. Senticol II compared the effect of sentinel-lymph-node biopsy (SLNB) to that of SLNB + pelvic lymphadenectomy (PLND) to determine the postoperative lymphatic morbidity in the two groups [25]. Disease-free survival and overall survival at 4 years were similar in patients treated with SLN biopsy and patients who underwent a lymphadenectomy. The European guideline strongly recommends sentinel node biopsy before pelvic lymphadenectomy with a combination of blue dye with radiocolloid or indocyanine green alone [21].

The uterus-11 study evaluated the impact of surgical staging with transperitoneal laparoscopy compared to standard clinical/radiological staging, followed by chemoradiation (CR) in locally advanced cervical cancer [26]. A total of 255 LACC patients (FIGO2009 IIB-IVA) were included. Though 33% of patients were upstaged because of surgical staging, improvements in PFS and OS were not statistically significant. An analysis of NCDB of stage IA2-IB2 cervical cancer patients who underwent radical hysterectomy with pelvic lymph node dissection with or without paraaortic node dissection showed extending paraaortic lymphadenectomy during radical hysterectomy has no survival advantage [27].

ABRAX, a retrospective cohort study, reported similar DFS, OS, and local control rates between patients who underwent planned surgery and patients who abandoned further surgery after intraoperative detection of pelvic node metastases. The result was published as an abstract in ESMO 2020 virtual congress.

2.6 Role of Conservative Surgery

The rationale for a conservative procedure in early cervical cancer is a low rate of parametrial involvement (<1%) with favorable characteristics like tumour size <2 cm, no deep stromal invasion, no LVSI, and negative nodes [28]. The prospective, single-arm, multicenter ConCerv trial included early-stage cervical cancer with squamous and grade 1/2 adenocarcinoma [29]. They were offered cervical conization or simple hysterectomy with pelvic lymph node dissection or sentinel node dissection. With a median follow-up of 36.3 months, the cumulative incidence of recurrence was 3.5%. The LESSER (LESs Surgical radicality for EaRly stage cervical cancer) study was a proof of concept randomized phase 2 noninferiority trial evaluating the safety and efficacy of simple hysterectomy compared to modified radical hysterectomy in patients with stages IA2-IB1 cervical cancer and tumours of ≤2 cm in size [30]. There were no significant differences in adjuvant therapy between groups (30% vs. 20%, $p = 0.48$) or quality-of-life. At 31 months of follow-up, there was no difference in disease-free survival. A population-based study compared less radical surgery like conization, trachelectomy, or hysterectomy with more radical surgery like modified radical or radical hysterectomy [31]. The disease-specific survival was similar in both groups.

2.7 Role of Chemotherapy in Advanced Cervical Cancer

The advantages of NACT include a decrease in tumour burden, increased tumour oxygenation, distant micrometastases are cured, and increased chances of operability in locally advanced cases. Two phase III trials have been conducted. A study done in India evaluated 633 patients with squamous cervical cancer with stage IB2, IIA, and IIB who were randomized between three cycles of NACT (paclitaxel + carboplatin) three weekly followed by radical hysterectomy versus standard CTRT [32]. The 5-year DFS in the neoadjuvant chemotherapy plus surgery group was 69.3% compared with 76.7% in the concomitant chemoradiation group ($p = 0.038$); the corresponding 5-year OS rates were 75.4% and 74.7%, respectively ($p = 0.87$). Preliminary results of EORTC 55994 show no difference in 5-year OS between NACTS and CCRT with increased short-term severe adverse effects in the neoadjuvant group [33]. Similarly, NACT prior to definitive CTRT in locally advanced cervical cancer has been studied in a phase II trial, the CIRCE trial (Chemotherapy Induction followed by chemoRadiation for locally advanced CErvical cancer) [34]. The complete response rate, PFS and OS were significantly lower with NACT followed by CTRT group compared to CTRT only group. The OUTBACK trial randomized women who had locally advanced cervical cancer to either cisplatin-based chemoradiation or cisplatin-based chemoradiation followed by adjuvant chemotherapy with four cycles of carboplatin and paclitaxel [35]. The PFS and OS were similar between the groups. The final results of GOG 240 showed significant improvement in OS with the addition of bevacizumab to systemic chemotherapy in recurrent, persistent, or metastatic cervical cancer [36].

2.8 Immune Checkpoint Inhibitor and PARP Inhibitor in Cervical Cancer

Recently, there have been some significant and fruitful researches that got materialized in advanced or recurrent metastatic cancer cervix. Immunotherapy (ADSX11-001) with or without Cisplatin and Pembrolizumab use in PD-L1 positive patients are some of the remarkable milestones [37, 38]. The phase II KEYNOTE-158 trial showed an antitumour activity of pembrolizumab in previously treated advanced cervical cancer (15% in PD-L1-positive tumour vs. 0% in PD-L1-negative tumour). Hence it was approved for patients with recurrent or metastatic cervical cancer with disease progression after chemotherapy and who express PD-L1 (Combined Positive Score [CPS] ≥1) as determined by an FDA-approved test in June 2018 [39]. EMPOWER-

Cervical1/GOG-3016/ENGOT-cx9 investigated the role of anti-programmed cell death (PD)-1 cemiplimab vs. investigator choice single-agent chemo in recurrent or metastatic cervical cancer that has progressed after first-line platinum-based treatment [40]. At the interim analysis, OS, PFS, and ORR were higher with cemiplimab. Conjugated monoclonal antibodies (Tisotumab vedotin) are the latest in oncologic therapeutics, and a phase II study in persistent, recurrent, and metastatic cervical cancer has been carried out with good median overall survival of 8.3 months [41]. Triapine (ribonucleotide reductase inhibitors) in combination with platinum-based concurrent chemotherapy has been tested in a phase II trial with good outcome [41]. New trials revealed increased progression-free survival and overall survival have been noticed with the use of Veliparib (PARP inhibitor) in combination with topotecan or in combination with Cisplatin and paclitaxel in the setting of advanced or recurrent cancer cervix [42].

2.9 Advances in Radiotherapy

The standard of care for the treatment of locoregionally advanced cervical cancer is external beam radiation therapy (EBRT), including brachytherapy with concurrent chemotherapy. Intensity-modulated radiation therapy (IMRT) has the ability to maintain tumouricidal doses to target volumes while reducing the dose to nearby critical structures. NRG Oncology/RTOG 1203 (TIME-C trial) compared patient-reported acute toxicity and health-related quality of life during treatment with standard pelvic radiation or intensity-modulated radiation therapy (IMRT) in women with cervical and endometrial cancer [43]. IMRT was associated with significantly less GI and urinary toxicity than standard RT. PARCER trial compared late toxicity of image-guided intensity-modulated radiotherapy (IG-IMRT) vs. three-dimensional conformal radiation therapy (3D-CRT) in cervical cancer patients undergoing postoperative radiation [44]. The cumulative incidence of late toxicity of grade ≥2 were 28.1% versus 48.9% in the IG-IMRT and 3D-CRT arms respectively. The pelvic relapse-free survival and disease-free survival in the IG-IMRT versus the 3D-CRT arm were 81.8% versus 84% ($p = 0.55$) and 76.9% versus 81.2% ($p = 0.89$), respectively. Gandhi et al. from India reported an RCT comparing Whole Pelvic Conventional Radiotherapy (WP-CRT) versus Intensity Modulated Radiotherapy (WP-IMRT) in 44 locally advanced cervical cancer [45]. Both early and late GI and bladder toxicities were significantly less in the IMRT group with similar 5 year DFS and OS, compared to WP-CRT. Another single-center RCT reported efficacy and feasibility of pelvic bone marrow sparing intensity-modulated radiotherapy (PBMS-IMRT) [46]. Hematologic toxicity in the PBMS-IMRT group was 50.0%, significantly lower than the 69.5% in the control group where only IMRT was given without marrow constraint. The American Society for Radiation Oncology (ASTRO) recommends intensity-modulated radiation therapy (IMRT) for postoperative EBRT and conditionally recommends definitive EBRT to reduce short-term and long-term toxicity [47]. STARS trial investigated the effect of sequential chemotherapy and radiotherapy (SCRT) compared to concurrent chemoradiation (CCRT) or radiation alone after radical hysterectomy in patients with adverse prognostic factors [48]. SCRT was associated with higher DFS and lower cancer deaths than CCRT and RT alone.

Simultaneous development in brachytherapy was reported in the EMBRACE trial. EMBRACE I showed MR-based image-guided adaptive brachytherapy (MR-IGABT) after external beam radiotherapy (EBRT) with concomitant chemotherapy and individualized dose prescription resulted in improved target dose coverage and decreased isodose surface volumes compared to standard plans used with classical Point A-based brachytherapy [49].

3 Ovarian Carcinoma

Ovarian cancer is considered the most lethal gynaecologic malignancy, with a median 5-year survival of just 47% [50]. In India, new ovar-

ian cancer cases were approximately 45,701, and about 32,077 deaths due to ovarian cancer were reported in 2020 [1]. Altogether, 313,959 new cases of ovarian cancer and 207,252 deaths due to ovarian cancer were reported worldwide in 2020 [1]. Most patients with epithelial ovarian cancer have advanced stage at presentation. Of those diagnosed with advanced-stage disease, more than 70% will have recurrence within the first 5 years [51]. The 5-year survival for ovarian cancer (all stages included) was about 47.62% during the years 2009–2015 [52].

3.1 Screening

The long-term follow-up results of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) were published in 2021 [53]. In this RCT, after a median follow-up of 16.3 years, the incidence of stage I or II disease was 39.2% higher in the MMS group than in the no screening group. In contrast, the incidence of stage III or IV disease was 10.2% lower; however, it did not translate to a significant reduction in ovarian and tubal cancer deaths in the MMS (p = 0.58) or USS (p = 0.36) groups compared with the no screening group. NCCN recommends no screening method for the population at average risk and transvaginal ultrasound with CA125 starting at 30–35 years, at physicians' discretion [54, 55].

3.2 Neoadjuvant Chemotherapy + IDS vs. PDS

Neoadjuvant chemotherapy has been proven to be noninferior in various RCTs, but all those trials were criticized for various reasons, and primary debulking surgery followed by chemotherapy remains the standard treatment for high-grade serous carcinoma. Scorpion trial randomized 171 patients with high tumour load assessed by a standardized laparoscopic predictive index to either primary debulking surgery (PDS) followed by adjuvant chemotherapy or neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) and adjuvant chemotherapy. The rate of complete cytoreduction was higher in the IDS arm (47.6% vs. 77.0%; p = 0.001); the major complication rate was higher in the PDS arm (25.9% vs. 7.6%; p = 0.0001). The PFS (HR 1.05, p = 0.73) and OS (HR 1.12, p = 0.56) were similar in both arms [56]. PDS is generally preferred, but NACT followed by IDS is an alternative for older patients, women with a large disease burden, or multiple comorbidities [57]. SCORPION trial was a single-center RCT to establish whether neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) is superior to primary debulking surgery (PDS) [58]. Only patients with high volume disease were included. The rates of complete cytoreduction were different between the arms (47.6% in PDS vs. 77.0% in IDS arm; p = 0.001) with significantly higher postoperative complication rate in the PDS arm, 25.9% vs. 7.6% [56]. Median progression-free survival and overall survival for patients assigned to primary debulking surgery were similar to the NACT-IDS arm (HR 1.05, p = 0.73; HR 1.12, p = 0.56). A Japanese RCT, JCOG0602, failed to show noninferiority of neoadjuvant chemotherapy compared with primary debulking surgery [59]. The median OS was 49.0 and 44.3 months in the PDS and NACT, and the median progression-free survival was 15.1 and 16.4 months in the PDS and NACT. This trial has been criticized for a low rate of complete cytoreduction and a significant percentage of patients in the PDS arm having IDS after initial incomplete surgery.

3.3 Lymph Node Assessment

The lymphatic spread has been an essential prognostic factor in early and advanced ovarian cancer. LION trial was the first RCT to study the benefit of systematic lymph node dissection in advanced ovarian cancer [60]. A total of 647 patients with stage IIB through operable stage IV disease who had undergone macroscopically complete resection and had normal lymph nodes both before and during surgery were intraoperatively randomized to either undergo or not undergo lymphadenectomy. The median OS and PFS between the groups were similar, with serious postopera-

tive complications observed more frequently in the lymphadenectomy group (repeat laparotomy, 12.4% vs. 6.5%; mortality within 60 days after surgery, 3.1% vs. 0.9%).

3.4 Frontline Chemotherapy

Paclitaxel and carboplatin every 3 weeks is the standard chemotherapy regimen for advanced ovarian cancer patients. JGOG 3016 reported a significant improvement in OS with weekly paclitaxel [61]. This benefit could not be replicated in GOG 262 or ICON 8. In GOG 262, 84% received Bevacizumab, and weekly paclitaxel was not associated with more prolonged progression-free survival than paclitaxel administered every 3 weeks [62]. However, among patients who did not receive bevacizumab, weekly paclitaxel was associated with better progression-free survival. ICON 8 randomized patients between three arms, 3 weekly Paclitaxel and Carboplatin vs. 3 weekly carboplatin and weekly Paclitaxel vs. weekly Paclitaxel and Carboplatin [63]. The PFS was not different between the groups. The suggested cause of the difference in JGOG 3016 and ICON 8 is pharmacogenomics and different categories of patients; 50% of ICON8 patients received chemotherapy in the neoadjuvant setting, whereas only 10% of JGOG patients underwent primary surgery [64].

Historically elderly and clinically frail women with advanced ovarian cancers receive single-agent carboplatin at least for the first one or two cycles, which is escalated to combination chemotherapy every 3 weekly after improvement in performance status. A GINECO/GCIG RCT (EWOC-1) compared the feasibility, efficacy, and safety of single-agent carboplatin every 3 weeks, weekly carboplatin-paclitaxel, or conventional every-3-weeks carboplatin-paclitaxel in vulnerable older patients with ovarian cancer [65]. This trial was terminated early because single-agent carboplatin was associated with significantly worse survival compared with every-3-weeks or weekly carboplatin-paclitaxel regimens.

Long-term follow-up results of GOG 0241 were published in 2019 [66]. This multicenter RCT compared four chemotherapy regimens for advanced or recurrent stage I mucinous ovarian cancer. The trial was stopped early because of slow accrual, but the recruited patients did not show any difference in OS or PFS with paclitaxel-carboplatin, oxaliplatin-capecitabine each with or without Bevacizumab [66].

3.5 Intraperitoneal Chemotherapy

Trials on intraperitoneal (IP) chemotherapy (CT) showed significantly better survival with IP CT compared to intravenous (IV) CT [67]. GOG 252 two intraperitoneal regimens (carboplatin and Cisplatin) were studied [68]. All patients received Bevacizumab concomitantly and maintenance for 22 cycles. The median PFS and OS were similar between IV chemotherapy vs. IP Carboplatin and IP Cisplatin arm in patients who received Bevacizumab [68]. The complications associated with the IP route have precluded it from being accepted worldwide even when not using Bevacizumab. Hyperthermic intraperitoneal chemotherapy (HIPEC) during surgery is an option hypothesized to give benefits of IP route of chemotherapy without catheter-related complications. HIPEC has been proposed in primary, interval, consolidation, and recurrent settings, but the most accepted evidence was the Dutch Trial which assessed the efficacy of HIPEC during interval cytoreductive surgery. Van Driel et al. evaluated 245 patients with advanced ovarian cancer who received neoadjuvant chemotherapy (NACT) and were randomized to HIPEC or no HIPEC [69]. The trial showed an improved PFS of 4 months and median overall survival (OS) benefit of almost 12 months (33.9 months versus 45.7 months). Another trial by Lim et al. with 184 patients in a similar setting showed somewhat dissimilar results [70]. The HIPEC was administered at a lower dose of 75 mg/m^2 for 90 min at 42–43 °C. The study showed no superiority of the HIPEC arm over the other in terms of 2-year PFS (43.2% vs. 43.5%) and 5-years OS (16.0% vs. 20.9%). Due to such conflicting results from these trials, more evidence is neces-

sary before HIPEC is integrated as standard care for the management of ovarian cancer. HIPEC has also been explored in the recurrent setting but mainly in retrospective and small prospective settings. Spillotis et al. randomized 120 patients with recurrent ovarian cancer to secondary cytoreduction with or without HIPEC and showed OS benefit (26.7 months vs. 13.4 months) [71]. The study was criticized for no PFS data collection, no data on complications, and the methodology of the procedure. It showed similar results for both platinum-sensitive and resistant patients, with PCI being an independent prognostic factor with PCI > 15 having a worse outcome.

3.6 Surgery vs. Chemotherapy for Recurrence

Despite a good response to primary treatment, nearly ¾th of patients relapse within 2 years of treatment, and platinum-free interval serves as a guide to planning treatment in such patients. Secondary cytoreductive surgery (SCS) has been shown to be beneficial in recurrent settings with careful patient selection criteria. GOG 213 evaluated 485 patients with a platinum-free interval of 6 months or more and had the investigator-determined resectable disease to undergo secondary surgical cytoreduction and then receive platinum-based chemotherapy or to receive platinum-based chemotherapy alone [72]. Complete gross resection was achieved in 67% of the patients who underwent SCS. Carboplatin + Paclitaxel or Gemcitabine with bevacizumab followed by bevacizumab maintenance till progression or unacceptable toxicity was administered to 84% of the patients. The hazard ratio for death (secondary cytoreduction vs. no surgery) was 1.29 ($p = 0.08$). DESKTOP III randomized recurrent ovarian cancer patients with a platinum-free interval of 6 months with positive AGO score (Eastern Cooperative Oncology Group performance status score of 0, ascites ≤500 mL, and complete resection at initial surgery) were randomized to platinum-based chemotherapy alone vs. cytoreductive surgery followed by the same chemotherapy [73]. A complete resection was achieved in 75.5%. The median overall survival was 53.7 months in the cytoreduction group and 46.0 months in the no-surgery group ($p = 0.02$). Patients with a complete resection had a median overall survival of 61.9 months, and patients with surgery and incomplete resection did worse than the no-surgery arm (median 28.8 months) [73]. A Chinese RCT evaluating the benefit of SCS included 357 patients with recurrent ovarian cancer with PFI of at least 6 months and potentially resectable disease according to the international model (iMODEL) score and PET-CT imaging [74]. iMODEL score is calculated using: FIGO stage at presentation, residual disease after primary surgery, platinum-free interval, performance status, presence of ascites, and level of CA-125 at recurrence. In the no-surgery group, 6% had secondary cytoreduction during second-line therapy, while 37% who had disease progression had surgery at a subsequent recurrence. At the interim analysis, median overall survival was 58.1 months in the surgery group and 53.9 months in the no-surgery group (HR 0.82). Median progression-free survival was 17.4 months in the surgery group and 11.9 months in the no-surgery group (HR 0.58, $p < 0.0001$).

3.7 Angiogenesis Inhibitor

GOG 218 established the addition of Bevacizumab to standard frontline chemotherapy for advanced high-grade epithelial ovarian cancer [75]. A total of 1873 women with incompletely resected stage III to IV disease were randomly assigned to carboplatin and paclitaxel versus chemotherapy plus concurrent bevacizumab versus chemotherapy plus concurrent and maintenance bevacizumab. The survival was similar in patients who received bevacizumab compared with chemotherapy alone. However, the median OS for stage IV bevacizumab-concurrent plus maintenance was 42.8 months vs. 32.6 months for the control arm. ENGOT-OV15/AGO-OVAR 17 (BOOST trial) included stage IIB–IV epithelial ovarian cancer who underwent primary cytoreductive surgery followed by chemotherapy and

bevacizumab [76]. Patients were randomized to receive bevacizumab for either 15 or 30 months. The PFS or OS were similar in both arms with increased adverse events with a longer duration of Bevacizumab.

3.8 Maintenance Therapy/ Monotherapy with PARP Inhibitors

Patients with BRCA 1 or BRCA 2 mutated ovarian cancer (BMOC) have improved survival, higher response to platinum, and longer treatment-free intervals compared with non-BRCA-mutated patients. This is because of an impaired ability of tumour cells to repair platinum-induced double-strand breaks, thereby conferring increased chemosensitivity and other DNA-damaging agents such as pegylated liposomal doxorubicin (PLD) [77]. The landmark change in the treatment of ovarian cancer has been the introduction of PARP inhibitors (PARPi). The principal mechanism of action is "synthetic lethality" wherein two genetic lesions which are not lethal singly but when combined in a cell become lethal [78].

Olaparib and Niraparib have been approved by FDA as maintenance therapy after first-line platinum-based chemotherapy [79]. SOLO-I randomized BRCA-mutated advanced, high-grade serous or endometrioid ovarian cancer with a complete or partial clinical response after platinum-based chemotherapy between Olaparib and placebo as maintenance monotherapy for up to 2 years [80]. After a median follow-up of 41 months, the risk of disease progression or death was 70% lower with Olaparib than with placebo [81]. After 5-year follow-up, the median progression-free survival was 56.0 months with Olaparib versus 13.8 months with placebo [80]. The most common grade 3–4 adverse events were anemia and neutropenia. PRIMA-III was another phase III RCT evaluating niraparib as maintenance in the frontline setting [82]. Patients with newly diagnosed advanced ovarian cancer were randomized to receive niraparib or placebo once daily after a response to platinum-based chemotherapy. Among the patients who had HR deficiency (50.9%), the median PFS was significantly longer in the niraparib group than in the placebo group. In the overall population, the corresponding progression-free survival was 13.8 months and 8.2 months ($p < 0.001$). At the 24-month interim analysis, the rate of overall survival was 84% in the niraparib group and 77% in the placebo group. Niraparib is the only PARPi approved for frontline maintenance treatment in advanced ovarian cancer regardless of biomarker status [83]. PAOLA-1 trial included all newly diagnosed, advanced, high-grade ovarian cancer after response to first-line platinum–taxane chemotherapy plus bevacizumab [84]. Patients were eligible regardless of the surgical outcome or BRCA mutation status. The patients were randomized to receive Olaparib or placebo for up to 24 months; all the patients received bevacizumab 15 mg/kg every 3 weeks for up to 15 months. The median PFS was 22.1 months with Olaparib plus bevacizumab and 16.6 months with placebo plus bevacizumab. VELIA/GOG-3005 was another three-arm phase III RCT exploring the addition of veliparib to frontline chemotherapy with carboplatin and paclitaxel and then continuing as maintenance therapy [85]. A reduction in risk to disease progression or death by 32% was noted (PFS 23.5 months vs. 17.3 months). The highest benefit was noted for BRCA-mutated (PFS 34.7 months vs. 22.0 months) and HR-deficient group (PFS 31.9 months vs. 20.5 months).

PARPi can be given as maintenance therapy in platinum-sensitive recurrent ovarian cancer (PSROC) or as monotherapy after multiple lines of chemotherapy. SOLO-II evaluated Olaparib in BRCAm PSROC after at least two lines of chemotherapy and demonstrated a benefit in PFS (19.1 months vs. 5.5 months) [86]. Median overall survival was 51.7 months (95% CI 41.5–59.1) with Olaparib and 38.8 months (31.4–48.6) with placebo (hazard ratio 0.74 [95% CI 0.54–1.00]; $p = 0.054$), unadjusted for the 38% of patients in the placebo group who received subsequent PARP inhibitor therapy [87]. NOVA evaluated niraparib in BRCAm PSROC and demonstrated a benefit in PFS (21.0 months vs. 5.5 months) [88]. Similarly, the non-gBRCAm with HRD+ cohort showed a benefit in PFS (12.9 months

vs. 3.8 months), and FDA approved niraparib as maintenance therapy in PROC in March 2017 [89]. On long-term follow-up however no difference in survival was observed. The authors concluded that the analysis is confounded by a high rate of crossover and missing data, thus limiting its interpretation [90]. NORA trial evaluated the effect of individualized dose of Niraparib on PFS in Chinese patients with platinum-sensitive recurrent ovarian cancer [91]. A significant improvement in PFS was seen in the Niraparib group even when receiving an individualized starting dose. ARIEL-III evaluated rucaparib in PSROC after at least two lines of chemotherapy and demonstrated the highest benefit in PFS for BRCAm (16.6 months vs. 5.4 months) and HRD+ (13.6 months vs. 5.4 months) versus ITT (10.8 months vs. 5.4 months) and was approved by FDA in April 2018 as maintenance therapy [92]. SOLO-III compared olaparib with investigators' choice of non-platinum chemotherapy (pegylated liposomal doxorubicin, paclitaxel, gemcitabine, or topotecan) in recurrent ovarian cancer (ROC) patients and demonstrated benefit in terms of objective response rate (ORR), with an odds ratio (OR) 2.53. In the subgroup who had already received two prior lines of treatment, the OR was 3.44 [93]. Rucaparib monotherapy vs. investigator's choice chemotherapy in patients with recurrent high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer with germline or somatic BRCA mutation has been investigated in ARIEL 4. It was presented in the first scientific Plenary Session of the Society of gynaecologic Oncology (SGO) 2021 Virtual Annual Meeting on Women's Cancer (Abstract ID 11479). The median progression-free survival was also 7.4 months in the experimental arm vs. 5.7 months in the chemotherapy arm (HR = 0.67, p = 0.002) with a similar objective response rate.

4 Endometrial Cancer

Uterine corpus cancer is the sixth most diagnosed cancer in women, more common in countries with a high human development index [1]. In 2020, the reported number of new uterine cancers was 417,367, and the number of uterine cancer-related deaths was 97,370 [1]. India reported 16,413 new cases and about 6385 deaths due to uterine malignancies. Heterogenicity in endometrial cancer is an emerging facet, and molecular profiling is enhancing the scope of precision medicine in gynaecologic oncology. In recent times, there have been advances in the understanding of molecular biology, adjuvant treatment for high-risk disease and HER2/neu-positive serous tumours, and immunotherapy.

4.1 Fertility Preserving Option

Young patients with well-differentiated endometrioid endometrial adenocarcinoma with no myometrial invasion are traditionally treated with high-dose oral progesterone [94]. The levonorgestrel-releasing intrauterine contraceptive device (LNG-IUS) in such subset of patients provides a possible role with 67–75% overall response at 6 months of use [95]. It has the advantage of lower side effects with respect to weight gain and venous thromboembolism when compared to oral progestins. Hysteroscopic resection in combination with oral progestin therapy is associated with a shorter treatment duration to achieve CR than treatment with progestin therapy alone [96]. There has been some growing evidence of the use of metformin in endometrial cancer. Decreased insulin sensitivity of the body tissues results in elevated levels of circulating insulin (increased insulin resistance). Subsequently, excessive insulin downregulates sex hormone-binding globulin levels and upregulates estrogen and androgen levels in the blood. Thus, insulin resistance leads to an increased risk for endometrial cancer. Metformin (insulin sensitizer) promotes the utilization of insulin by the body tissues and thus reduces the circulating levels of insulin. Metformin also suppresses endometrial cancer cell growth via cell cycle arrest, concomitant autophagy, and apoptosis by inhibition of the LKB1-AMPK-mTOR, PI3K-Akt, IGF-1-associated pathways [97].

4.2 Sentinel Node (SLN) Evaluation

Sentinel lymph nodes showed a high degree of diagnostic accuracy in detecting metastases and can safely replace complete lymphadenectomy in the staging of early stage well-differentiated endometrial cancer. Thus, the morbidity of lymphadenectomy can be avoided. SLN biopsies offer a compromise between omitting lymph node dissection and increased risk of systematic lymphadenectomy like lymphocyst formation or morbidity due to increased duration of surgery. The Fluorescence Imaging for Robotic Endometrial Sentinel lymph node biopsy (FIRES) trial is a multicenter, prospective cohort study evaluating the role of the sentinel node in clinical stage I endometrial cancer [98]. A sensitivity of 97.2% and a negative predictive value of 99.6% were reported. The accuracy of sentinel lymph node procedure compared with lymphadenectomy in women with intermediate- and high-grade endometrial cancer was assessed by Cusimano et al. (SENTOR trial) [99]. In this cohort study of 156 patients with endometrial cancer, including serous carcinoma, carcinosarcoma, and undifferentiated histology, SLNB had a sensitivity of 96% and a negative predictive value of 99% for the detection of nodal metastasis. A total of 26% of patients with node-positive cancer were identified outside lymphadenectomy boundaries or required immunohistochemistry for diagnosis. A prospective validation study by Solimon et al. included only high-risk histology [100]. Only blue dye was used in 28% and a sensitivity of 95% and False-negative rate of 5% was reported. The SHREC trial assessed the diagnostic accuracy of a pelvic sentinel lymph node algorithm in high-risk endometrial cancer [101]. The specific algorithm proposed by the authors had a sensitivity of 100% and a negative predictive value of 100%. The bilateral mapping rate was 95%. Based on these and other retrospective studies, SGO recommends both sentinel lymph node mapping and an algorithm-based approach to staging as acceptable alternatives to complete nodal staging in all grades and types of endometrial cancer [102].

4.3 Molecular Markers Guiding Therapy

The TCGA project determined four molecularly defined subgroups of endometrial cancer, which yielded excellent prognostic results [103]. It grouped endometrial cancer into four groups, namely group 1 (7%), which is an ultra-mutated group with DNA polymerase mutation and is associated with a good prognosis. Group 2 (28%) is a hyper-mutated group with microsatellite instability and defects in mismatch repair; group 3 (39%) has a low-copy number group that also exhibited microsatellite instability. Lastly, group 4 (26%) is characterized by a low mutation group, chromosomal instability, and high-copy number variations, and they are primarily with TP53 mutations, grade 3 tumours, and serous carcinomas. Group 4 is associated with worst prognosis.

However, the methods required for classification are currently quite expensive and require special handling of the tissue, limiting applicability. The Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) classification identifies molecularly distinct subgroups with a prognostic signature similar to that of the TCGA classification scheme [104]. The four groups were MMR-deficient (MMR-D), POLE exonuclease domain mutations (POLE EDMs), p53 abnormal, and p53 wild-type. The GOG 210/NRG group classification parallels TCGA classification. In the post-hoc analysis of the PORTEC-3 trial, patients with p53 abnormal tumours regardless of histology had significantly improved recurrence-free survival with combined chemotherapy and radiotherapy group compared to radiotherapy alone. Patients with POLE ultra-mutated cancers had excellent recurrence-free survival regardless of treatment modality [105]. Molecular classification is encouraged in all endometrial carcinomas, especially high-grade tumours, and prognostic risk groups are stratified based on this in recent ESGO/ESTRO/ESP guidelines [94].

HER2/neu overexpression in all histologic types of endometrial cancers is not similar. In the high-risk group of the PORTEC-3 study population, HER2 positivity was seen in 37.5% serous,

25% endometrioid, and 20.8% clear cell histology [106]. The association was strong between HER2 positivity and the p53 abnormal subgroup. Carboplatin and Paclitaxel with and without Trastuzumab in patients with advanced or recurrent uterine serous carcinoma who overexpress HER2/neu showed improved PFS and OS [107].

GOG 3007 evaluated the efficacy of everolimus and letrozole (EL) in women with recurrent endometrial cancer [108]. A 24% response rate in the everolimus/letrozole arm (PFS 6.4 months and OS 20.0 months) and a 22% response rate in the progestin/tamoxifen arm (PFS 3.8 months and OS 16.6 months) were reported.

4.4 Immunotherapy

PD-1 and PD-L1 are overexpressed in 75% and 25–100% of endometrial cancers, respectively [109]. These tumours show mutational overload with neoantigens and tumour-infiltrating lymphocytes, which make them an ideal candidate for immunotherapy. Keynote-028 evaluated the safety and efficacy of pembrolizumab, an anti-programmed death one monoclonal antibody, in patients with programmed death-ligand 1 (PD-L1)-positive advanced solid tumours. Pembrolizumab demonstrated a durable antitumour activity in a subgroup of patients with heavily pretreated advanced PD-L1-positive endometrial cancer [110]. This led to the FDA's first tissue/site-agnostic approval of Pembrolizumab for patients with microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) solid tumours progressed following prior treatment and has no satisfactory alternative treatment options. KEYNOTE-158 reported an overall response rate of 48% with pembrolizumab in patients with heavily pretreated, advanced microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) endometrial cancer [111, 112]. KEYNOTE-775/Study 309 compared pembrolizumab and multikinase inhibitor, Lenvatinib, with single-agent chemotherapy standard single-agent chemotherapy in patients with advanced, metastatic, or recurrent endometrial cancer progressing after a prior platinum-based regimen [113]. Lenvatinib/pembrolizumab led to a doubling in response rate: 31.9% vs. 14.7% with physician's choice of treatment. There was a significant improvement in overall survival and progression-free survival regardless of MMR status. The FDA approved pembrolizumab with lenvatinib for patients with advanced endometrial carcinoma, which is not MSI-H or dMMR, who have disease progression following prior systemic therapy, and who are not candidates for curative surgery or radiation [114].

4.5 Adjuvant Treatment in High-Risk Endometrial Cancers

Approximately 15–20% of endometrial cancer patients are at increased risk of recurrence or distant metastases and are thus classified as high risk [115]. Multiple studies have characterized the risk of postsurgical recurrence and tried to identify adjunctive therapies to reduce it. PORTEC-3 investigates the benefit of adjuvant chemotherapy during and after radiotherapy versus pelvic radiotherapy alone for women with high-risk endometrial cancer [116]. At a median follow-up of 72.6 months, 5-year overall survival was 81.4% with chemoradiotherapy versus 76.1% with radiotherapy alone (HR 0.70, $p = 0.034$), and 5-year failure-free survival was 76.5% versus 69.1% (HR 0.70, $p = 0.016$) [117]. The benefit was mainly for women with stage III and serous cancers. GOG 249 compared vaginal cuff brachytherapy and chemotherapy (VCB/C) with pelvic radiation therapy (RT) in high-intermediate and high-risk early-stage endometrial carcinoma concerning recurrence-free survival (RFS) [118]. The 5-year RFS and OS were similar in both the groups but pelvic or paraaortic nodal recurrences were more common with VCB/C (9% vs. 4%). GOG 258 compared a similar chemoradiotherapy regimen as in PORTEC-3 with six cycles of chemotherapy alone in stage III and IVA endometrial cancer [119]. The relapse-free survival was similar in both groups. Vaginal, pelvic, and paraaortic nodal recurrence was more common in the chemotherapy arm, and distant recurrences were more common with chemoradiotherapy. The use

of chemoradiation maximizes RFS and OS and nodal control in women with stage III disease or serous histology. In the translational study of PORTEC-3, patients with p53abn endometrial cancer had the worst outcome. They showed a significant survival benefit of added adjuvant chemotherapy: Mismatch repair-deficient endometrial cancers had an intermediate prognosis, and RFS was similar in radiotherapy and chemoradiation arms. Hence, adding chemotherapy to radiotherapy did not reduce mismatch repair-deficient endometrial cancer recurrence [120].

5 Vulvar Carcinoma

These are rare malignancies, representing 4% of all gynaecological cancers. Emerging evidence suggests an increase in both vulvar intraepithelial neoplasia and invasive vulvar cancer in young women. This rising trend has been attributed to smoking, Human Papilloma Virus (HPV) infection, and changing sexual behavior [121]. HPV positivity in vulval cancer is a good prognostic factor. Recently, genomic alteration revealed a new category of HPV-negative vulval cancer with NOTCH1 and HRAS mutations and normal p53 expression. This new subtype of vulval cancer is considered to have an intermediate 5-year survival rate [122].

5.1 Updated Staging

FIGO staging of vulvar cancer was updated in 2021 for all morphologic types except melanoma [123]. FIGO 2021 staging allows incorporation of cross-sectional imaging findings into vulvar cancer staging similar to cervical cancer, and documentation regarding the HPV status of the carcinoma of the vulva is strongly recommended. Main changes were made in stage III disease; stage IIIA included an extension to upper two-thirds of the urethra and vagina or extension to bladder mucosa, rectal mucosa, or regional lymph node metastases ≤5 mm, stage IIIB being any regional nodal metastases >5 mm, and IIIC being regional lymph node metastases with extracapsular spread.

5.2 Sentinel Node

Groningen International Study on Sentinel nodes in Vulvar cancer, GROINSS V I, was an observational validation study on vulvar cancer's sentinel node (SLN) procedure [124]. After a median follow-up of 105 months, the isolated groin recurrence rate was 2.5% for sentinel node-negative patients, and disease-specific 10-year survival was 91%. This European guideline recommended the SLN procedure in patients with unifocal cancers of less than 4 cm, without suspicious groin nodes [125]. When an ipsilateral sentinel lymph node is not detected, a complete ipsilateral inguinofemoral lymphadenectomy must be done, and if an ipsilateral sentinel lymph node is positive, a complete bilateral inguinofemoral lymphadenectomy is recommended [126]. The sequel to the GROINSS-V trial, GROINSS-V II, investigates the efficacy of groin radiation without inguinofemoral lymphadenectomy for patients with positive sentinel nodes [127]. Among patients with SN micrometastases (≤2 mm), patients who received groin radiotherapy had a groin recurrence rate at 2 years of 1.6%. In patients with SN macrometastases (>2 mm), the isolated groin recurrence rate at 2 years was 22% after radiotherapy only, and 6.9% in those who underwent inguinofemoral lymphadenectomy followed by radiotherapy ($p = 0.011$) [127]. NCCN version 1.2022 incorporates this into the guideline and recommends only EBRT with or without chemotherapy for single sentinel node-positive with ≤2 mm metastases. Complete inguinofemoral lymphadenectomy is the preferred approach for sentinel node metastases more than 2 mm [128]. GROINSS-V III is investigating whether the efficacy of treatment can be increased by enhancing the dose of radiotherapy and by adding concurrent chemotherapy to inguinofemoral radiotherapy.

5.3 Tumour-Free Surgical Margin

NCCN recommends a gross surgical margin of 1 cm and 8 mm pathologic margin [128]. A smaller margin is acceptable to preserve critical structures like the clitoris, urethra, and anal sphincter. Re-excision or adjuvant radiotherapy is advised only for margin positive for invasive cancer [128], whereas FIGO 2021 report on vulvar cancer states, cases with close, i.e., less than 5 mm surgical margin, may benefit from adjuvant radiotherapy if re-excision of the margins is not possible without severe morbidity [126].

5.4 Systemic Therapy

New therapies for recurrent, progressive, and metastatic disease include testing for mismatch repair/microsatellite instability, PD-1 and NTRK gene fusion, and use of Larotrectinib or Entrectinib for NTRK gene fusion-positive tumours [128].

6 Gestational Trophoblastic Neoplasia

Hemida et al. reported an RCT, where patients with low-risk gestational trophoblastic neoplasia were randomized to a second curettage or no curettage group before methotrexate treatment, and its effect on the number of chemotherapy courses and the relapse rate was studied [129]. The mean number of chemotherapy courses required to reach hCG normalization was 4.4 in the control group vs. 3.8 in the intervention group (p = 0.14). Immunotherapy has made its way into the armamentarium against chemotherapy-resistant gestational trophoblastic neoplasia (GTN) since PD-L1 is constitutively expressed in all subtypes of GTN. TROPHIMMUN is a phase II trial that assessed avelumab in women with chemotherapy-resistant GTN [130]. In patients with single-agent chemotherapy-resistant GTN, 53.3% had hCG normalization after a median of 9 avelumab cycles with a favorable safety profile. CAP 01 trial evaluated the activity and safety of camrelizumab (PD-1 inhibitor) plus apatinib (VEGF receptor inhibitor) in patients with high-risk chemorefractory or relapsed gestational trophoblastic neoplasia [131]. This is a single-center phase II study including 20 patients. The objective response rate was 55%; ten (50%) patients had a complete response.

7 Uterine Mesenchymal Tumours

ESMO-EURACAN-GENTURIS Clinical Practice Guideline for soft tissue and visceral sarcoma has outlined some definitive recommendations for managing uterine sarcoma [132]. Adjuvant radiotherapy does not improve RFS or OS. Still, it can be an option in selected cases, considering risk factors, including local relapse, cervical involvement, parametrial involvement, serosal involvement, and UES histology. Adjuvant chemotherapy in the uterus-confined leiomyosarcoma is not the standard. Adjuvant hormonal therapy (HT) is not the standard treatment for endometrial stromal sarcoma, though there is retrospective evidence of decreased relapse [133]. GOG 277 is a phase III trial to determine whether adjuvant chemotherapy with gemcitabine-docetaxel followed by doxorubicin improves survival compared to observation in women with resected, uterus-confined, high-grade LMS [134]. Despite international collaboration, the study was closed for accrual futility. The observed OS and RFS data do not suggest superior outcomes for patients treated with additional doxorubicin after gemcitabine and docetaxel.

8 Conclusion

Genetic and molecular alterations in oncology are now being integrated and translated into clinical practice with significant benefits. Precision surgery is individual tumour biology coupled with image-guided surgery, and new developments are giving

encouraging results [135]. Emerging and meaningful contemporary research is being carried out worldwide to evolve the best practice available in the treatment of cancer patients. The social media platform is a helpful tool wherein any latest development can be shared for the benefit of humankind. In the future, the advancement and integration of preventive oncology into primary health care facilities would be an important milestone to combat the increasing trend of cancers worldwide.

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