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REVIEW ARTICLE

Gynecological Cancers—the Changing Paradigm

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Abstract
Outstanding research in the last few decades led to newer insights into the management of gynecological cancers. In the preventive arena, the efficacy and safety of HPV vaccination are well accepted and is now in addition to bi- and quadrivalent vaccines; there is a nonavalent vaccine against nine oncogenic HPV strains. Recent studies also looked into the dosaging schedules and age of vaccination against HPV to improve the vaccine efficacy and coverage. HPV testing is now approved as a primary screening test for cervical cancer in women aged more than 30 years with better sensitivity than the traditional cytology. Opportunistic salpingectomy for ovarian cancer prevention and neoadjuvant chemotherapy for advanced ovarian cancers are accepted practices. The role of personalized medicine in ovarian cancer and comprehensive genomic analysis of endometrial cancers are also covered in this review.

Keywords Gynecological cancers · HPV vaccination · Personalized treatment · Molecular characterization endometrial cancers

Introduction

Gynecological cancers form 12% of female cancers and 15% of female cancer survivors were treated for gynecological cancers. The last few years witnessed the intense research into the development and progression of these cancers which resulted in the evolution of new and advanced strategies for detection, prevention, and treatment of these cancers.

Update on HPV Vaccination

Cervical cancer is the most common cause of cancer-related mortality among women in developing countries including India [1]. The incidence of cervical cancer as reported by various population-based cancer registries is showing a declining trend but there is a marked geographic variation. India lacks an effective screening program, and less than 5% of eligible women undergo screening in India [2]. Considering the fact that HPV infections cause almost all of the cervical cancers, primary prevention of cervical cancer by HPV vaccination is the logical solution to this dreaded disease. When HPV vaccines were licensed in 2006 after extensive trials, it was speculated that this could lead to the eradication of cervical cancer, the major cancer killer among females [3, 4]. Although this has not happened due to the so-called barriers in immunization, the vaccine has probably stood the test of time [5, 6]. We have now long-term results of safety and efficacy of the vaccine and the vaccine has been introduced in the immunization program of over 60 countries [7–10].

One major issue with the implementation of a vaccination program in our country is the cost of the vaccine. There has been a considerable reduction in the vaccine costs recently and an Indian vaccine at a much lower cost is under clinical trials. Another strategy for cost reduction is reducing the number of dosages. There are studies looking into the immunogenicity of HPV infection after one, two, or three doses of the vaccine including a large randomized study from India by Sankaranarayanan et al. concluding that in girls less than 15 years, two doses of vaccine at a 6–12-month interval has an equally good immunological response [11, 12].

HPV vaccine is recommended by the Indian Academy of Pediatrics (IAP) [13]. The minimum age for vaccination is 9 years. For girls aged 9–14 years, two dosage schedule, and for more than 15 years, three dosage schedule with the second dose at 1–2 months after the first, and a third at 6–12 months after the first dose is followed. For immuno-compromised individuals, including HIV-infected, the three-dose schedule is recommended irrespective of age. Both bivalent and quadrivalent vaccines are licensed in India and either of the two

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brands can be used but the same brand should be used for the entire series.

Trials on vaccination of women more than 25 years have also been conducted which showed that the vaccine is effective even in older women as there is a continued risk of acquiring HPV infection throughout the reproductive age [14–17]. So catch-up vaccination is permitted up to 45 years. This expands the indications of HPV vaccination, but the cost-effectiveness of the vaccine in this age group especially in our country is yet to be evaluated.

In addition to the quadrivalent and bivalent vaccine, now a nonavalent vaccine also has been licensed. It is effective against HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58. It has a similar immunological response as the quadrivalent vaccine and greater efficacy compared to older vaccines [18–21].

HPV Testing for Cervical Cancer Screening

Newer developments in cervical cancer screening include the development of HPV testing for primary screening for cervical cancer in women more than 30 years [22]. HPV testing has a better sensitivity in comparison to cytology and is more reproducible. The ATHENA study for HPV DNA tests versus liquid-based cytology for cervical cancer screening found that HPV test outperformed cytology in detecting cervical precancerous lesions [23, 24]. A 5-year screening with HPV DNA testing is now accepted in the age group of 30–65 years, and for HPV-negative patients, the 5-year cancer risk is < 0.016% [25, 26]. HPV infections in women less than 30 years regress in the majority within 2 years and hence, HPV testing as cervical cancer screening is not useful in women less than 30 years.

The major hurdle in implementing screening programs in our country is non-attendance in screening camps due to practical issues including the unpleasant nature of the examination. This can be overcome to some extent by HPV self-sampling which can increase the participation in screening camps. Women can be encouraged to collect vaginal samples for HPV testing which gives the same sensitivity as clinician-collected samples [27–29].

Hope for Ovarian Cancer Prevention

Ovarian cancer is the most lethal gynecological cancer as majority of ovarian cancers are diagnosed in advanced stages, and in spite of cytoreductive surgery and platinum-based chemotherapy, the recurrence rates are quite high. It is asymptomatic in early stages and screening is also not found to be effective for ovarian cancers. Transvaginal ultrasound and CA125-based screening techniques for ovarian cancer are associated with low sensitivity and specificity and high false-positive rates [30–32].

Patients with hereditary breast-ovarian cancer syndromes are at higher risk of ovarian cancer. BRCA 1 mutation associated with 40–60% risk and BRCA 2 mutation with 16–24% risk. In patients with BRCA mutation before completion of family, oral contraceptive pills give a 40–50% risk reduction. In these patients, after childbearing, a completed risk-reducing salpingo-oophorectomy is an accepted procedure between 35 and 40 years which gives a 60–80% protection [33, 34]. This is not applicable to the general population considering the lower risk of ovarian cancer and the dangers of early surgical menopause.

Now, a recent insight into the etiopathogenesis of ovarian cancer revealed the distal fallopian tube to be the site of origin of these cancers [35]. So opportunistic salpingectomy during benign hysterectomy or any abdominopelvic surgery has been incorporated in gynecological practice [36]. Salpingectomy does not affect the ovarian blood supply and hence the ovarian function. In a patient who has completed childbearing salpingectomy does not have any side effects, the procedure is easy and does not increase the operative time, bleeding, or complication rates. In a retrospective study by Danish researchers, the risk of ovarian cancer in the general population was reduced by 42% by performing salpingectomy along with benign hysterectomy [37]. In a large Swedish study with 30,000 patients by Falconer et al., unilateral salpingectomy was associated with a 29% risk reduction while bilateral salpingectomy reduced the risk by 65% [38, 39]. This evidence substantiates the incorporation of opportunistic salpingectomy for reducing the risk of ovarian cancer in the general population.

Newer Trends in the Treatment of Advanced Ovarian Cancer

The treatment of advanced ovarian cancer was under much-heated discussion when the EORTC trial by Vergote et al. was published in 2010 [40]. This trial concluded that neoadjuvant chemotherapy (NACT) was non-inferior to primary surgical cytoreduction in patients with advanced ovarian cancer. The results were consistent with the JGOG trial and the CHORUS trial which also showed lesser morbidity after NACT [41, 42]. This contradicts with decades of retrospective studies validating the advantage of primary cytoreduction in improving patient survival [43–45]. The prospective randomized trials can never be compared to the retrospective data but the trials concluded that neoadjuvant chemotherapy was non-inferior to upfront surgery, meaning there is no better survival in NACT than with primary surgery. The most important predictor of survival in these trials is attaining optimal cytoreduction (OCR) which according to GOG definition in absence of gross

residual disease which depends on the surgical expertise available [46]. So the consensus now is if OCR can be attained with minimum post-operative morbidity in primary surgery, it should be considered for the individual patient. Patients in whom the extent of the disease suggests a low likelihood of getting OCR or when the general condition is too poor to withstand primary surgical procedure, NACT should be considered. In assessing the disease status to assess operability, imaging modalities including CT scans have low accuracy. Hence, diagnostic laparoscopy to assess the disease extent before primary cytoreduction has been proposed to reduce the rates of inoperability [47].

Ovarian cancer spreads directly into the peritoneal cavity, and administering chemotherapy into the peritoneal cavity helps in achieving several folds of high-drug concentration in the peritoneum and may help to eliminate the microscopic residual disease. Three large randomized trials GOG 104, 114, and 172 have demonstrated a survival benefit associated with intraperitoneal chemotherapy after attaining optimal cytoreduction in primary cytoreduction [48–50]. Following these trials, IP chemotherapy is an accepted treatment after primary cytoreduction. Recently, a study on intraperitoneal chemotherapy given under hyperthermic conditions at the end of cytoreductive surgery after NACT was published. This was a multicentric phase III trial with 245 patients, who underwent single administration of hyperthermic intraperitoneal chemotherapy (HIPEC) along with interval cytoreduction compared to surgery alone. Recurrence and death were less in the HIPEC arm (HR, 0.66; 95 CI%, 0.50–0.87; $P = .003$) and recurrence-free survival was more (14.2 vs 10.7 months) in patients who received HIPEC [51, 52].

Endometrial Cancer—Newer Insights

Endometrial cancers are the third common gynecological cancers in India [53]. Although the incidence is now less compared to cervical and ovarian cancers, there is a recent trend of increasing incidence, especially in the urban population. Majority of patients present with early stage disease and have a good prognosis; however, there is a subgroup of patients with a high-grade tumor which behaves in a more aggressive way and have poor survival. Nodal metastasis is a poor prognostic factor but the value of routine lymphadenectomy for endometrial cancer is controversial as randomized studies did not show a survival benefit. SENTI-Endo was a large prospective multicenter study which showed a good detection rate and diagnostic accuracy of sentinel node biopsy for endometrial cancer. Sentinel lymph node biopsy may resolve the debate on node dissection for endometrial cancer.

Based on the etiopathogenesis and clinical behavior, endometrial cancers are classified into two groups [54]. Type 1 endometrial cancers are associated with hyperestrogenism, preceded by endometrial hyperplasia, and have a favorable prognosis unlike type 2 tumors which occur in the atrophic endometrium, in older patients, and have a worse outcome. Type 1 cancers are of an endometrioid histological type, while type 2 tumors include serous or clear cell cancers. However, there is a group of high-grade endometrioid cancers which show clinical behavior similar to type 2 cancers.

Hence, a new classification based on the whole genome sequencing of cancer endometrium has been put forward by The Cancer Genome Atlas Research network [55]. They analyzed samples from 373 patients with whole-genome sequencing, exome sequencing, MSI assays, and copy number analysis. This TCGA classification groups cancer endometrium into four molecular subgroups—group 1 with p53 mutation identified, group 2 with microsatellite instability (MSI), group 3 with POLE ultramutated (POLE is a catalytic subunit of DNA polymerase epsilon involved in nuclear DNA replication and repair), and group 4, a group with no specific molecular profile (NSMP). They found that this classification correlated most with the clinical behavior of cancer. The ultramutated POLE and MSI subgroup had more favorable outcomes even with high-grade tumors while p53 mutant group and the NSMP had early recurrence and distance metastasis. So understanding the genetic alterations in endometrial cancer is very important in deciding on the aggressiveness of surgery, selection of patients for fertility-sparing management, and for deciding adjuvant therapy [56–58]. So molecular genetics would lead to a more personalized medicine in cancer endometrium.

Minimally Invasive Surgery for Gynecological Cancers

Since the 1990s, laparoscopic surgery is quite popular in the management of gynecological cancers. It has the advantages of shorter hospital stay, less complications, less blood loss, and lower transfusion rates compared to traditional laparotomy. Many patients with endometrial cancer are obese and minimally invasive surgery (MIS) is especially advantageous in these patients in reducing postoperative wound complications. Robotic surgery with 3D vision and more flexible instruments further enhance the efficacy. The oncological safety of MIS in endometrial cancer has been confirmed by various retrospective and prospective studies. The largest prospective randomized trial was the LAP2 trial by the Gynecologic Oncology Group with 2616 patients, which compared laparoscopy to laparotomy in patients with stages I and IIA uterine cancer. The study concluded that laparoscopic staging for endometrial cancer is feasible and safe in terms of short-term outcomes and results in fewer complications and shorter hospital stay compared to laparotomy [59]. The long-term data from the same study also showed that survival was not

adversely affected after laparoscopic staging in patients with endometrial cancer establishing the oncological safety [60].

Minimally access surgery for performing a radical hysterectomy for early cervical cancer was also popular in many cancer centers throughout the world. There are many retrospective and observational studies on the feasibility and safety of the procedure but recently, two studies were reported at the Society of Gynecologic Oncology Annual Meeting on Women's Cancer in March 2018 showing increased recurrence rate and lower overall survival after minimally invasive surgery for cervical cancer. The LACC (Laparoscopic Approach to Carcinoma of the Cervix) study was a randomized trial comparing minimally access surgery to laparotomy for cervical cancer [61]. The recurrence rate after MIS was almost four times higher than open surgery with a hazard ratio for disease-free survival (DFS) of 3.74 (at 4.5 years) for MIS compared to open surgery. The second study was a retrospective analysis from the Surveillance, Epidemiology, and End Result (SEER) database with 2221 patients comparing MIS to open surgery [62]. This also showed a 50% higher risk of dying within 4 years of surgery with minimally invasive hysterectomy compared with open surgery. In the light of these two studies, it is suggested that laparoscopic or robotic radical hysterectomy was associated with higher recurrence rates and worse overall survival than the open approach in women with early cervical cancer.

Targeted Therapy in Gynecological Cancer

The introduction of targeted therapy in oncology has resulted in much less treatment-related morbidity than traditional chemotherapy. The study of the molecular basis of cancers has led to the development of targeted therapy which inhibits cancer-specific pathways while sparing the normal cells. Targeted therapies used in advanced ovarian cancer include antiangiogenic drugs and poly (ADP-ribose) polymerase (PARP) inhibitors. Vascular endothelial growth factor (VEGF) which facilitates angiogenesis is targeted by bevacizumab. Two large randomized trials, GOG 218 and ICON7, in patients with advanced ovarian cancer showed that the addition of bevacizumab to conventional chemotherapy improved the progression-free survival [63, 64]. PARP inhibitors act on cells with a defect in homologous recombination pathways to PARP inhibition which is seen in BRCA mutations. Olaparib, a PARP inhibitor has been proven to be effective in preventing recurrence of platinum-sensitive ovarian cancer [65]. GOG 240 trial showed that bevacizumab in combination with chemotherapy is effective in patients with recurrent or metastatic cervical cancer [66].

Low-grade endometrial stromal sarcomas are slow-growing tumors with estrogen and progesterone receptor positivity and adjuvant hormonal treatment with aromatase inhibitors and progestogens are now popular with literature showing equally good results as chemotherapy [67].

Conclusion

There have been various practice-changing studies in the field of gyneoncology recently. The most significant of these are the so-called personalized or precision medicine which takes into account the individual genetic variations to decide on the treatment strategy. Future research advances in this field will probably improve the results of gynecological cancer treatment.

Compliance with Ethical Standards

Ethical Statement This is a review article and did not include the study of patients, medical records, or volunteers, so as per our institutional guidelines, this article did not require the approval of a hospital ethical committee. The research did not include human or animal participants.

Conflict of Interest The author declares no conflict of interest.

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