

Review Article

Gynecological cancers: A summary of published Indian data

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Abstract

Gynecological cancers are among the most common cancers in women and hence an important public health issue. Due to the lack of cancer awareness, variable pathology, and dearth of proper screening facilities in developing countries such as India, most women report at advanced stages, adversely affecting the prognosis and clinical outcomes. Ovarian cancer has emerged as one of the most common malignancies affecting women in India and has shown an increase in the incidence rates over the years. Although cervical cancer is on a declining trend, it remains the second most common cancer in women after breast cancer. Many researchers in India have published important data in the field of gynecologic oncology, covering all domains such as basic sciences, preventive oncology, pathology, radiological imaging, and clinical outcomes. This work has given us an insight into the in-depth understanding of these cancers as well as the demographics and survival rates in the Indian population. This aim of this review is to discuss the important studies done in India for all gynecological cancers.

Key words: Cancer, gynecological, India, Indian

Introduction

Ovarian and cervical cancers are the most common gynecological cancers affecting women worldwide and in India. Cervical cancer is on a declining trend, but remains the second most common cancer in women after breast cancer. Every year in India, 122,844 women are diagnosed with cervical cancer and 67,477 die from this disease.^[1] Over the past years, many Indian researchers have published studies in gynecologic oncology, and this review discusses the important work done in this field. The review covers

the studies published in various domains of each gynecological cancer and will discuss the demographics and clinical and survival outcomes of these cancers in the Indian population.

Ovarian Cancer

Basic sciences

A lot of research have made headway to study the behavior and etiology of the heterogeneous group of ovarian cancers,

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and several studies by Indian scientists demonstrate the development in this direction. Basu *et al.* studied the status of transforming growth factor beta (TGF- β) signaling in human ovarian tissues by immunohistochemistry (IHC) and found that pituitary homeobox 2 (PITX2)-induced TGF- β pathway regulated the expression of invasion-associated genes, SNAIL, CDH1, and MMP9 ($P < 0.01$) that accounted for enhanced motility and invasion in ovarian cancers.^[2] SNAIL and MMP9 acted as important mediators of PITX2-induced invasiveness of ovarian cancer cells. PITX2 overexpression resulted in the loss of epithelial markers ($P < 0.01$) and gain of mesenchymal markers ($P < 0.01$) that contributed significantly to ovarian oncogenesis. A study by Choudhuri *et al.* investigated biomarkers to help in the detection and assessment of therapeutic response in epithelial ovarian cancer (EOC).^[3] Besides CA-125, levels of plasma tyrosine-lysine-leucine-40 were significantly raised in patients with EOC (77.0%; $P < 0.0001$) and significantly decreased post-therapy. Circulating cell-free DNA ($P < 0.0001$) and cell-free nuclear DNA ($P < 0.0001$) levels also decreased significantly post-treatment as compared to pretreatment levels. Chemotherapy plays a major role in ovarian cancer therapeutics and remains one of the most important aspects of management of these patients. A group of researchers studied the primary cultures of EOC cells established from ascitic fluids of untreated ovarian cancer patients and the SKOV-3 ovarian cancer-derived cell lines.^[4] The respective cells were treated with metformin, carboplatin, and paclitaxel alone, and its various combinations and their effects, including the ability to induce apoptosis, were examined. Metformin induced apoptosis in the ovarian cancer cells by downregulating Bcl-2 and Bcl-xL expression and upregulating Bax and cytochrome c expression and provoked a cell cycle arrest in the G0/G1 and S-phase. The apoptosis induction by metformin could be enhanced by a combinatorial use of carboplatin and/or paclitaxel. Another study from a tertiary cancer center in India reported an upregulated insulin-like growth factor 1 receptor (IGF-1R) expression in the early stages of cisplatin-paclitaxel and cisplatin-taxol resistance.^[5] Picropodophyllin, an IGF-1R inhibitor, alone and in combination with cisplatin, paclitaxel, or both at lowest possible doses, could reverse the resistance at early stages.

Khandakar *et al.* studied the tissue biomarkers in the prognostication of serous ovarian cancer following neoadjuvant chemotherapy (NACT) and found that MIB-1 was significantly lower in cases treated with NACT, and the survival outcome was significantly better in cases with low MIB-1.^[6] Estrogen receptor expression was associated with a poor overall survival (OS). No other markers (p53, progesterone receptors, Her-2/neu, E-cadherin, and Bcl-2) displayed any significant difference in the expression or correlation with survival between the two groups. Many recent trials have explored the use of vascular endothelial growth factor (VEGF) inhibitors in ovarian cancers. Ravikumar and Crasta reported VEGF expression in forty cases of ovarian serous carcinomas.^[7] Thirty-two cases (80%) had a VEGF score of >2 (positive) and eight cases had a VEGF score of <2 (negative). The median Ki-67 index, indicator of tumor proliferation, was much higher in VEGF-positive cases as compared to VEGF-negative tumors (57.5% vs. 40%).

The role of genetics in the etiopathogenesis of ovarian cancer is well known. Shilpa *et al.* studied the BRCA1 promoter hypermethylation and protein expression in ovarian carcinoma in Indian population.^[8] They found that the frequencies of methylation in EOCs and low-malignant potential tumors were 51.2% and 57%, respectively, significantly higher ($P = 0.000$ and $P = 0.001$) in comparison to benign tumors and normal ovarian tissue where no methylation was seen. Expression of BRCA1 was significantly lower in EOCs ($P = 0.003$). Lack of protein expression correlated with tumor grade and type, and the methylation status correlated well with downregulation of BRCA1 expression. A pilot study involving thirty women with EOC conducted at a university hospital identified five sequence variants in BRCA1, of which three novel sequence variants were found in 23 patients while in BRCA2, one novel sequence variant was found. The three founder mutations 187delAG, 5385insC in BRCA1, and 6174delT in BRCA2 were not seen in any of the patients.^[9]

Demographics and pathology

A study of 957 ovarian neoplasms showed that most of the benign tumors occurred between 20 and 40 years of age, while the malignant lesions presented commonly between 41 and 50 years of age.^[10] The most common benign tumors were serous cystadenoma (29.9%), followed by mature teratoma (15.9%) and mucinous cystadenoma (11.1%). Serous cystadenocarcinoma was the predominant malignant tumor (11.3%) and 49.5% them were bilateral. Borderline serous tumors showed bilateral involvement more commonly (27.4%) than borderline mucinous tumors (15.7%). Most of the malignant tumors presented as Stage III (60%) or Stage II (20%) disease. The OS rate was 85% for Stage I tumors, 65% for Stage II, 30% for Stage III, and 15.5% for Stage IV tumors.

A few clinicopathological studies of relatively uncommon ovarian tumors have been published by Indian authors. In a study of 28 cases of immature teratoma, neuroepithelium was seen in 26 cases (6 were Grade 1, 13 were Grade 2, and 7 were Grade 3); two cases showed immature mesenchymal tissue (IM) only.^[11] IM was seen in all the 28 cases, but no correlation with the grade was found. The follow-up was available for 23 cases - 13 Stage I, 3 Stage II, and 7 Stage III immature teratomas. Out of 23 patients, 17 patients were alive without evidence of disease recurrence while six patients either recurred or died from the disease. In a series of 27 cases of primary ovarian malignant mixed mullerian tumors, 14 patients had advanced stage (Stages III and IV) at presentation.^[12] Cytoreductive surgery was done in 18 cases, and seven cases received upfront chemotherapy. Histologically, ten cases had epithelial predominance ($>50\%$ epithelial component) and 11 had sarcoma predominance. The most frequent epithelial component was endometrioid type and most common sarcoma component was rhabdomyosarcomatous.

A retrospective analysis of 31 cases of borderline ovarian tumors showed that the serous tumors were bilateral in 39%, revealed surface growth in 17%, and had peritoneal implants in 11% of the cases.^[13] The mucinous tumors were bilateral in 11% of the cases and had associated pseudomyxoma peritonei in 22% of the cases. Nuclear grade appeared to correlate with

extraovarian spread and surface growth in the serous borderline tumors, but not in the mucinous borderline tumors. Surface growth correlated with recurrences. The prognosis remained good in serous borderline tumors even in the presence of implants as these were noninvasive. The mean disease-free survival (DFS) was 43.03 months. There was no statistical difference in DFS of patients with and without implants. A clinicopathological study of adult granulosa cell tumors of the ovary reported that optimal cytoreduction ($P = 0.02$), presence of nuclear atypia ($P < 0.001$), and increased mitoses ($P = 0.03$) impacted significantly on the survival of patients.^[14] Age, stage of the tumor, parity, and size of the tumor had no significant effect on the survival. Patients who received chemotherapy had a better median DFS than those who did not (60 vs. 48 months), but this did not reach statistical significance ($P = 0.08$).

Many women present with suspicious adnexal masses in an oncologist's practice, and besides the tumor markers and radiological imaging, some patients merit biopsy or fine-needle aspiration cytology (FNAC) from the adnexal mass. Preoperative FNAC has been found to have a sensitivity for a diagnosis of malignancy of 85.7%, specificity of 98.0%, positive predictive value of 97.7%, negative predictive value of 87.7%, and accuracy of 92.0%.^[15] Intraoperative frozen section has been used in the diagnosis of ovarian neoplasms during exploratory laparotomy, and a study from tertiary oncology center in 210 patients revealed that frozen section report had a sensitivity of 100%, 93.5%, and 45.5% for benign, malignant, and borderline tumors, respectively.^[16] The corresponding specificities were 93.2%, 98.3%, and 98.5%, respectively. The overall accuracy of frozen section diagnosis was 91.2%. The majority of cases of disagreement were in the mucinous and borderline tumors.

IHC has been found to be a valuable tool in differentiating ovarian cancers from other cancers, especially those arising from gastrointestinal tract.^[17] In an analysis of twenty cases of ovarian involvement by metastatic colorectal adenocarcinomas and colorectal involvement by metastatic ovarian adenocarcinomas, 45% were colorectal adenocarcinomas metastatic to the ovary, and on biopsy showed a "garland-like" tumor necrosis, with desmoplasia and predominantly exhibited a tubuloalveolar pattern (67% of the cases). On IHC, all eight of the nine such cases, where staining for cytokeratin 20 (CK20) was performed, displayed strong positivity and seven cases, where staining for carcinoembryogenic antigen was performed, revealed positivity for the marker (100%). Other 11 cases (55%) were ovarian adenocarcinomas, metastatic to the colorectum. Morphologically, psammomatous calcification was noted in 73% of these cases, whereas "garland-like" necrosis was absent in all. On IHC, CK7 and CA-125 were positive in all 6 of 11 such cases, whereas CK20 was negative in all these cases.

Imaging

The role of positron emission tomography (PET) scan in gynecological cancers has been studied by many authors in literature. A pilot study explored the role of fluorodeoxy glucose PET-computed tomography (FDG PET-CT) in asymptomatic EOC with rising serum CA-125.^[18] The sensitivity and specificity of PET-CT scan to detect recurrent

disease were 100%. This could be confirmed on histopathology/FNAC in 66.7% of the true-positive cases.

While primary cytoreduction has been the standard of care in the management of ovarian cancers, NACT followed by interval debulking has been shown to have similar survival rates. NACT has been found to be especially useful in patients with extensive upper abdomen and extensive peritoneal disease. Preoperative evaluation of peritoneal deposits using multidetector CT by Chandrashekhara *et al.* showed that the most common sites to have peritoneal deposits were the pouch of Douglas and the right subdiaphragmatic region.^[19] The sensitivity of CT in the detection of peritoneal deposits ranged from 33.3% to 88.9% (mean 61.58%). Sensitivity was low (33.3%) in the umbilical and left lumbar region and high in the pelvis (80%) and epigastrium (88.9%). The specificity for all findings was quite high, ranging from 88.9% to 97.1%.

Clinical outcomes

NACT followed by interval debulking and then adjuvant chemotherapy has been found to be noninferior to primary cytoreduction followed by adjuvant chemotherapy. A 7-year audit from a tertiary care center reported that 41.4% of the patients of advanced EOC underwent primary surgery and 58.6% received NACT.^[20] An optimal debulking rate of 81% was achieved with 70% for primary surgery and 88% following NACT. The optimal cytoreduction rate has improved from 55% in 2004 to 97% in 2010. The progression-free survival (PFS) and OS in patients undergoing primary surgery were 23 and 40 months, respectively, while it was 22 and 40 months, respectively, in patients who received NACT.

In a retrospective analysis of 82 patients with advanced EOCs (Stage IIIC and IV) who were treated with NACT followed by surgical cytoreduction, complete response (CR) occurred in 17 patients (20.7%), 50 (61.0%) had partial response (PR), and no response was documented in 15 (18.3%) patients.^[21] Optimal surgical cytoreduction could be achieved in 72% of the patients. At the median follow-up of 34 months (range 6–102 months), 5-year DFS and OSs were 31 and 32%, respectively. The median disease-free interval was 25.4 months. On multivariate analysis, degree of optimal cytoreduction was the only factor ($P < 0.05$) affecting survival. NACT has also been used in advanced germ cell tumors of ovary, and in a study of 23 such patients, 21 responded as CR in 16 patients and PR in 5 patients. Eighteen of the 21 responders underwent surgery; 13/18 had pathological CR and 5/18 had residual disease and achieved CR following two more cycles of BEP. At a median follow-up of 74 months, 21 of the 23 patients were alive and disease-free.^[22]

Intraperitoneal chemotherapy (IPCT), though accompanied by its complications, has been shown to improve survival in optimally cytoreduced advanced EOC and primary peritoneal cancers. Maheshwari *et al.* reported on the feasibility of IPCT in advanced EOC.^[23] The total number of IPCT cycles planned in 11 patients was 36, of which 30 cycles (85.8%) could be given. The D8 chemotherapy (IP paclitaxel) could not be given in 36.7%, and dose reduction by $\geq 25\%$ was required in 6.7%, due to significant toxicity. Various toxicities (Grade 3/4) were vomiting in 13 women (43.3%), abdominal pain in 10 (33.3%), diarrhea in 3 (10%), dyselectrolytemia in 8 (26.7%), neutropenia in 12 (40%), febrile neutropenia in

3 (10%), anemia in 5 (16.7%), thrombocytopenia in 1 (3.3%), and postoperative radiation therapy (PORT) site extravasation of cisplatin in 1 (3.3%). There was no treatment-related mortality. In another study on IPCT, 100 consecutive patients of Stage III EOC who had optimal cytoreduction underwent chemoport insertion during laparotomy.^[24] Out of a total of 600 IP cycles, 516 cycles (86%) were completed. Seventy patients (70%) received all the 6 cycles by IP route. Nine patients (9%) had port-related complications, which included catheter block in five cases and backflow of fluid around catheter in four cases. Two patients had severe abdominal pain due to dense adhesions, and further cycles were completed by IV route. With a median follow-up of 1.8 years, 70% of the patients were disease-free on follow-up.

Chitrathara *et al.* in a study entitled, “Is hysterectomy needed in ovarian cancer?” found that in 128 patients of EOC, most of them presenting with Stage III or above, uterus was grossly involved in only 19 patients and microscopic involvement was noted in twenty patients.^[25] Involvement of the uterus was found to be independent of stage, type of tumor, laterality, and preoperative chemotherapy. The grade of tumor and gross uterine involvement were the only factors that showed statistically significant correlation with microscopic uterine involvement. Hence, the absence of gross uterine involvement reliably predicted the absence of microscopic disease.

Majority of the ovarian cancers present at advanced stage, and unfortunately, most of them are known to relapse after primary treatment which includes cytoreduction and chemotherapy. Secondary cytoreduction has a limited role in recurrent ovarian cancer and is reserved for patients with a long disease-free interval and isolated site(s) of recurrence. A study of 48 patients with recurrent ovarian cancer (disease-free interval >6 months after completion of primary treatment with clinical and/or radiographic findings suggestive of recurrence) undergoing secondary cytoreduction reported that optimal cytoreduction was attained in 29 patients (60.4%) and the estimated 5-year OS was 32.25%.^[26] While many lines of intravenous chemotherapy have been effective in relapsed ovarian cancer, a recent Phase II study reports on the use of oral metronomic combination therapy.^[27] Twenty-six patients of relapsed EOC were accrued, of whom 21 had received two prior lines of CT and five had received three lines. Twenty-five patients who were evaluable for analysis received a median of 6 (1–19) cycles of metronomic regimen - etoposide (50 mg/m²) and cyclophosphamide (50 mg/m²) for 21 of a 28-day cycle plus tamoxifen (20 mg/m², twice per day) continuously. Thirteen (52%) patients needed dose reduction after a median of 3 (1–9) cycles. The most common Grade 3 or 4 toxicities included anemia, neutropenia, febrile neutropenia, nausea, vomiting, and diarrhea in 44%, 36%, 12%, 16%, 16%, and 12% patients, respectively. Nineteen (76%) patients had serological CR or PR and eleven (45.8%) patients achieved radiological CR or PR. The median serological PFS, radiological PFS, and OS were 7.9, 7.97, and 22.3 months, respectively. Shetty *et al.* studied the feasibility of image-guided intensity-modulated whole abdominal RT in eight patients of relapsed EOCs.^[28] With a median follow-up of 15 months (10–24 months, mean: 14 months), three patients developed disease recurrence. All

three recurred in peritoneum and one progressed to intestinal obstruction and fatal septicemia.

Cervical Cancer

Screening and prevention

Cervical cancer is a preventable disease, and regular Pap smears have long been used in developed countries to screen for cervical cancers, accounting for their low-incidence rates. Unfortunately, in developing nations such as India, due to lack of awareness programs and no formal screening programs, most women have presented in the advanced stages of cervical cancer. However, with the advent of visual inspection screening which can be done by primary health workers and better screening programs, the incidence of cervical cancer has been declining in the country.

A cluster randomized controlled trial of visual, cytology, and human papillomavirus (HPV) screening for cancer of the cervix conducted in rural India randomized 142,701 women aged 30–59 years into four arms with visual inspection with acetic acid (VIA), cytology, or HPV testing as well as a control group.^[29] Test-positive women underwent colposcopy and biopsy. The detection rate of high-grade lesions was similar in all intervention arms (0.7% for VIA, 1.0% for cytology, and 0.9% for HPV testing, $P = 0.06$). In a pooled analysis of cervical screening tests, VIA showed a sensitivity of 79% and 83% and a specificity of 85% and 84% for the outcomes cervical intraepithelial neoplasia (CIN)2+ or CIN3+, respectively.^[30] VILI was on average 10% more sensitive and equally specific. VIAM showed similar results as VIA. The Pap smear showed lowest sensitivity, even at the lowest cutoff of ASCUS (57%) for CIN2+, but the specificity was high (93%). The hybrid capture 2 (HC2) assay showed a sensitivity for CIN2+ of 62% and a specificity of 94%. In a comparative evaluation of HPV-DNA test versus colposcopy as secondary cervical cancer screening test to triage screen positive women on primary screening by VIA, Pimple and Shastri found that HPV DNA and colposcopy had a sensitivity of 61% and 43% and specificity of 99% and 99%, respectively, for detecting CIN2+ lesions.^[31]

Sankaranarayanan *et al.* in a cluster-randomized trial, with 131,746 healthy women, randomly assigned women to undergo screening by HPV testing, cytologic testing, or VIA, or to receive a standard care (control group).^[32] In the HPV-testing group, cervical cancer was diagnosed in 127 patients (of whom 39 had Stage II or higher), as compared with 118 patients (of whom 82 had advanced disease) in the control group (hazard ratio for the detection of advanced cancer in the HPV-testing group, 0.47; 95% confidence interval [95% CI]: 0.32–0.69). There were 34 deaths from cancer in the HPV-testing group, as compared with 64 in the control group (hazard ratio, 0.52; 95% CI: 0.33–0.83). No significant reductions in the number of advanced cancers or deaths were observed in the cytologic-testing group or in the VIA group, as compared with the control group. Shastri *et al.* studied the effect of VIA screening by primary health workers in a randomized controlled study.^[33] Four rounds of cancer education and VIA screening were conducted by primary health workers at 24-month intervals in the screening group, while cancer education was offered once at recruitment to the control group. The incidence of invasive

cervical cancer was 26.74 per 100,000 in the screening group and 27.49 per 100,000 in the control group. Compliance to treatment for invasive cancer was 86.34% in the screening group and 72.29% in the control group. The screening group showed a 31% reduction in cervical cancer mortality (mortality rate ratio risk ratio = 0.69; 95% CI: 0.54–0.88; $P = 0.003$) compared to the control group.

Deodhar *et al.* studied the prevalence of HPV types in cervical lesions from women in rural Western India.^[34] They found that the overall prevalence of high-risk (HR) HPV was 37.6% in inflammatory lesions or Grade 1 CIN, 63.5% in Grade 2, 97.2% in Grade 3, and 92% in cervical cancer cases. HPV 16 and HPV 18 were detected in 80.6% of Grade 3 CIN and 86.5% of cervical cancer cases. In a study comparing HPV DNA testing of self-collected vaginal samples with physician-collected cervical samples and cytology, Bhatla *et al.* found that PCR detected oncogenic HPV in 12.3% of self-collected samples and 13.0% of physician-collected samples.^[35] There was 93.8% agreement between physician- and self-collected samples. The sensitivity, specificity, PPV, and NPV of self-sampling for the detection of CIN2+ disease were 82.5%, 93.6%, 52.4%, and 98.4%, respectively, and concordance between HC2 and PCR was 90.9% for self-collected samples and 95.3% for physician-collected samples.

Although the HPV has been shown to be the etiological agent in the pathogenesis of cervical cancer, there has been much debate over the need and efficacy of HPV vaccine in the recent past. The Indian HPV vaccine study group conducted a double-blind, randomized trial that included two parallel groups, the vaccine group-given HPV-16/18 AS04-adjuvanted cervical cancer vaccine and the placebo group-given aluminum hydroxide placebo, according to a 0-, 1-, and 6-month schedule and followed up until month 7.^[36] Serum samples were drawn at prevaccination and at month 7. One month postdose 3, all initially seronegative patients in the vaccine group had seroconverted for HPV-16 and HPV-18 antibodies. Local (injection-site pain) and general (fatigue, headache, and fever) side effects were similar in both groups. Compliance to the three-dose vaccination course was >97%.

While Pap smears, visual inspection, and colposcopies have long been used to assess cervical lesions, *in vivo* Raman spectroscopy is an upcoming technique. A study from a central cancer institute explored this technique utilizing the vagina as an internal control.^[37] A total of 228 normal and 181 tumor *in vivo* Raman spectra were acquired from 93 patients under clinical supervision. The spectral features in normal conditions suggest the presence of collagen, while DNA and noncollagenous proteins were abundant in tumors. Principal component linear discriminant analysis of tumor, normal cervix, and vaginal controls yielded 97% classification efficiency between normal and tumor groups, supporting the utility of the vagina as an internal control.

Imprint cytology (IC) has also been studied in early presumptive diagnosis in clinically suspicious cervical cancer. The overall accuracy of IC in detecting cervical cancers in a study by Halder *et al.* was 96.2%. About 78% of squamous cell carcinomas, 60% of adenocarcinomas, and 100% of small cell carcinoma could be accurately typed on imprints.

The sensitivity and specificity of imprint smear cytology to detect malignancy was 96.2% and 100%, respectively. Agreement between IC and Pap smear diagnosis of malignancy was 95.3%.^[38]

Imaging

Maharjan *et al.* studied the qualitative and quantitative ¹⁸F-FDG PET-CT parameters for predicting survival in recurrent carcinoma of the cervix.^[39] The qualitative parameters were vaginal involvement, regional nodal metastasis, and distant metastasis. The quantitative PET-CT parameters included were standardized uptake value (SUVmax), metabolic tumor volume, and total lesion glycolysis. On multivariate analysis, SUVmax of up to 4.9 and distant metastasis were independent predictors of PFS, and SUVmax >9 and distant metastasis were predictors of OS. A study by Chopra *et al.* evaluated diffusion-weighted imaging as a predictive marker for tumor response in patients undergoing chemoradiation for postoperative recurrences of cervical cancer.^[40] On univariate analysis, bulky disease (77.7% vs. 27%; $P = 0.03$), lateral disease (66.6% vs. 25%; $P = 0.08$), and focal regions of restricted diffusion (66.6% vs. 25%; $P = 0.06$) predicted for PR to chemoradiation. All factors continued to be significant on multivariate analysis.

Clinical outcomes

Several investigators have reported the effectiveness and safety of loop electrosurgical excision procedure (LEEP) for CIN. In a study of 1141 women who underwent LEEP (569 see-and-treat; 572 unsatisfactory colposcopy), 634 had histologically proven CIN. Of those, 489 reported for follow-up and 459 (93.9%) had no evidence of disease. Cure rates were 98.1% for women with CIN 1, 93.6% for CIN 2, and 85.0% for CIN 3.^[41]

In a retrospective study of 6234 patients with carcinoma of the cervix - 11% Stage Ib, 5% Stage IIa, 30% Stage IIb, 1% Stage IIIa, and 53% Stage IIIb, with a median follow-up of 68 months, there was no significant difference in the outcome of patients with Stage Ib-IIa treated with radical surgery, preoperative RT + surgery or radical radiation; their DFS was 60–62% at 8 years. In Stage IIb and Stage IIIb, a respective DFS of 56% and 40% was achieved at 8 years.^[42] In a study of 601 cases of Stage Ib-IIa carcinoma cervix who underwent radical hysterectomy followed by tailored therapy, the overall event-free survival (EFS) at 5 years was 74.37%, with EFS of 86.5% in those from the low-risk (LR) group, 73% in those from the intermediate-risk (IR) group, and 64% in those from the HR group.^[43] A multivariate analysis of 360 cases of carcinoma of the cervix with clinical Stage IB and IIA who had undergone radical hysterectomy and pelvic node dissection showed lymph node metastasis in 21.9% cases. Multiple logistic regression indicated that only lymphovascular space involvement and full-thickness stromal invasion were statistically significant ($P < 0.001$ and $P < 0.002$, respectively) for lymph node metastasis.^[44]

We routinely follow-up patients of cervical cancer postradical hysterectomy with vault cytology. A study explored the role of vault cytology in the follow-up of hysterectomized women and detected malignant cells in 141/1949 (7.2%) follow-up smears from treated cervical cancer cases (140 recurrences and 1 VAIN). Around 92% of the recurrences of cervical cancer were

detected within 2 years of follow-up and 75% of these women were symptomatic.^[45]

Since most women in India still present to oncology clinics at an advanced stage, concurrent chemoradiation has remained one of the pillars of management of cervical cancers. Mahantshetty *et al.* reported the outcomes of high-dose rate interstitial brachytherapy in 113 patients (37 patients of cervical cancer postinadvertent surgery, 57 patients with vault cancers, and 19 patients with primary vaginal cancers) treated with Martinez Universal Perineal Interstitial Template brachytherapy boost after EBRT.^[46] The 3-year actuarial DFS and OS for the three groups were 61%, 61%, 59% and 64%, 64%, and 56%, respectively. Grade 3/4 rectal toxicity was seen in 11 (10%) patients, bladder toxicity in five (4.5%) patients, whereas seven (6%) patients developed Grade 3 small bowel toxicity. Residual disease at brachytherapy had a significant impact on DFS and OS. Other factors such as age, disease volume, parametrial extension, and vaginal extension did not impact the survivals. A study from the same institute explored the role of re-irradiation using high-dose rate brachytherapy in thirty previously irradiated patients of carcinoma cervix diagnosed with central recurrence.^[47] CR was seen in 23 (76%) patients. With a median follow-up of 25 months, 2-year local control, DFS, and OS were 44%, 42%, and 52%, respectively. Fifteen patients developed local recurrences; local control rate was significantly higher with doses >40 Gy EQD2 (52% vs. 34%; $P = 0.05$). DFS was better for patients with longer interval (>25 months) between two radiotherapy schedules. Grade 3 radiation proctitis and cystitis was seen in three patients each, and Grade 2 small bowel toxicity was seen in three patients.

In a study of 100 patients with advanced carcinoma of cervix, treated with palliative radiation monthly up to a maximum of three fractions (10 Gy/fraction), the overall response rates in terms of control of bleeding, discharge, and pain were 100%, 49%, and 33%, respectively.^[48] The treatment was generally well tolerated with a median survival of 7 months. Singh *et al.* studied the HPV prevalence in postradiotherapy uterine cervical carcinoma patients.^[49] HPV DNA was detected in exfoliated cells of 78% (44/56) of the patients postradiotherapy (HPV-16, 68%; HPV-18, 14%) and in plasma in 25% (11/44) of the HPV-positive exfoliated cells. The recurrence of the disease was significantly associated with the presence of HPV in the exfoliated cell ($P = 0.01$) and plasma ($P = 0.007$) as well as high viral load in the exfoliated cells ($P = 0.0002$).

While squamous carcinomas are the most common histology in cervical cancers followed by adenocarcinoma and adenosquamous carcinomas, we may come across rare tumors such as neuroendocrine carcinomas in our practice. In a series of fifty cases of neuroendocrine carcinomas of the cervix, Rekhi *et al.* reported that 52% were small cell carcinoma (SMCA), 28% were large cell neuroendocrine carcinomas (LCNECs), 8% were SMCA + LCNECs, and 12% were mixed carcinomas. On IHC, synaptophysin was positive in 22 (59.4%) of 37 tumors, chromogranin in 27 (72.9%) of 37, CD56 in 8 (100%) of 8, and neuron-specific enolase in 7 (87.5%) of 8 tumors. Among thirty patients, 20% underwent radical hysterectomy, 26.6% had surgery with adjuvant treatment, and 33.3% were

offered chemotherapy and/or radiotherapy. On follow-up, from the available 27 patients, 59.2% patients were alive with disease and 25.9% were free of disease. Thirteen patients had metastasis, most commonly to liver.^[50]

Endometrial Cancer

Endometrial cancer is the most common gynecological malignancy in the West, but in India, the incidence rates are low. Most of these cancers present at an early stage and are associated with a good prognosis. The treatment comprises surgical staging and adjuvant radiotherapy and/or chemotherapy depending on the final surgico-pathological stage.

Mahantshetty *et al.* reported the clinical outcomes of early-stage endometrioid adenocarcinoma at the Tata Memorial Centre, Mumbai.^[51] With a median age of 54 years (26–72 years), 136 patients (55%) had undergone surgery elsewhere while 118 (47.3%) underwent a complete surgical staging. There were 60 (24.1%), 124 (49.8%), and 65 (26.1%) patients in the LR, IR, and HR groups, respectively. Adjuvant radiation was given in 160 patients (LR: 18; IR: 85; and HR: 57). With a median follow-up of 36 months (mean, 40 months), ten patients had vault recurrences, (LR: 3; IR: 4; and HR: 3), 11 had nodal recurrences (five also had local recurrence; LR: 2; IR: 4; and HR: 5), and 16 had distant recurrences (three also had nodal; LR: 4; IR: 5; HR: 7). The 5-year DFS and OS rates were 80% and 95%, respectively. The DFS and OS rates at 5 years were 84% and 97%, 85% and 98%, and 60% and 85% for the LR, IR, and HR groups, respectively. On multivariate analysis, grade ($P = 0.002$) and type of radiation ($P = 0.027$) had a significant impact on DFS and OS. Late toxicities (Grade 3/4) were vaginal stenosis in four (1%) and radiation proctitis in three (1%) patients.

Rathod *et al.* reported that following complete surgical staging, 32.7% of the patients with IR and HR endometrial cancers were found to have retroperitoneal node metastasis; 52.9% in this group had both pelvic and para-aortic lymph nodal metastasis, and 5.9% had isolated para-aortic lymph nodal metastasis. The high-grade tumors (Grade 3) revealed 41.4% pelvic and 20.7% para-aortic lymph nodes metastasis, and there was statistically significant higher nodal metastasis in both pelvic and para-aortic lymph nodes with increasing depth of myometrial invasion ($P = 0.0119$ and $P = 0.0001$) and increasing size of the lesion ($P = 0.04$ and $P = 0.0501$).^[52]

Gholkar *et al.* reported that for the detection of pelvic nodes in HR endometrial cancers, ¹⁸F-FDG PET-CT had a sensitivity of 100%, specificity of 61.11%, PPV of 22.22%, NPV of 100%, and accuracy of 65%. For the detection of para-aortic nodes, ¹⁸F-FDG PET-CT had a sensitivity of 100%, specificity of 66.67%, PPV of 20%, NPV of 100%, and accuracy of 69.23%.^[53] In the detection of recurrent endometrial cancer, the sensitivity, specificity, positive and negative predictive values, and accuracy of ¹⁸F-FDG PET-CT were 88.9%, 93.6%, 94.1%, 88%, and 91%, respectively, significantly higher than conventional imaging (CT and magnetic resonance imaging).^[54]

Minimal access surgery including laparoscopic and robotic hysterectomies and lymphadenectomies are increasingly being used in surgical staging of endometrial cancers. In a prospective randomized study comparing robotic-assisted hysterectomy and regional lymphadenectomy with traditional laparotomy

for the staging of endometrial carcinoma, estimated blood loss (81.28 ml), hospital stay (1.94 days), and perioperative complications were significantly less in robotic-assisted group in comparison to open method. Mean number of lymph nodes removed were 30.56 in robotic group versus 27.6 in open surgery.^[55]

While endometrioid adenocarcinomas have been extensively studied in literature, uterine sarcomas are a group of rare uterine tumors characterized by less favorable outcomes. A study from a regional cancer center in North India in patients of uterine sarcomas found that the median OS was 7.67 months (mean 30.19 months), and 1- and 2-year actuarial survival rates were 45.45% and 36.36%, respectively.^[56] Stratified by histology, median survival in patients with carcinosarcoma, endometrial stromal sarcoma, leiomyosarcoma, and undifferentiated endometrial sarcoma were, respectively, 6.57, 18.7, 6.8, and 9.38 months. On univariate analysis, response to therapy ($P = 0.0003$), disease stage ($P = 0.00001$), tumor size ($P = 0.02$), and performance status ($P = 0.03$) were the significant predictors of OS. Disease stage ($P = 0.005$) and response to therapy ($P = 0.01$) retained significance on multivariate analysis. A retrospective analysis of twenty patients of carcinosarcoma of uterus reported that 75% of the patients belonged to Stages I and II. Ninety-five percent of the patients underwent hysterectomy with bilateral salpingo-oophorectomy and 60% had lymphadenectomy along with hysterectomy. Eight patients had disease recurrence. In patients who had gross extrauterine disease at the time of surgery, the survival was only 9 months whereas in patients who had complete staging with disease confined to the uterus, the survival was 36 months.^[57] Uterine smooth muscle tumors of uncertain malignant potential and atypical leiomyoma are rare uterine tumors, and in a study of 21 cases, the mean age was 45 years (range 24–67 years). Coagulative tumor cell necrosis was seen in two cases on examination of additional material, wherein a revised diagnosis of leiomyosarcoma had been given. Infarction type necrosis and individual cell necrosis were seen in two and three cases, respectively. Mitoses were $<5/10$ hpf in all the cases. On follow-up (median 15 months), from the available 11 patients, nine patients were alive and disease-free, one patient had metastatic liver disease, and one had died due to an unknown cause.^[58]

Vulval Cancer

A recent study has reported decreasing trends of vulval cancer over 24 years - 2.25% between 1984 and 1988, down to 0.33% between 2004 and 2008.^[59] Leading presenting complaints of these patients were dyspareunia, pruritus, ulcer, vulvar swelling, and urinary problems. In an audit of sixty cases, two were Stage I, 17 were Stage II, 31 were Stage III, 9 were Stage IV, and 1 was unknown stage. Age ranged from 24 to 92 years (median 63 years). Thirty-three patients underwent surgery (wide local excision 3 and radical vulvectomy 30). Eleven patients received PORT, 12 received palliative RT, and 15 underwent definitive RT (5 of them received concurrent chemotherapy). Median follow-up period was 23 months (range 2–144 months). The 5-year OS for all stages was 41%. FIGO stage and pathological node positivity were statistically significant prognostic factors for survival.^[60]

Vaginal Cancer

A study of 75 patients of vaginal carcinoma treated with radiotherapy reported that the DFS for the whole group was 50% and OS was 60%. DFS at 5 years for Stage I, Stage IIA, Stage IIB, Stage III, and Stage IV was 40%, 55%, 60%, 50%, and 25%, respectively. Patients receiving brachytherapy within 4 weeks of external radiation had a DFS of 60% as compared to 30% when the interval was more than 4 weeks.^[61]

Gestational Trophoblastic Neoplasia

In a retrospective review of seventy gestational trophoblastic neoplasia (GTN) patients, 68% were in LR and 32% were in the HR categories. The lung was the most common site of metastasis, seen in 21% of the patients. Among the LR patients, 77% received chemotherapy, of whom 68% were treated with methotrexate (MTX) and 96% achieved a CR. Thirty-two percent of LR patients received etoposide, MTX, actinomycin D, cyclophosphamide, and vincristine (EMA/CO) therapy, 83% of whom achieved a CR. The HR patients received EMA/CO, and of these, 73% achieved a CR. Grade 3/4 toxicities with MTX included mucositis in 8% and neutropenia in 21% of the patients. At a median follow-up of 16.6 months, OS in the LR and HR groups was 100% and 88.8%, respectively.^[62] Another study reported the outcomes of HR GTN. Women with HR GTN received EMA-CO as the first-line chemotherapy. EMA-EP (etoposide, MTX, actinomycin, and cisplatin), PVB (cisplatin, vinblastine, and bleomycin), and BEP (bleomycin, etoposide, and cisplatin) were used as the second-line therapy in resistant cases. Of the 78 women, 66.7% had complete remission with the first-line chemotherapy and 16.6% achieved remission with the second-line chemotherapy, resulting in a total of 83.3% (65/78) attaining remission.^[63] Rathod *et al.* reported on the usage of paclitaxel and carboplatin 3 weekly regimens in eight patients with refractory GTN.^[64] One patient was in the LR group (12.5%) and seven patients were in the HR group (87.5%). Six (75%) of the eight patients had a good response, whereas two patients had progression. Five patients (62.5%) were in remission at median 30 months' follow-up period, and 3 (37.5%) of the eight patients had died.

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Conflicts of interest

There are no conflicts of interest.

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