Cervical cancer accounts for more than 570,000 new cases and 300,000 deaths worldwide. As a result, cervical cancer remains the second most common cancer among women and fourth in terms of mortality across genders. The impact of cervical cancer differs across geographies, with literature showing more than 85 per cent of cases occurring in low- and middle-income countries. For example, in India, data show cervical cancer prevalence as third only to breast cancer and colorectal cancers, with greater than 120,000 women newly diagnosed and 77,000 losing their battle with cervical cancer each year. Effective prevention with human papilloma virus (HPV) vaccination is important to consider at a population level, in addition to screening to detect pre-malignant and early cancers. Early-stage disease is usually asymptomatic but can be diagnosed early with effective screening tests such as Pap smears. These strategies have been adopted in many countries and are having a significant impact on the detecting and treating pre-malignant or early invasive disease, as well as reducing the burden of cervical cancer significantly.

The proportion of cervical cancer diagnosis differs across disease stages, with majority of patients diagnosed in mid-to-late stages (35%-stage II, 44%-stage III and 8%-stage IV), with only a minority of patients presenting in early stage (13% stage I).
when intervention is most successful\textsuperscript{7,8}. Similar to cancers in other settings, cure of cervical cancer is predicated based on the stage at diagnosis, with a five-year overall survival (OS) reaching around 66 per cent\textsuperscript{9}. While localized disease has a survival of around 92 per cent, locally advanced disease and distant metastatic diseases have survival rates of 58 and 17 per cent, respectively\textsuperscript{10}. Recurrence of disease can be local or distant. Substantial variance exists with local disease recurrence (10% stage IA, 42% stage II, 74% stage IVA) as well as distant recurrence, which has been documented to occur in 15-61 per cent of patients depending on the initial stage at diagnosis\textsuperscript{10}. Recurrent and metastatic disease, however, remains difficult to treat. This review briefly discusses standard systemic therapy for cervical cancer and the latest updates in the field.

**Current standards of care**

In 2018/19, FIGO (International Federation of Gynecology and obstetrics) staging of cervical cancer underwent revision, with a significant update to the acceptance of imaging and pathology for staging\textsuperscript{11}. Previous staging practices employed clinical examination alone; however, the revised FIGO staging now incorporates computed tomography scan, magnetic resonance imaging, or positron emission tomography scans being accepted as a staging technique wherever resources are not constrained. The impetus underpinning this revision was to identify more prognostically significant information, thereby avoiding multimodal therapies to reduce morbidities. Based FIGO staging, the currently accepted treatment guidelines of the various major societies are outlined in Table\textsuperscript{12-14}.

**Systemic therapy as concurrent treatment**

Literature shows that the optimal approach to treatment of locally advanced cervical cancer is concurrent chemotherapy with radiotherapy (CCRT)\textsuperscript{12}. The benefit of adding concurrent chemotherapy to radiation therapy (RT) is greater in earlier stages such as stage IB to stage IIB than stage III and stage IVA diseases\textsuperscript{15}. Cisplatin is the most preferred agent for CCRT\textsuperscript{16}. Various other agents were tried for CCRT, but none have been found to be as effective or superior to cisplatin. In patients who cannot tolerate cisplatin, 5-FU (Fluouracil) is an alternative\textsuperscript{17}.

Over the last couple of decades, multiple other agents have been tried in the concurrent strategy. Dueñas-González \textit{et al}\textsuperscript{18} showed improvements in progression-free survival (PFS) and OS with the addition of gemcitabine to cisplatin in CCRT regimen followed by adjuvant gemcitabine plus cisplatin, versus CCRT with cisplatin alone in stage IIIB-IV A cervical cancers, but with added toxicity. The phase III data were unable to discern whether improvements in PFS and OS were the results of adjuvant chemotherapy or due to the addition of gemcitabine to concurrent chemotherapy\textsuperscript{18}. Additional trials are underway to confirm the value of adding chemotherapy following CCRT.

A recently concluded phase III randomized controlled trial (RCT) showed sequential chemoradiation (paclitaxel-cisplatin followed by radiotherapy, again followed by paclitaxel-cisplatin) after surgery resulted in improved disease-free survival (DFS) and lowered the risk of death from cervical cancer in patients with adverse pathological factors\textsuperscript{19}. In this study, 1048 patients were equally randomized across three arms to receive either adjuvant RT, CCRT or sequential chemotherapy followed by RT after radical surgery\textsuperscript{19}. Data showed that DFS and OS were significantly improved in the sequential arm as compared to RT alone [three-year DFS rate, 90 vs. 82%; hazard ratio (HR) 0.52; 95% confidence interval (CI), 0.35-0.76 and five-year risk of death, 92 vs. 88%; HR, 0.58; 95% CI, 0.35-0.95]\textsuperscript{19}. There was improved DFS for sequential arm as compared to concurrent arm (90 vs. 85%; HR 0.65; 95% CI, 0.44-0.96)\textsuperscript{19}; however, there was no difference between the CCRT versus RT alone arms\textsuperscript{19} and requires confirmation in future trials.

Various targeted agents have been tried alongside chemotherapy in CCRT setting but to date have not been proven to be better than cisplatin alone. Erlotinib and bevacizumab were found to be safe in phase II trials, but their added benefit is yet to be proven in a randomized trial\textsuperscript{20,21}. Another anti-epidermal growth factor receptor (EGFR) monoclonal antibody, cetuximab unfortunately did not show any major advantage in the CCRT setting\textsuperscript{22}.

**Consolidation systemic therapy after concurrent chemotherapy with radiotherapy (CCRT)**

Though not standard practice, adjuvant chemotherapy in cervical cancer has been examined in various settings, especially in advanced non-metastatic disease\textsuperscript{18,23-26}. Earlier studies with mitomycin and 5-FU as adjuvant treatment did not prove to beneficial\textsuperscript{27}, whereas studies with cisplatin plus gemcitabine were associated with increased toxicity, though beneficial\textsuperscript{18}. 
Another interesting study by Tang et al. in 2012 in cervical adenocarcinoma showed that cisplatin and paclitaxel as adjuvant therapy improved survival with minimal toxicity, thus supporting the idea that histology plays an important role in cervical cancers.

On a similar note, the ACTLACC trial tested paclitaxel plus carboplatin as adjuvant therapy after CCRT but was closed prematurely as there was no significant improvement in response rate and survival. A large RCT was recently presented at ASCO (American Society of Clinical Oncology) comparing CCRT followed by adjuvant chemotherapy versus CCRT alone for locally advanced (stage IIA-IIIB) cervical cancers, reporting failure to achieve benefits for adjuvant chemotherapy with increasing toxicity.

We do not, however, recommend routine systemic chemotherapy after CCRT for squamous cell carcinoma of the cervix, as there is still debate regarding the true magnitude of benefit to substantiate the additional toxicity risks. The results of the ongoing OUTBACK trial (NCT01414608) (weekly cisplatin during CCRT followed by four cycles of paclitaxel plus carboplatin as adjuvant) may provide further evidence for the role of chemotherapy in the adjuvant setting.

**Systemic therapy as a neoadjuvant strategy**

Neoadjuvant chemotherapy (NACT) in cervical cancer still remains a topic of inquiry. Advantage of NACT was thought to be reduction of tumour bulk such that subsequent local treatment is more effective and less toxic with the likelihood of distant metastases as it can eliminate micro-metastases. Squamous cell carcinoma of the cervix has been shown to be chemosensitive and thus thought to benefit from neoadjuvant strategy.

In locally advanced disease, a meta-analysis of NACT a significant improvement of all outcomes with NACT was reported; however, this was the era before concurrent chemotherapy. Subsequently, other phase III trials were conducted using different regimens to determine whether the combination of NACT with surgery was superior to surgery alone but failed to show a benefit for NACT. A limitation of these studies is the absence of CCRT as a comparator arm. Lessons learned from these studies and the meta-analysis led to trial designs with chemotherapies at...
shorter duration and comparative arm as CCRT, which by then was the standard of care for locally advanced cervical cancer.

A phase II single-centre randomized study from Brazil showed that NACT followed by CCRT was inferior to CCRT³³. The strongest evidence against NACT in cervical cancer comes from a recently published phase III RCT from Mumbai comparing NACT with paclitaxel and carboplatin given in a three weekly schedule followed by surgery versus CTRT³⁴. Patients in the neoadjuvant group who underwent surgery had received postoperative adjuvant RT or CTRT³⁴. In terms of the primary end point of DFS, CTRT was found to be superior to NACT followed by radical surgery³⁴. An intriguing question remaining is how NACT followed by CTRT would compare against standard CTRT, which is being addressed in the ongoing phase III INTERLACE study (NCT01566240)³⁵.

**Systemic therapy as a maintenance strategy**

Maintenance chemotherapy regimens are intended to prevent relapse of disease following successful primary treatments. These should be effective, well tolerated and cost-effective. Objective evidence of improvement of survival is important. Contemporary data have not provided convincing evidence of any single agent active in the maintenance setting. However, Tewari et al.³⁶ demonstrated that chemotherapy plus bevacizumab improved outcome over chemotherapy alone. In this setting, both chemotherapy and bevacizumab were continued until progression in women with advanced disease. The trial, however, did not address if bevacizumab alone could be an effective maintenance strategy, and this is currently being considered as a trial concept.

A retrospective study from Japan examining the role of oral maintenance therapy with antimetabolites (5-FU) showed that oral adjuvant chemotherapy with antimetabolites may be useful for cervical adenocarcinoma, but not for squamous cell carcinoma³⁷. Another 5-FU derivative studied was tegafur-uracil, which is an oral combination of tegafur and uracil in a 1:4 molar ratio³⁸. Tegafur is slowly metabolized by cytochrome P450 to 5-FU³⁹ and uracil is a competitive inhibitor of dihydropyrimidine dehydrogenase, which increases the tumour 5-FU concentrations³⁸. A retrospective review of maintenance treatment with tegafur-uracil in cervical cancer patients suggested that this might lead to a favourable prognosis in stage III squamous cell carcinoma cervix³⁸.

**Systemic therapy in recurrent and metastatic disease**

For recurrent and metastatic disease, systemic chemotherapy with palliative intent has been the mainstay of treatment; however, the addition of local therapy in isolated metastases alongside introduction of novel targeted agents has improved outcomes in this patient population. For stage IVB disease amenable to local therapy, the same treatment algorithm followed by systemic therapy would be the treatment of choice. The principles of systemic therapy in this situation are guided as for metastatic disease, with appropriate consideration for local therapy.

Before the CCRT era, based on multiple studies, cisplatin monotherapy was considered as the optimal treatment for metastatic cervical cancer³⁴. After the introduction of cisplatin-based CCRT in the locally advanced stage³⁴, various non-platinum compounds were tested in the metastatic setting, with agents such as paclitaxel, irinotecan, topotecan and ifosfamide, showing the modest single-agent benefit³⁵-³⁶. These formed the basis for subsequent combination therapies.

Different platinum-based multidrug combinations with paclitaxel, ifosfamide, topotecan or other drugs were attempted³⁷-³⁹. Although a few of these combinations improved PFS, most combinations were too toxic to be considered for a metastatic and palliative setting (with the exception paclitaxel + platinum) and phase II randomized evidence was lacking for most³⁷. Replacement of cisplatin by carboplatin can be considered if patients have renal dysfunction. In the metastatic setting, though the median OS still remains around a year, cisplatin remains the most widely used agent, with combination therapies providing higher response rates³⁰. This points to the need to improve contemporary understanding of the pathogenesis and the role of newer modalities of treatments such as targeted therapy and immunotherapy for these patients.

**Emerging biology and genomes in cervical cancer**

The Cancer Genome Atlas project³¹ published the integrated genomic and molecular characterization of cervical cancer in 2017³². A new genomic classification of cervical cancer was proposed based on HPV and molecular data, which included keratin high and low squamous and adenocarcinoma cluster. Although the real implication of this classification is yet to be understood, the genome project revealed a clearer picture of the various targetable and non-targetable mutations and copy number changes in cervical cancer.
Currently, multiple clinical trials are using these data, attempting to match driver mutations with their best targets\textsuperscript{53}.

**Bevacizumab and other anti-angiogenesis targeted agents**

Vascular endothelial growth factors (VEGFs) help in the growth of blood vessels, and inhibition of VEGF-A prevents endothelial proliferation and angiogenesis\textsuperscript{54}. Bevacizumab is a recombinant humanized monoclonal immunoglobulin-G1 antibody directed against VEGF-A and has been shown to be beneficial in other tumours such as ovarian, glioblastoma or renal cell carcinomas\textsuperscript{55}. The GOG 240 trial (NCT00803062) compared paclitaxel with topotecan or cisplatin, with or without bevacizumab\textsuperscript{56}. This was a 1:1:1:1 four-arm randomization study where the maintenance strategy with bevacizumab was tested. The trial enrolled 452 patients from 81 centres. Addition of bevacizumab increased median OS by four months without affecting the quality of life in a significant manner. Though relatively safe, certain specific vasculature-related toxicities such as hypertension, gastrointestinal perforations, venous thromboembolic events, delayed wound healing, fistula formation, nephrotic syndrome and others were, however, seen with the use of bevacizumab. Timing of salvage or palliative surgery while on bevacizumab therapy has to be decided judiciously due to the risk of delayed wound healing. While other potential drugs with antiangiogenic properties including sunitinib, pazopanib, cediranib and brivanib have been investigated in early-stage trials with some associated toxicities\textsuperscript{56,57}, bevacizumab is the only agent which has shown an improvement in survival in a phase III trial.

In the metastatic setting, the current best treatment remains cisplatin-based chemotherapy\textsuperscript{12}. Addition of bevacizumab with chemotherapy improves the OS with acceptable toxicities\textsuperscript{36}, but the added cost of this treatment in a developing country like India should always be considered.

**Epidermal growth factor receptor (EGFR) targeted treatments**

Role of EGFR is important in malignant transformation and tumorigenesis in many cancers including cervical cancer\textsuperscript{58}. EGFR was found to be overexpressed in normal squamous epithelium as well as in squamous cell cancers. It was also found that EGFR plays a pivotal role in HPV-16–mediated malignant transformation of keratinocytes\textsuperscript{59}. In squamous cell cancers of the cervix, EGFR is expressed in >75 per cent of cases engendering it as an attractive potential therapeutic target\textsuperscript{60,61}.

Though there was much hope with this modality of treatment, multiple phase II trials using EGFR antagonists such as erlotinib, gefitinib and cetuximab in recurrent cervical cancer showed no major benefit over standard of care\textsuperscript{62-65}.

Cervical cancer tumours co-expressing EGFR and HER-2 or VEGF receptors (VEGFRs) has poor prognosis, and this led to trials that looked into drugs targeting these receptors together\textsuperscript{66}. Though the concept looked good, regimens with dual EGFR/HER-2 inhibitors such as lapatinib alone or with pazopanib (multi-target tyrosine kinase inhibitor of VEGFRs) did not translate into clinical benefit or had increased toxicity\textsuperscript{57}. Another area of interest is double Her2 inhibition, which is successfully being used in other diseases. This involved combining drugs such as trastuzumab and lapatinib\textsuperscript{67}. Though this looked promising in pre-clinical models, larger clinical trial results are needed to validate this.

**Checkpoint inhibitor therapy**

Multiple interactions between immune cells such as T-lymphocytes and tumour cells regulate the antitumour activity of immune cells\textsuperscript{68}. Important among these interactions which has proven to be clinically significant include the cytotoxic T-lymphocyte antigen programmed cell death protein-1 (CTLA4/B7) interactions and the programmed cell death protein-1 (PD-1) interactions. These interactions generally ‘switch off’ the T-cell activation against tumour cells\textsuperscript{69}. Thus, antibody-mediated inhibition of these proteins could lead to antitumor T-cell activation. PD-L1 is overexpressed in high proportion of cervical cancer cells, making PD-L1 inhibition a potential therapeutic target in this\textsuperscript{69}. Important molecules in this context are ipilimumab (anti-CTLA-4), nivolumab, pembrolizumab (anti-PD-1) and durvalumab, atezolizumab, avelumab (anti-PDL-1)\textsuperscript{70}.

**Pembrolizumab**\textsuperscript{71}: The KEYNOTE-028 (NCT02054806) was a phase Ib trial evaluating pembrolizumab (10 mg/kg every two weekly) in squamous cervical cancer patients who had expressed PD-L1 [Combined Positive Score (CPS) ≥1%] at a dose for a maximum duration of two years\textsuperscript{72}. Overall response rate was 17 per cent with results showing four partial responses and three stable disease
results reported. Similarly, the phase II basket trial, KEYNOTE-158 enrolled 98 patients with advanced cervical cancer, irrespective of PDL-1 expression and received pembrolizumab 200 mg three weekly for a duration of two years or until progression. Data show overall response rate of 13.3 percent, with three subjects achieving complete response, 10 partial responses and 17 reaching stable disease. Based on the results of these trials, the US Food and Drug Administration granted approval of pembrolizumab in the setting of metastatic cervical cancer after failure of frontline chemotherapy.

Results of KEYNOTE-826, a phase III, randomized study evaluating the role of chemotherapy with pembrolizumab and bevacizumab in the first-line setting will provide important new insights into the optimal use of pembrolizumab.

**Nivolumab:** Nivolumab is another PD-1 immune checkpoint inhibitor. An ongoing phase I/II trial, CheckMate 358 (NCT02488759) is evaluating nivolumab-based therapy in tumours with a viral aetiology. The trial included patients with HPV positive or unknown status disease. Report on 24 patients with recurrent or metastatic squamous cell carcinoma of the cervix showed a tolerable safety profile and an objective response rate of 26.3 percent for cervical cancer. Median OS, irrespective of PDL-1 status, was 21.9 months. The NRG phase 2 trial evaluating nivolumab in the treatment of persistent or recurrent cervical cancer is awaited (NCT02257528).

**Vaccines and adoptive T-cell transfer therapies for cervical cancer**

Vaccines are used to train the immune system to fight against specific pathogens, thereby preventing infections. The same principle is extended into the use of cancer vaccines as well. These can either be vaccines used before development of disease (prophylactic vaccines) or those used to treat cancers after its occurrence (therapeutic vaccines). Cervical cancer is perhaps the best example where both these have promising roles.

HPV infection causes around 90 percent of cervical cancers, making it an ideal candidate for a therapeutic vaccine. Innate immune responses play a crucial role in controlling HPV infection. Beyond its ability, the acquired immune system involving the T-cells and antibodies helps in HPV infection control. Persistent HPV infection despite these immune responses can progress to cervical cancer. Thus, using HPV as a target has been a successful way of preventing HPV infection and subsequently cervical cancer.

Two important aspects of therapeutic vaccines are the availability of an immunogenic antigen, to produce a T-cell response and a vaccine vector, which acts as a platform for this. Vaccine vectors can be cellular components such as dead cancer cells or bacteria, or viral vectors or peptides, DNA or RNA. For cervical cancers, the HPV oncoproteins E6 and E7 are expressed strongly in cervical cancers and are ideal antigens for the development of a therapeutic vaccine.

One of the promising agents in this field is the *Listeria monocytogenes*-based axalimogene filolisbac (ADXS11-001) being evaluated in phase III setting (NCT02853604). In the phase II setting, Basu et al. examined ADXS11-001 in combination with cisplatin versus cisplatin alone for recurrent or refractory cervical cancer in patients who had previously received chemotherapy and/or RT. Data show no significant difference between the combination arm versus cisplatin alone, with an impressive 12-month OS reaching 35 percent and similar tolerance with respect to adverse events.

Another interesting approach is combination of vaccines with agents with similar or different mechanism. Trials combining the same vaccine with chemo-radiotherapy in cervical cancer are ongoing (NCT02853604). Pre-clinical and early clinical trials have shown promise in the use of vaccines with HPV-16 SLP along with paclitaxel and carboplatin in murine models as well as patients of cervical cancer.

Adaptive T-cell therapies, either using the lymphocytes from blood (CAR-T cell therapy) or using the tumour infiltrating lymphocytes (TILs) therapy, are becoming more and more important in the treatment of various malignancies. A study from NIH showed good response in metastatic cervical cancer patients treated with TILs selected for HPV E6 and E7 antigenicity. Modifications of this approach using E7 T-cell receptor-based therapies are also ongoing (NCT 02858310).

**Conclusion**

Overall, the systemic treatment paradigm of cervical cancer is slowly changing with increasing knowledge regarding disease biology, particularly genomics and immunology. In locally advanced cervical cancers, CCRT remains the standard of care, whereas NACT followed by local therapy has been reported to be beneficial but requires further validation. Cisplatin-
based chemotherapy regimens remain the standard of care in metastatic disease with addition of bevacizumab shown to improve survival. Immunotherapy agents such as pembrolizumab show promise in the treatment of advanced disease. Therapeutic vaccine strategies and adoptive cell transfer therapies hold hope for advanced or incurable disease. The best agents, combinations and treatment sequences continue to evolve with continued clinical trials. The biggest challenge will remain determining how to incorporate novel treatments into accepted treatment protocols of low- and middle-income countries where there is higher prevalence of the disease. This again highlights the importance of effective prevention with vaccination against pathogenic HPV subtypes and screening with Pap smears to detect asymptomatic pre-malignant and early cancers.

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