Indian J Med Res 154, August 2021, pp 293-302
DOI: 10.4103/ijmr.IJMR_4454_20

Quick Response Code:

Review Article

Updates on systemic therapy for cervical cancer

Paul Gopu[1], Febin Antony[1], Sunu Cyriac[2], Katherine Karakasis[3] & Amit M. Oza[3]

Departments of [1]Radiation Oncology & [2]Medical Oncology & Haematology, Amala Institute of Medical Sciences, Thrissur, Kerala, India & [3]Division of Medical Oncology & Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, Canada

Received November 3, 2020

Cervical cancer is one of the most common cancers in the world both in terms of incidence and mortality, more so important in low- and middle-income countries. Surgery and radiotherapy remain the backbone of treatment for non-metastatic cervical cancer, with significant improvement in survival provided by addition of chemotherapy to radiotherapy. Survival as well as quality of life is improved by chemotherapy in metastatic disease. Platinum-based chemotherapy with/without bevacizumab is the mainstay of treatment for metastatic disease and has shown improvement in survival. The right combinations and sequence of treatment modalities and medicines are still evolving. Data regarding the molecular and genomic biology of cervical cancer have revealed multiple potential targets for treatment, and several new agents are presently under evaluation including targeted therapies, immunotherapies and vaccines. This review discusses briefly the current standards, newer updates as well as future prospective approaches in systemic therapies for cervical cancer.

Key words Cervical cancer - immunotherapy - systemic therapy - targeted therapy - update

Cervical cancer accounts for more than 570,000 new cases and 300,000 deaths worldwide[1]. As a result, cervical cancer remains the second most common cancer among women and fourth in terms of mortality across genders[1]. 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[2]. For example, in India, data show cervical cancer prevalence as third only to breast cancer and colorectal cancers[3], with greater than 120,000 women newly diagnosed and 77,000 losing their battle with cervical cancer each year[3]. 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[4,5], as well as reducing the burden of cervical cancer significantly[6].

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[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[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[9]. 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[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[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[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)[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[15]. Cisplatin is the most preferred agent for CCRT[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 (Fluorouracil) is an alternative[17].

Over the last couple of decades, multiple other agents have been tried in the concurrent strategy. Dueñas-González *et al*[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 IIB-IVA 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[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[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[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][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)[19]; however, there was no difference between the CCRT versus RT alone arms[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[20,21]. Another anti-epidermal growth factor receptor (EGFR) monoclonal antibody, cetuximab unfortunately did not show any major advantage in the CCRT setting[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[18,23-26]. Earlier studies with mitomycin and 5-FU as adjuvant treatment did not prove to beneficial[23], whereas studies with cisplatin plus gemcitabine were associated with increased toxicity, though beneficial[18].

Table. Comparison of different guidelines for treatment of cervical cancer

Stage	NCCN[12]	NCG[13]	ESMO[14]
IA1 and IA2	Type II RH + PLND	RH and PLND or Radical trachelectomy and PLND if fertility is desired or radical brachy alone	Simple hysterectomy if no LVSI If LVSI/IA2 then RH + PLND followed by adjuvant treatment depending on risk
IB1 and IIA1	Type III RH + PLND	RH with PLND Adjuvant RT for 2/3 intermediate risk factors	RH + PLND followed by adjuvant treatment depending on risk
IB2 and IIA2	Pelvic EBRT + brachy therapy + cisplatin based CCRT	CCRT for any high-risk features Additional Brachy in some cases	CCRT or NACT followed by surgery or RT CCRT for IVA pelvic exenteration
IIB to IVA	Pelvic EBRT + brachy therapy + cisplatin based CCRT±EBRT to para-aortic nodes	Pelvic CCRT	
IVB or recurrent disease not amenable to local therapy	Chemotherapy + bevacizumab	Palliative chemotherapy and/or palliative RT	Chemotherapy + bevacizumab±pall RT

CCRT, concurrent chemoradiotherapy; EBRT, external beam radiotherapy; ESMO, European Society of Medical Oncology; LN, lymph node; LVSI, lymphovascular space invasion; NACT, neoadjuvant chemotherapy; NCCN, National Comprehensive Cancer Network; NCG, National Cancer Grid; PLND, pelvic lymph node dissection; RH, radical hysterectomy; RT, radiotherapy

Another interesting study by Tang *et al*[24] 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[25] tested paclitaxel plus carboplatin as adjuvant therapy after CCRT but was closed prematurely as there was no significant improvement in response rate and survival[25]. A large RCT was recently presented at ASCO (Americian Society of Clinical Oncology) comparing CCRT followed by adjuvant chemotherapy versus CCRT alone for locally advanced (stage IIA-IIIB) cervical cancers[26], reporting failure to achieve benefits for adjuvant chemotherapy with increasing toxicity[26].

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)[27] (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[27].

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 chemo-sensitive and thus thought to benefit from neoadjuvant strategy[28,29].

In locally advanced disease, a meta-analysis of NACT a significant improvement of all outcomes with NACT was reported[30]; 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[31,32] but failed to show a benefit for NACT[31,32]. 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[15].

A phase II single-centre randomized study from Brazil showed that NACT followed by CCRT was inferior to CCRT[33]. 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 CTRT[34]. Patients in the neoadjuvant group who underwent surgery had received postoperative adjuvant RT or CTRT[34]. In terms of the primary end point of DFS, CTRT was found to be superior to NACT followed by radical surgery[34]. An intriguing question remaining is how NACT followed by CTRT would compare against standard CTRT, which is being addressed in the on-going 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 carcinoma[37]. Another 5-FU derivative studied was tegafur-uracil, which is an oral combination of tegafur and uracil in a 1:4 molar ratio[38]. Tegafur is slowly metabolized by cytochrome P450 to 5-FU[39] and uracil is a competitive inhibitor of dihydropyrimidine dehydrogenase, which increases the tumour 5-FU concentrations[38]. 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 cervix[38].

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 cancer[40-42]. After the introduction of cisplatin-based CCRT in the locally advanced stage[16], various non-platinum compounds were tested in the metastatic setting, with agents such as paclitaxel, irinotecan, topotecan and ifosfamide, showing the modest single-agent benefit[43-46]. These formed the basis for subsequent combination therapies.

Different platinum-based multidrug combinations with paclitaxel, ifosfamide, topotecan or other drugs were attempted[47-49]. 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 most[47]. 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 rates[50]. 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 project[51] published the integrated genomic and molecular characterization of cervical cancer in 2017[52]. 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[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[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[55]. The GOG 240 trial (NCT00803062) compared paclitaxel with topotecan or cisplatin, with or without bevacizumab[36]. 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[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[12]. Addition of bevacizumab with chemotherapy improves the OS with acceptable toxicities[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[58]. EGFR was found to be over-expressed 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[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[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[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[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[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[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 anti-tumour activity of immune cells[68]. Important among these interactions which has proven to be clinically significant include the cytotoxic T-lymphocyte antigen programmed cell death protein-1(CTLA)4/B7 interactions and the programmed cell death protein-1(PD-1)Programmed cell death ligand-1(PDL-1) interactions. These interactions generally 'switch off' the T-cell activation against tumour cells[68]. Thus, antibody-mediated inhibition of these proteins could lead to antitumor T-cell activation. PDL-1 is overexpressed in high proportion of cervical cancer cells, making PDL-1 inhibition a potential therapeutic target in this[69]. Important molecules in this context are ipilimumab (anti-CTLA-4), nivolumab, pembrolizumab (anti-PD-1) and durvalumab, atezolizumab, avelumab (anti-PDL-1)[70].

Pembrolizumab[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 PDL-1 [Combined Positive Score (CPS) ≥1%] at a dose for a maximum duration of two years[72]. Overall response rate was 17 per cent with results showing four partial responses and three stable disease

results reported[72]. 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 per cent, with three subjects achieving complete response, 10 partial responses and 17 reaching stable disease[73]. 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[74].

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[75].

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[76]. 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 per cent for cervical cancer[76]. Median OS, irrespective of PDL-1 status, was 21.9 months[76]. The NRG phase 2 trial evaluating nivolumab in the treatment of persistent or recurrent cervical cancer is awaited (NCT02257528)[77].

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[78].

HPV infection causes around 90 per cent of cervical cancers[79], 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[80]. Thus, using HPV as a target has been a successful way of preventing HPV infection and subsequently cervical cancer[81].

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[82]. Vaccine vectors can be cellular components such as dead cancer cells or bacteria, or viral vectors or peptides, DNA or RNA[78]. 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[83].

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*[84], 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 per cent and similar tolerance with respect to adverse events[84].

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[70].

Adoptive 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[85]. 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.

***Financial support & sponsorship*:** None.

***Conflicts of Interest*:** None.

References

1. Arbyn M, Weiderpass E, Bruni L, de Sanjosé S, Saraiya M, Ferlay J, *et al.* Estimates of incidence and mortality of cervical cancer in 2018: A worldwide analysis. *Lancet Glob Health* 2020; *8* : e191-203.
2. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; *65* : 87-108.
3. World Health Organization. *Cancer today*. Available from: *http://gco.iarc.fr/today/home,* accessed on April 20, 2020.
4. Yang DX, Soulos PR, Davis B, Gross CP, Yu JB. Impact of widespread cervical cancer screening: Number of cancers prevented and changes in race-specific incidence. *Am J Clin Oncol* 2018; *41* : 289-94.
5. Brisson M, Kim JJ, Canfell K, Drolet M, Gingras G, Burger EA, *et al.* Impact of HPV vaccination and cervical screening on cervical cancer elimination: A comparative modelling analysis in 78 low-income and lower-middle-income countries. *Lancet* 2020; *395* : 575-90.
6. Mix JM, Dyne EA, Saraiya M, Hallowell BD, Thomas CC. Assessing impact of HPV vaccination on cervical cancer incidence among women aged 15–29 years in the United States, 1999–2017: An ecologic study. *Cancer Epidemiol Prev Biomark* 2020; *30* : 30-37.
7. ICO/IARC Information Centre on HPV and Cancer. *HPV information centre*. Available from: *https://hpvcentre.net/datastatistics.php,* accessed on April 20, 2020.
8. Jain A, Ganesh B, Bobdey SC, Sathwara JA, Saoba S. Sociodemographic and clinical profile of cervical cancer patients visiting in a tertiary care hospital in India. *Indian J Med Paediatr Oncol* 2017; *38* : 291-5.
9. National Institute of Health. National Cancer Institute: Surveillence, Epidemiology and End Results Program. *Cancer stat facts: Cervix Cancer*. Available from: *https://seer.cancer.gov/statfacts/html/cervix.html*, accessed on June 12, 2020.
10. National Institute of Health. National Cancer Institute: Surveillence, Epidemiology and End Results Program. *SEER cancer statistics review 1975-2003*. Available from: *https://seer.cancer.gov/archive/csr/1975_2003/index.html*, accessed on April 26, 2020.
11. Bhatla N, Berek JS, Cuello Fredes M, Denny LA, Grenman S, Karunaratne K, *et al*. Revised FIGO staging for carcinoma of the cervix uteri. *Int J Gynaecol Obstet* 2019; *145* : 129-35.
12. National Comprehensive Cancer Network. *NCCN clinical practice guidelines in oncology*. Available from: *https://www.nccn.org/professionals/physician_gls/default.aspx*, accessed on April 20, 2020.
13. National Cancer Grid. *Cervical Cancer*. Available from: *https://tmc.gov.in/NCG/docs/PDF/Gynaecology/Cervical_cancer%20.pdf*, accessed on April 20, 2020.
14. European Society for Medical Oncology. *Cervical Cancer: ESMO clinical practice guidelines*. Available from: *https://www.esmo.org/guidelines/gynaecological-cancers/cervical-cancer*, accessed on April 20, 2020.
15. NCI issues clinical announcement on cervical cancer: Chemotherapy plus radiation improves survival; February 22, 1999. Available from: *https://www3.scienceblog.com/community/older/archives/B/nih478.html*, accessed on April 20, 2020.
16. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: A systematic review and meta-analysis of individual patient data from 18 randomized trials. *J Clin Oncol* 2008; *26* : 5802-12.
17. Lanciano R, Calkins A, Bundy BN, Parham G, Lucci JA 3rd, Moore DH, *et al.* Randomized comparison of weekly cisplatin or protracted venous infusion of fluorouracil in combination with pelvic radiation in advanced cervix cancer: A gynecologic oncology group study. *J Clin Oncol* 2005; *23* : 8289-95.
18. Dueñas-González A, Zarbá JJ, Patel F, Alcedo JC, Beslija S, Casanova L, *et al.* Phase III, open-label, randomized study comparing concurrent gemcitabine plus cisplatin and radiation followed by adjuvant gemcitabine and cisplatin versus concurrent cisplatin and radiation in patients with stage IIB to IVA carcinoma of the cervix. *J Clin Oncol* 2011; *29* : 1678-85.
19. Huang H, Feng Y, Wan T, Zhang Y, Cao X, Huang Y, *et al.* Sequential chemoradiation versus radiation alone or concurrent chemoradiation in adjuvant treatment after radical hysterectomy for stage IB1-IIA2 cervical cancer (STARS Study): A randomized, controlled, open-label, phase III trial. *J Clin Oncol* 2020; *38* (Suppl 15) : 6007.
20. Schefter T, Winter K, Kwon JS, Stuhr K, Balaraj K, Yaremko BP, *et al.* RTOG 0417: Efficacy of bevacizumab in combination with definitive radiation therapy and cisplatin chemotherapy in untreated patients with locally advanced cervical carcinoma. *Int J Radiat Oncol Biol Phys* 2014; *88* : 101-5.

21. Nogueira-Rodrigues A, Moralez G, Grazziotin R, Carmo CC, Small IA, Alves FV, *et al.* Phase 2 trial of erlotinib combined with cisplatin and radiotherapy in patients with locally advanced cervical cancer. *Cancer* 2014; *120* : 1187-93.
22. Scholl SM, De la Rochefordiere A, Petrow P, Floquet A, Petit T, Alran S, *et al.* CETUXICOL, a phase II trial randomizing standard treatment with or without cetuximab in primary cervical cancer treatment. *J Clin Oncol* 2012; *30* (Suppl 15) : e15535.
23. Lorvidhaya V, Chitapanarux I, Sangruchi S, Lertsanguansinchai P, Kongthanarat Y, Tangkaratt S, *et al.* Concurrent mitomycin C, 5-fluorouracil, and radiotherapy in the treatment of locally advanced carcinoma of the cervix: A randomized trial. *Int J Radiat Oncol Biol Phys* 2003; *55* : 1226-32.
24. Tang J, Tang Y, Yang J, Huang S. Chemoradiation and adjuvant chemotherapy in advanced cervical adenocarcinoma. *Gynecol Oncol* 2012; *125* : 297-302.
25. Tangjitgamol S, Tharavichitkul E, Tovanabutra C, Rongsriyam K, Asakij T, Paengchit K, *et al.* A randomized controlled trial comparing concurrent chemoradiation versus concurrent chemoradiation followed by adjuvant chemotherapy in locally advanced cervical cancer patients: ACTLACC trial. *J Gynecol Oncol* 2019; *30* : e82.
26. Kou L, Zhang T, Peng S, Wang Y, Yuan M, Li M. Adjuvant chemotherapy after concurrent chemoradiation therapy for locally advanced cervical cancer. *J Clin Oncol* 2020; *38* (Suppl 15) : 6031.
27. Mileshkin LR, Narayan K, Moore KN, Rischin D, King M, Kolodziej I, *et al.* A phase III trial of adjuvant chemotherapy following chemoradiation as primary treatment for locally advanced cervical cancer compared to chemoradiation alone: Outback (ANZGOG0902/GOG0274/RTOG1174). *J Clin Oncol* 2014; *32* (Suppl 15) : TPS5632.
28. Chen H, Liang C, Zhang L, Huang S, Wu X. Clinical efficacy of modified preoperative neoadjuvant chemotherapy in the treatment of locally advanced (stage IB2 to IIB) cervical cancer: Randomized study. *Gynecol Oncol* 2008; *110* : 308-15.
29. Das S, Subhashini J, Rami Reddy JK, Kanti Pal S, Isiah R, Oommen R. Low-dose fractionated radiation and chemotherapy prior to definitive chemoradiation in locally advanced carcinoma of the uterine cervix: Results of a prospective phase II clinical trial. *Gynecol Oncol* 2015; *138* : 292-8.
30. Neoadjuvant chemotherapy for locally advanced cervical cancer meta-analysis collaboration, Tierney J, *et al*. Neoadjuvant chemotherapy for locally advanced cervical cancer: A systematic review and meta-analysis of individual patient data from 21 randomised trials. *Eur J Cancer* 2003; *39* : 2470-86.
31. Katsumata N, Yoshikawa H, Kobayashi H, Saito T, Kuzuya K, Nakanishi T, *et al.* Phase III randomised controlled trial of neoadjuvant chemotherapy plus radical surgery vs radical surgery alone for stages IB2, IIA2, and IIB cervical cancer: A Japan Clinical Oncology Group trial (JCOG 0102). *Br J Cancer* 2013; *108* : 1957-63.
32. Eddy GL, Bundy BN, Creasman WT, Spirtos NM, Mannel RS, Hannigan E, *et al.* Treatment of ("bulky") stage IB cervical cancer with or without neoadjuvant vincristine and cisplatin prior to radical hysterectomy and pelvic/para-aortic lymphadenectomy: A phase III trial of the gynecologic oncology group. *Gynecol Oncol* 2007; *106* : 362-9.
33. da Costa SC, Bonadio RC, Gabrielli FC, Aranha AS, Dias Genta ML, Miranda VC, *et al.* Neoadjuvant chemotherapy with cisplatin and gemcitabine followed by chemoradiation versus chemoradiation for locally advanced cervical cancer: A randomized phase II trial. *J Clin Oncol* 2019; *37* : 3124-31.
34. Gupta S, Maheshwari A, Parab P, Mahantshetty U, Hawaldar R, Sastri Chopra S, *et al.* Neoadjuvant chemotherapy followed by radical surgery versus concomitant chemotherapy and radiotherapy in patients with stage IB2, IIA, or IIB squamous cervical cancer: A randomized controlled trial. *J Clin Oncol* 2018; *36* : 1548-55.
35. Induction Chemotherapy Plus Chemoradiation as First Line Treatment for Locally Advanced Cervical Cancer - ClinicalTrials.gov. Available from: *https://clinicaltrials.gov/ct2/show/NCT01566240*, acessed on April 28, 2020.
36. Tewari KS, Sill MW, Penson RT, Huang H, Ramondetta LM, Landrum LM, *et al.* Bevacizumab for advanced cervical cancer: Final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). *Lancet* 2017; *390* : 1654-63.
37. Wada K, Koyama M, Iijima Y, Inagaki M, Hirota Y, Hongo J, *et al.* Usefulness of adjuvant chemotherapy with antimetabolites for cervical invasive cancer. *Nihon Sanka Fujinka Gakkai Zasshi* 1995; *47* : 244-8.
38. Sakaguchi I, Motohara T, Saito F, Takaishi K, Fukumatsu Y, Tohya T, *et al.* High-dose oral tegafur-uracil maintenance therapy in patients with uterine cervical cancer. *J Gynecol Oncol* 2015; *26* : 193-200.
39. Aronson JK, editor. Tegafur. In: *Meyler's side effects of drugs*, 16th ed. Oxford: Elsevier; 2016. p. 711-2.
40. Bonomi P, Blessing JA, Stehman FB, DiSaia PJ, Walton L, Major FJ. Randomized trial of three cisplatin dose schedules in squamous-cell carcinoma of the cervix: A gynecologic oncology group study. *J Clin Oncol* 1985; *3* : 1079-85.
41. Reichman B, Markman M, Hakes T, Budnick A, Rubin S, Jones W, *et al.* Phase II trial of high-dose cisplatin with sodium thiosulfate nephroprotection in patients with advanced carcinoma of the uterine cervix previously untreated with chemotherapy. *Gynecol Oncol* 1991; *43* : 159-63.
42. Thigpen T, Shingleton H, Homesley H, Lagasse L, Blessing J. Cis-platinum in treatment of advanced or recurrent squamous cell carcinoma of the cervix: A phase II study of the gynecologic oncology group. *Cancer* 1981; *48* : 899-903.
43. McGuire WP, Blessing JA, Moore D, Lentz SS, Photopulos G. Paclitaxel has moderate activity in squamous cervix cancer. A gynecologic oncology group study. *J Clin Oncol* 1996; *14* : 792-5.

44. Lhommé C, Fumoleau P, Fargeot P, Krakowski Y, Dieras V, Chauvergne J, *et al.* Results of a European organization for research and treatment of cancer/early clinical studies group phase II trial of first-line irinotecan in patients with advanced or recurrent squamous cell carcinoma of the cervix. *J Clin Oncol* 1999; *17* : 3136-42.
45. Bookman MA, Blessing JA, Hanjani P, Herzog TJ, Andersen WA. Topotecan in squamous cell carcinoma of the cervix: A phase II study of the gynecologic oncology group. *Gynecol Oncol* 2000; *77* : 446-9.
46. Thigpen T. The role of chemotherapy in the management of carcinoma of the cervix. *Cancer J* 2003; *9* : 425-32.
47. Moore DH, Blessing JA, McQuellon RP, Thaler HT, Cella D, Benda J, *et al.* Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: A gynecologic oncology group study. *J Clin Oncol* 2004; *22* : 3113-9.
48. Long HJ 3rd, Cross WG, Wieand HS, Webb MJ, Mailliard JA, Kugler JW, *et al.* Phase II trial of methotrexate, vinblastine, doxorubicin, and cisplatin in advanced/recurrent carcinoma of the uterine cervix and vagina. *Gynecol Oncol* 1995; *57* : 235-9.
49. Omura GA, Blessing JA, Vaccarello L, Berman ML, Clarke-Pearson DL, Mutch DG, *et al.* Randomized trial of cisplatin versus cisplatin plus mitolactol versus cisplatin plus ifosfamide in advanced squamous carcinoma of the cervix: A gynecologic oncology group study. *J Clin Oncol* 1997; *15* : 165-71.
50. Gadducci A, Tana R, Cosio S, Cionini L. Treatment options in recurrent cervical cancer (Review). *Oncol Lett* 2010; *1* : 3-11.
51. The Cancer Genome Atlas (TCGA). Available form: *https://www.genome.gov/Funded-Programs-Projects/Cancer-Genome-Atlas*, accessed on December 23, 2020.
52. Burk RD, Chen Z, Saller C, Tarvin K, Carvalho AL, Scapulatempo-Neto C, *et al.* Integrated genomic and molecular characterization of cervical cancer. *Nature* 2017; *543* : 378-84.
53. A Study of T-DXd for the Treatment of Solid Tumors Harboring HER2 Activating Mutations - ClinicalTrials.gov. Available from: *https://clinicaltrials.gov/ct2/show/NCT04639219,* accessed on Jan 6, 2022.
54. Sherbet GV. Vascular endothelial growth factor. In: Sherbet GV, editor. *Growth factors and their receptors in cell differentiation, cancer and cancer therapy*. London: Elsevier; 2011. p. 55-64.
55. AVASTIN (Bevacizumab). Available from: *https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125085s301lbl.pdf*, accessed on June 2, 2020
56. Mackay HJ, Tinker A, Winquist E, Thomas G, Swenerton K, Oza A, *et al.* A phase II study of sunitinib in patients with locally advanced or metastatic cervical carcinoma: NCIC CTG Trial IND.184. *Gynecol Oncol* 2010; *116* : 163-7.
57. Monk BJ, Mas Lopez L, Zarba JJ, Oaknin A, Tarpin C, Termrungruanglert W, *et al.* Phase II, open-label study of pazopanib or lapatinib monotherapy compared with pazopanib plus lapatinib combination therapy in patients with advanced and recurrent cervical cancer. *J Clin Oncol* 2010; *28* : 3562-9**.**
58. Sherbet GV. 13 – Epidermal growth factors and their signalling systems. In: Sherbet GV, editor. *Growth factors and their receptors in cell differentiation, cancer and cancer therapy*. London: Elsevier; 2011. p. 141-71.
59. Kersemaekers AM, Fleuren GJ, Kenter GG, Van den Broek LJ, Uljee SM, Hermans J, *et al.* Oncogene alterations in carcinomas of the uterine cervix: Overexpression of the epidermal growth factor receptor is associated with poor prognosis. *Clin Cancer Res* 1999; *5* : 577-86**.**
60. Bellone S, Frera G, Landolfi G, Romani C, Bandiera E, Tognon G, *et al.* Overexpression of epidermal growth factor type-1 receptor (EGF-R1) in cervical cancer: Implications for Cetuximab-mediated therapy in recurrent/metastatic disease. *Gynecol Oncol* 2007; *106* : 513-20**.**
61. Scambia G, Ferrandina G, Distefano M, D'Agostino G, Benedetti-Panici P, Mancuso S. Epidermal growth factor receptor (EGFR) is not related to the prognosis of cervical cancer. *Cancer Lett* 1998; *123* : 135-9.
62. Schilder RJ, Sill MW, Lee YC, Mannel R. A phase II trial of erlotinib in recurrent squamous cell carcinoma of the cervix: A gynecologic oncology group study. *Int J Gynecol Cancer* 2009; *19* : 929-33**.**
63. Goncalves A, Fabbro M, Lhommé C, Gladieff L, Extra JM, Floquet A, *et al.* A phase II trial to evaluate gefitinib as second- or third-line treatment in patients with recurring locoregionally advanced or metastatic cervical cancer. *Gynecol Oncol* 2008; *108* : 42-6.
64. Farley J, Sill MW, Birrer M, Walker J, Schilder RJ, Thigpen JT, *et al.* Phase II study of cisplatin plus cetuximab in advanced, recurrent, and previously treated cancers of the cervix and evaluation of epidermal growth factor receptor immunohistochemical expression: A gynecologic oncology group study. *Gynecol Oncol* 2011; *121* : 303-8**.**
65. Santin AD, Sill MW, McMeekin DS, Leitao MM Jr., Brown J, Sutton GP, *et al.* Phase II trial of cetuximab in the treatment of persistent or recurrent squamous or non-squamous cell carcinoma of the cervix: A gynecologic oncology group study. *Gynecol Oncol* 2011; *122* : 495-500**.**
66. Pérez-Regadera J, Sánchez-Muñoz A, De-la-Cruz J, Ballestín C, Lora D, García-Martín R, *et al.* Negative prognostic impact of the coexpression of epidermal growth factor receptor and c-erbB-2 in locally advanced cervical cancer. *Oncology* 2009; *76* : 133-41**.**
67. Oh DY, Kim S, Choi YL, Cho YJ, Oh E, Choi JJ, *et al.* HER2 as a novel therapeutic target for cervical cancer. *Oncotarget* 2015; *6* : 36219-30.
68. Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. *Proc Natl Acad Sci U S A* 2002; *99* : 12293-7**.**
69. Karim R, Jordanova ES, Piersma SJ, Kenter GG, Chen L, Boer JM, *et al.* Tumor-expressed B7-H1 and B7-DC in

relation to PD-1+ T-cell infiltration and survival of patients with cervical carcinoma. *Clin Cancer Res* 2009; *15* : 6341-7.

70. Kagabu M, Nagasawa T, Sato C, Fukagawa Y, Kawamura H, Tomabechi H, *et al*. Immunotherapy for uterine cervical cancer using checkpoint inhibitors: Future directions. *Int J Mol Sci* 2020; *21* : 2335.
71. Khoja L, Butler MO, Kang SP, Ebbinghaus S, Joshua AM. Pembrolizumab. *J Immunother Cancer* 2015; *3* : 36.
72. Frenel JS, Le Tourneau C, O'Neil B, Ott PA, Piha-Paul SA, Gomez-Roca C, *et al.* Safety and efficacy of pembrolizumab in advanced, programmed death ligand 1-positive cervical cancer: Results from the phase Ib KEYNOTE-028 trial. *J Clin Oncol* 2017; *35* : 4035-41.
73. Chung HC, Schellens JH, Delord JP, Perets R, Italiano A, Shapira-Frommer R, *et al.* Pembrolizumab treatment of advanced cervical cancer: Updated results from the phase 2 KEYNOTE-158 study. *J Clin Oncol* 2018; *36* (Suppl 15) : 5522.
74. FDA approves pembrolizumab for advanced cervical cancer with disease progression during or after chemotherapy. FDA; February 9, 2019. Available from: *https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-advanced-cervical-cancer-disease-progres sion-during-or-after-chemotherapy*, accessed on December 23, 2020.
75. Fujiwara K, Shapira-Frommer R, Alexandre J, Monk B, Fehm T, Colombo N, *et al*. KEYNOTE-826: A phase III randomized study of chemotherapy with or without pembrolizumab for first-line treatment of persistent, recurrent, or metastatic cervical cancer. *Ann Oncol* 2019; *30* : ix89-90.
76. Naumann RW, Hollebecque A, Meyer T, Devlin MJ, Oaknin A, Kerger J, *et al.* Safety and efficacy of nivolumab monotherapy in recurrent or metastatic cervical, vaginal, or vulvar carcinoma: Results from the phase I/II CheckMate 358 trial. *J Clin Oncol* 2019; *37* : 2825-34.
77. Nivolumab in treating patients with persistent, recurrent, or metastatic cervical cancer – Full text view – Clinical trials. Available form: *https://clinicaltrials.gov/ct2/show/NCT02257528*, accessed on December 23, 2020.
78. Hollingsworth RE, Jansen K. Turning the corner on therapeutic cancer vaccines. *NPJ Vaccines* 2019; *4* : 1-10.
79. Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri. *Int J Gynaecol Obstet* 2018; *143* (Suppl 2) : 22-36.
80. Su JH, Wu A, Scotney E, Ma B, Monie A, Hung CF, *et al.* Immunotherapy for cervical cancer: Research status and clinical potential. *BioDrugs* 2010; *24* : 109-29.
81. Lei J, Ploner A, Elfström KM, Wang J, Roth A, Fang F, *et al.* HPV vaccination and the risk of invasive cervical cancer. *N Engl J Med* 2020; *383* : 1340-8.
82. Schlom J, Hodge JW, Palena C, Tsang KY, Jochems C, Greiner JW, *et al*. Therapeutic cancer vaccines. *Adv Cancer Res* 2014; *121* : 67-124.
83. Barra F, Della Corte L, Noberasco G, Foreste V, Riemma G, Di Filippo C, *et al.* Advances in therapeutic vaccines for treating human papillomavirus-related cervical intraepithelial neoplasia. *J Obstet Gynaecol Res* 2020; *46* : 989-1006.
84. Basu P, Mehta A, Jain M, Gupta S, Nagarkar RV, John S, *et al.* A randomized phase 2 study of ADXS11-001 *Listeria monocytogenes*-Listeriolysin O immunotherapy with or without cisplatin in treatment of advanced cervical cancer. *Int J Gynecol Cancer* 2018; *28* : 764-72.
85. Stevanović S, Draper LM, Langhan MM, Campbell TE, Kwong ML, Wunderlich JR, *et al.* Complete regression of metastatic cervical cancer after treatment with human papillomavirus-targeted tumor-infiltrating T cells. *J Clin Oncol* 2015; *33* : 1543-50.

For correspondence: Dr Sunu Cyriac, Department of Medical Oncology & Haematology, Amala Institute of Medical Sciences, Amala Nagar P.O., Thrissur - 680 555, Kerala, India
e-mail: drsunucyriac@gmail.com