Recent Advances in Cervical Cancer
Chapter 1

Recent Research and Review Works in Cervical Cancer Treatment

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Abstract

Cancer of the cervix is the most common gynecological malignancy worldwide [1]. More than 85% of the global burden occurs in developing countries, where it accounts for 13% of all female cancers [2]. Furthermore, the mortality due to cervical cancer is higher in the developing countries where screening and treatment modalities are not commonly available or accessible compared with the developed countries [3]. Cervical carcinoma has its origins at the squamous-columnar junction; it can involve the outer squamous cells, the inner glandular cells, or both. The precursor lesion is dysplasia: cervical intraepithelial neoplasia (CIN) or adenocarcinoma in situ, which can subsequently become invasive cancer. This process of tumorigenesis is slow. Longitudinal studies have shown that in 30% to 70% of patients with untreated in situ cervical cancer, will develop invasive carcinoma over a period of 10 to 12 years. However, in about 10% of patients, pre-cancerous lesions can progress from in situ to invasive in a period of less than 1 year. As it becomes invasive, the tumor breaks through the basement membrane invading the cervical stroma. Extension of the tumor in the cervix may ultimately present as ulceration, exophytic tumor, or extensive infiltration of underlying tissue, including the bladder or rectum.
Conventional Management of Cervical Cancers

The management of cervical cancer requires a multidisciplinary approach, role of a gynecologic oncologist, radiation oncologist and medical oncologist may be mandatory. The treatment of cervical cancer varies with the stage of the disease. The management of cervical cancer varies worldwide, largely due to access to surgeons skilled in radical pelvic surgery and the recent emergence of “Fertility-Sparing Surgery” in developed nations.

For early invasive cancers, surgery is generally considered the treatment of choice. In more advanced cases, a combination of radiation with chemotherapy is considered the current standard of care. In patients with advanced and disseminated disease, chemotherapy or radiation is used for symptomatic palliative care as deemed appropriate.

Stage Based Management as per Current Guidelines

Stage 0 Cancer

The management options in Carcinoma in situ (Stage 0) include local ablative or excisional measures such as cryosurgery, laser ablation or loop excision. Surgical removal is preferred as it allows tissue for further pathologic evaluation to rule out microinvasive disease. These patients require continued surveillance post treatment.

Stage IA1 Cancer

Surgery is the treatment of choice for stage IA1 Carcinoma cervix. The surgical options include conisation, total hysterectomy and radical hysterectomy. Lymph node dissection may not be required if the depth of invasion is < 3 mm and in the absence of lymphovascular invasion. Fertility Sparing Surgery in the form of therapeutic conization can be offered for selected patients with stage IA1 carcinoma cervix with no lymphovascular space invasion. These patients however require close follow-up, with cytology, colposcopy, and endocervical curettage. In patients with comorbidities, medical conditions precluding surgical resection can be successfully managed with radiation therapy. Definitive radiation therapy should consist of pelvic external beam radiation therapy with high-energy photons and intra-cavitary brachytherapy. It should be administered at high doses (>80–90 Grey) and in a short time (<55 days), with the best technological resources available.

The National Comprehensive Cancer Network (NCCN) guidelines recommend adjuvant pelvic radiation for women with stage IA carcinoma cervix and negative lymph nodes in patients who have high-risk factors like a large primary tumor, deep stromal invasion or lymphovascular space invasion.
Management of early cervical cancer by laparoscopic radical hysterectomy

The adoption of laparoscopic surgery for the surgical management of cervical cancer has been slower due to the technical difficulties associated with laparoscopic surgery in cervix and the diversity of the approaches employed. However, with recent improvements in laparoscopic instruments and surgical techniques, laparoscopic radical hysterectomy is becoming the preferred surgical approach for the surgical management of early cervical cancer. Laparoscopic radical hysterectomy has better surgical outcomes than other methods without affecting survival outcomes or increasing the number of complications. Studies have shown the use of laparoscopic radical hysterectomy limited to small cervical tumors <2 cm [4,5]. However, with the increase in surgical experience, the radicality of laparoscopic radical hysterectomy has become comparable to that of open radical hysterectomy [6]. Currently, the indication for radical hysterectomy has been extended to cervical tumors >4 cm [7]. Recent studies suggest that the benefit of laparoscopic surgery extends to elderly and obese patients [8,9].

Stage IA2, IB, or IIA Cancer

Combined external beam radiation with brachytherapy or radical hysterectomy with bilateral pelvic lymphad-ectomy are the conventional management options for patients with stage IB or IIA disease. Both the procedures are equally effective, but differ in terms of morbidity. There is only one randomized trial that has directly compared radical hysterectomy and radical radiation therapy done in 343 women with stage IB-IIA disease. The overall and disease-free survivals at 5 years were similar for the two treatment groups, (83% and 74%, respectively). Study showed that 66% of the patients in the surgical arm had adjuvant radiation in view of the associated risk factors. The rate of severe morbidity was 28% in the surgery group and 12% in the radiotherapy group [10]. There is no evidence to state that that concurrent chemoradiation would be useful in patients with early cervical cancer (stages IB1 and IIA <4 cm).

Fertility Sparing Surgery

Fertility-preserving radical trachelectomy has been accepted as a reasonable alternative treatment for young women with early cervical cancer to preserve their fertility. Currently, several types of surgical approaches for radical trachelectomy are used in real practice, including vaginal, abdominal, laparoscopic, and robotic radical trachelectomy. However, the use of vaginal radical trachelectomy is suited for small cervical cancers with a tumor size <2 cm. Radical vaginal trachelectomy with pelvic lymph node dissection has been shown to be appropriate in women...
with stage IA2 carcinoma cervix and in women with stage IB1 carcinoma cervix whose tumors are 2 cm or less previously [11,12]. However there are studies that have shown that the recurrence rate is significantly higher when the tumor size is >2 cm [13,14]. The recent investigators however suggest that with wider extirpation of parametrial tissue made possible by other surgical approaches including abdominal, laparoscopic and robotic trachelectomy [15], radical trachelectomy can be extended to selected patients with a tumor size >2 and <4 cm [16-18].

The principal problems with pregnancy after trachelectomy are premature labour and the need to undergo caesarean section for delivery [19]. Study by Lakhman et al [20] showed that among patients with stage IB1 cervical carcinoma (n=62) who underwent radical trachelectomy, the pretrachelectomy MRI scans helped identify high-risk patients who were likely to need radical hysterectomy and helped confirm the absence of residual tumor after a cone biopsy with negative margins. A tumor size of >2 cm and deep cervical stromal invasion on MRI scans was associated with an increased chance of radical hysterectomy.

The current management guidelines for stage IA2 to IIA cervical cancers allow for minimally invasive techniques, such as traditional laparoscopic and robotically assisted laparoscopic techniques. Many studies have shown that these less minimally invasive procedures are oncologically safe while possessing the added advantage of shorter postoperative recovery times [21-23]. An analysis of patients from the Surveillance, Epidemiology, and End Results (SEER) database who underwent radical hysterectomy with lymphadenectomy revealed that patients with node-negative early-stage cervical cancer who underwent a more extensive lymphadenectomy had improved survival. The study showed that when compared with patients who had < 10 nodes removed, patients who had 21-30 nodes removed had 24% less mortality due to disease and those who had > 30 nodes removed had 37% less mortality due to disease [24].

Recent Views on Role of Sentinel Node Biopsy in Cervical Cancer Management

In patients with cervical cancer, metastatic spread to lymph nodes is a well known prognostic parameter, crucial for selection of therapy. Radical lymphadenectomy is known to cause lymphedema, voiding disorders, seroccele formation, paresthesia and possibly reduced immune competence. The risk of lymph node metastases in women with early stage cervical cancer (up to FIGO stage IB1) is approximately 15% only and majority of patients do not benefit from lymphadenectomy [25,26].

The use of sentinel lymph node (SLN) biopsy concept is based on the assumption that if the first draining lymph node is free of disease, all other lymph nodes in the nodal basin should also be free of disease [27]. An initial study
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based on examining the utility of SLN biopsy in patients diagnosed with cervical cancer showed great promise with a detection rate, sensitivity and negative predictive value of 94%, 90.9% and 99.1%, respectively for patients with tumors measuring 2cm or less in diameter [28].

Reports from meta-analysis of 67 studies based on sentinel node biopsy for lymph nodal staging of uterine cervix cancer, shows that detection rate and sensitivity were related to mapping method (blue dye, radiotracer, or both) and history of pre-operative neoadjuvant chemotherapy. Bilaterally detected pelvic sentinel nodes had higher sensitivity compared unilateral sentinel nodes. Lymphatic mapping could identify sentinel nodes outside the routine lymphadenectomy limits [29].

Other studies have shown that sensitivity was close to 100% in patients where SLNs were detected bilaterally. Ultrastaging with multiple serial sectioning and immunohistochemical staining of the SLN has successfully improved the detection of nodal metastasis [30-32]. Recent reports suggest sentinel lymph node biopsy in early stage cancer as a more sensitive procedure in detecting pelvic lymph node metastases compared to complete lymphadenectomy [33]. Though sentinel node mapping can be an accurate method for the assessment of lymph nodal involvement in uterine cervical cancer, selection of a population with small tumor size and lower stage can ensure the lowest false negative rate. Lymphatic mapping can also be used to detect sentinel nodes outside of routine lymphadenectomy areas provided there are additional histological information available to improve the staging. There is need for further studies to explore the impact of sentinel node mapping in fertility sparing surgery and in patients with history of neoadjuvant chemotherapy.

Role of Molecular Markers in SLN to Identify Micrometastasis

By definition, macrometastasis are tumor deposits >2mm, micrometastasis are deposits between >0.2 and 2mm, and isolated tumour cells (ITC) are deposits ≤0.2mm including the presence of single non-cohesive cytokeratin-positive tumor cells [34]. Molecular markers can help in detection of low volume disease as an aid to ultrastaging methods. However the prognostic implications of low volume metastatic disease (micrometastasis and ITC) for patients with cervical cancer are not yet fully understood and serve only partly as prognostic indicators [31].

The first multicenter prospective study in patients with cervical cancer and tumor free lymph nodes by conventional histopathology, has addressed the prognostic potential of HPV mRNA in SLN of patients with pN0-status by systematic lymphadenectomy and conventional histopathology. The results have shown HPV-mRNA-positive SLN with a prognostic value independent of tu-
mor size. This study suggests that particularly in patients with tumors larger than 20mm diameter, HPV mRNA as a molecular marker could help in risk stratification. The recurrence-free survival was significantly longer for patients with HPV-mRNA negative SLN conversely, the presence of HPV-E6-E7-mRNA in SLN of patients with pN0 status was associated with a significantly decreased recurrence free survival [35].

**Post Operative Adjuvant Radiation Therapy as per Risk Assessment**

**Intermediate Risk**

A Gynecologic Oncology Group (GOG) trial that randomly assigned 277 women to receive pelvic RT (without chemotherapy) or no further treatment demonstrated a benefit for postoperative RT in women with deep cervical stromal invasion (to the middle or one-third depth), lymphovascular space invasion, and large tumor size (>4 cm). A significant benefit has been shown for progression-free survival, but not for overall survival with a median follow-up of 10 years. Postoperative adjuvant radiation therapy is hence recommended in patients who have at least 2 intermediate risk factors (including tumor size > 2 cm, deep stromal invasion or lymphovascular space invasion.

**High Risk**

Women with one or more worse prognostic factors such as positive or close surgical margins, positive lymph nodes, or microscopic parametrial involvement are considered to be at high risk of relapse [36]. A randomized trial showed that patients with parametrial involvement, positive pelvic nodes or positive surgical margins benefit from a postoperative combination of cisplatin-containing chemotherapy and pelvic irradiation. The use of chemotherapy has been shown associated with a substantially better 4-year overall survival (81% versus 71%) and progression-free survival (80% versus 63%), and the outcome was better for patients who completed three to four cycles of chemotherapy [37]. A combined approach of radiation along with chemotherapy is used in patients with IB2 or IIA cervical cancer and with tumors > 4 cm. Although there are risks associated with combined therapy, many of these patients will meet either the intermediate or the high-risk criteria after radical hysterectomy and are hence strong candidates for this approach.

**Treatment of Locally Advanced Cervical Cancer (Stage IIB, III, or IVA)**

**Radiation Therapy**

For locally advanced cervical carcinoma (stages IIB, III and IVA), radiation therapy has been the treatment of choice for many years. Radiation therapy begins with a course of external beam radiation to reduce tumor mass and thereby enabling subsequent intra-cavitary application. Brachytherapy is delivered by means of after load-
Tailored Radiation Therapy - Intensity Modulated Radiation therapy/Proton Therapy

New techniques for delivering radiation to targets, including intensity-modulated radiotherapy (IMRT) and proton therapy, for the management of gynecologic cancers have been introduced. IMRT was shown to be better at reducing the delivery of radiation to adjacent normal tissue, such as rectum, bladder, and small bowel, resulting in the delivery of a higher tumor dose compared with conventional or 3-dimensional conformal radiotherapy. It has been shown to provide benefits in terms of increased tumor control and decreased toxicity to normal tissues; however, the study of the clinical significance of IMRT in the management of gynecologic cancers still limited [38-42]. A randomized phase 3 clinical trial is ongoing aimed at comparing the standard radiotherapy to IMRT for the postoperative treatment of endometrial and cervical cancer (RTOG protocol 1203).

Proton therapy has energy delivery at a defined depth and has no exit energy after the Bragg peak. It can decrease the irradiated volume and reduce the dose to adjacent normal tissues beyond the possible achievement by IMRT; however, there is no clinical data to confirm that proton therapy can reduce normal tissue toxicity. Photon therapy still remains mostly an investigational tool for the management of gynecologic cancers. Prospective clinical trials are therefore required to evaluate the efficacy of IMRT and proton therapy in the management of gynecologic cancers.

Advent of Chemo-Radiation

There are 5 randomized, phase III trials (GOG-85, RTOG-9001, GOG-120, GOG-123, SWOG-8797) that have shown an overall survival advantage for cisplatin-based therapy given concurrently with radiation therapy [43-47]. This was subsequently also confirmed in further reviews and meta-analysis, the most recent of which was based on individual patient data from 18 randomized trials which demonstrated an absolute 5-year survival benefit of 8% for overall disease-free survival, 9% for loco-regional disease-free survival, and 7% for metastases-free survival across all stages [48]. The advantage is also shown for non-platinum-based chemotherapy. Consequently, the use of cisplatin-based chemotherapy in combination with radiation has become the standard of care for primary management of patients with locally advanced cervical cancer.
Optimal Schedule of Concurrent Chemoradiation

The optimal radiation therapy, consisting of high doses (80–90 Grey) administered over a short time (<50–55 days), significantly impacts on outcome. The optimal regimen for chemotherapy has yet to be defined, but weekly single-agent cisplatin at 40 mg/m²/week during external beam therapy is widely used; concurrent carboplatin or non-platinum chemo-radiation regimens are other options for patients who may not tolerate cisplatin-containing schedules. A recent study indicates a significant benefit for the use of adjuvant chemotherapy following chemoradiation. Patients with locally advanced cervical cancer (stages IIB to IV) treated with cisplatin–gemcitabine, both during and after radiation therapy, demonstrated a great improvement in progression-free survival and overall survival. Despite these encouraging results, systemic consolidation has not been used in regular practice [49]. A systematic review from 18 trials and 2074 patients demonstrated that the timing and dose intensity of cisplatin-based neoadjuvant chemotherapy before radiation could affect outcome. However, the data was heterogeneous and merits further confirmation.

Role of Neoadjuvant Chemotherapy

A meta-analysis of neoadjuvant chemotherapy followed by radical hysterectomy showed an absolute improvement of 14% in 5-year survival compared with radiotherapy [50]. Despite several objections to this meta-analysis because patients in the control arm received only radiation therapy not in combination with chemotherapy and radiation therapy. Neoadjuvant chemotherapy followed by radical surgery could have an important role in the treatment of locally advanced cervical cancer, but the appropriate indications still need to be established. The on-going trial EORTC 55994 will help clarify whether neoadjuvant chemotherapy followed by surgery will result into a better outcome compared with chemoradiotherapy in patients with stages IB2 to IIB cervical cancer.

Response Evaluation and Follow Up

No definitive agreement exists on the best post-treatment surveillance. A gynecological examination including Pap smear is usually performed every 3 months for the first 2 years, every 6 months for the next 3 years, and yearly thereafter CT or PET/CT scan can be performed as clinically indicated.

Management of Recurrent Cervical Cancers

For recurrent disease, the choice of therapy is largely influenced by the prior treatment employed. The management of pelvic recurrences after primary surgical management should include single-agent chemotherapy and radiation, whereas the management for recurrences elsewhere
should include combination chemotherapy [51]. For central pelvic recurrence after radiation therapy, a modified radical hysterectomy (only if the recurrence is < 2 cm) or pelvic exenteration should be undertaken [52]. For tumors recurring after chemotherapy and radiation therapy, a disease-free interval of > 16 months is considered to designate the tumor as platinum-sensitive [53]. The standard of care in these cases is chemotherapy with a platinum-based doublet of paclitaxel and cisplatin. Recurrences arising in a previously irradiated field or after a disease-free interval of < 16 months are less likely to respond to subsequent therapies. Patients with such early recurrences should be strongly encouraged to participate in clinical trials.

**Stage IVB and Advanced Recurrent Cancer**

Although early-stage disease can be cured with radical and even fertility-sparing surgery, patients with metastatic and recurrent cervical cancer have poor prognosis with historically limited treatment options and incurable disease. Significant advances in cervical cancer treatment have emerged as the result of clinical trials that have sought to determine the best therapy to prolong overall and progression-free survival. Most recently, trials that have involved angiogenesis blockade in addition to standard chemotherapy have demonstrated improved overall and progression-free survival.

Patients with metastatic or advanced recurrent cervical cancer are commonly symptomatic. The role of chemotherapy/radiotherapy in such patients is palliative, with the primary objective to relieve symptoms and improve quality of life. Cisplatin is considered the single most active cytotoxic agent. Overall, the duration of the objective response to cisplatin in patients with metastatic or recurrent disease has remained disappointing with a survival of approximately 7 months. There is not a clear dose-response effect. Cisplatin-based combination therapy, such as cisplatin–paclitaxel and cisplatin–topotecan, has been extensively investigated in clinical trials. Only the cisplatin–topotecan combination reported an overall survival advantage compared with monotherapy. A recent phase III trial assessed four cisplatin-doublet regimens. (cisplatin–paclitaxel, cisplatin–topotecan, cisplatin–gemcitabine, and cisplatin–vinorelbine) No significant differences in overall survival were seen; however, the trends for response rate, PFS, and OS suggest that cisplatin–paclitaxel is the preferred regimen [54]. The NCCN also recommends docetaxel, gemcitabine, ifosfamide, 5-fluorouracil, mitomycin, irinotecan, and topotecan as possible candidates for second-line therapy (category 2B recommendation), as well as pemetrexed and vinorelbine (category 3 recommendation). In addition, bevacizumab as single-agent therapy is also acceptable.
Role of Anti-Angiogenic Agents for Targetted Therapy

Bevacizumab

Antiangiogenesis agents are efficacious in other solid malignant tumors with similar tumor biology, such as non–small cell lung cancer. Bevacizumab is the most studied agent in gynecologic neoplasms and other solid tumors. Bevacizumab is an anti-VEGF monoclonal antibody that blocks tumor angiogenesis by binding and inactivating VEGF and thereby inhibiting endothelial cell activation and proliferation, thus denying tumors the ability to recruit new vessel development. Bevacizumab also counteracts the survival (antiapoptotic) signaling that supports the immature vasculature usually associated with neoplastic growth and prevents constant endothelial remodeling required for local tumor spread, thus restoring normal structure and function to disorganized, highly permeable vessels typically seen in malignant tumors [51].

The first prospective Phase II trial of bevacizumab in cervical cancer was conducted through the cooperative research network led by the Gynecologic Oncology Group (GOG). GOG 227C was a multicenter Phase II study of bevacizumab monotherapy that revealed the tolerability and efficacy of the drug in heavily pretreated patients with recurrent cervical cancer. Bevacizumab was found to be effective even better than expected particularly compared with other historical control groups in this setting. Subsequently, other agents with antiangiogenic activity have also been studied in advanced and recurrent cervical cancer, including oral tyrosine kinase inhibitors. Treatment with bevacizumab plus cisplatin and paclitaxel or topotecan and paclitaxel was approved by the FDA in August 2014 for persistent, recurrent, or metastatic cervical cancer as per NCCN reports. Statistically significant improvement in overall survival and an increase in the rate of tumor shrinkage was shown in women treated with bevacizumab plus chemotherapy compared with chemotherapy alone. However, hypertension, thromboembolic events, and GI fistulas were higher in the bevacizumab group. Bevacizumab/paclitaxel/cisplatin or topotecan is considered a first-line regimen for recurrent or metastatic cervical cancer [55].

Pazopanib

Pazopanib (targets VEGF receptor, platelet-derived growth factor receptor, and c-kit) and lapatinib (dual anti–epidermal growth factor receptor and anti-HER2/neu) were studied in a Phase II trial comparing pazopanib (800 mg/d) or lapatinib (1,500 mg/d) monotherapy versus combination therapy with both drugs. The combination therapy treatment arm was closed for futility and imbalanced toxic effects after the first interim analysis. This head-to-head comparison revealed the superiority of antiangiogenesis over anti-EGF therapy [51]. Pazopanib treated patients showed improved PFS compared to lapatinib treated patients, however there was no OS benefit.
The study supports further investigations of anti-VEGF treatments in cervical cancer, but unfortunately epidermal growth factor receptor–based therapies, such as cetuximab and erlotinib, have resulted in several negative clinical trials.

**Role of HPV Vaccines**

The primary prevention using prophylactic vaccines has been shown in several reports. The prophylactic vaccine stimulates the development of the humoral immune response, which occurs after contact with the “virus-like particles” (VLPs), which are non-infectious structures and simulate a natural HPV infection [56-63]. The two oncogenic types included in both vaccines are HPV 16 and 18, responsible for at least 70% of the cases of cervical cancer worldwide. In the case of the quadrivalent vaccine, it also included two non-oncogenic types of HPV, 6 and 11, responsible for approximately 90% of cases of anogenital condylomata acuminata. Safety and tolerability of both vaccines have been evaluated extensively with similar profiles in the vaccinated and control groups, irrespective of age or ethnicity. Studies about safety assessment indicated that local and systemic injection-related symptoms were generally mild. Serious adverse effects (AE) that are considered to be vaccine related are rare and similar to other vaccine types [64,65].

The implementation of HPV vaccination in low- or middle-income countries has encountered many hurdles, including that of cost. Malaysia was the first middle-income country in the world to implement a national HPV vaccination program in 2010. This is a school-based vaccination program targeting girls attending grade seven in schools (13-year-old girls). Immunization in the clinic is proposed to 13-year-old out-of-school girls. This program has been very successful as 95.9% and 97.9% of parents gave consent to their daughters to be vaccinated and 97.9% and 95.9% of girls who obtained parental consent completed all three courses of the vaccination in 2010 and 2011, respectively. In 2012, a catch-up vaccination program was introduced targeting girls aged 18 years. The reasons for the success of this program includes endorsement and recommendation by the medical profession, political will and leadership, the involvement of stakeholders early on in the program, predicting and managing potential risks, monitoring implementation closely, a good existing school health program, the involvement of the Ministry of Education, and giving sufficient information about the vaccine and its safety to parents.

**Prognosis**

The prognosis of cervical cancer is largely influenced by its stage, with survivals touching 100% for women with microscopic forms of cervical cancer. The five-year overall rate of cervical cancer (all stages combined) is about 72%. With standard treatment, 80 to 90% of women with stage I cancer and 60 to 75% of those with stage II cancer are alive 5 years after diagnosis. Survival rates decrease to 30%
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to 40% for women with stage III cancer and 15% or fewer of those with stage IV cancer 5 years after diagnosis.

**Other Promising Therapies**

The development of targeted therapies that selectively target specific molecular pathways involved in tumorigenesis may lead to other major advances in the management of cervical cancer. The role of immunotherapy is a promising and exciting new area of research that can potentially lead to further advancements in the treatment of locally advanced, recurrent, or metastatic cervical cancer. Development of the immune checkpoint blockade PD-1 and CTLA-4 inhibitors has shown promise and will need to be further studied as a means to achieve a durable response in cervical cancer.

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