Cervical cancer

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Paul A Cohen, Anjua Jhingran, Ana Oaknin, Lynette Denny

Each year, more than half a million women are diagnosed with cervical cancer and the disease results in over 300 000 deaths worldwide. High-risk subtypes of the human papilloma virus (HPV) are the cause of the disease in most cases. The disease is largely preventable. Approximately 90% of cervical cancers occur in low-income and middle-income countries that lack organised screening and HPV vaccination programmes. In high-income countries, cervical cancer incidence and mortality have more than halved over the past 30 years since the introduction of formal screening programmes. Treatment depends on disease extent at diagnosis and locally available resources, and might involve radical hysterectomy or chemoradiation, or a combination of both. Conservative, fertility-preserving surgical procedures have become standard of care for women with low-risk, early-stage disease. Advances in radiotherapy technology, such as intensity-modulated radiotherapy, have resulted in less treatment-related toxicity for women with locally-advanced disease. For women with metastatic or recurrent disease, the overall prognosis remains poor; nevertheless, the incorporation of the anti-VEGF agent bevacizumab has been able to extend overall survival beyond 12 months. Preliminary results of novel immunotherapeutic approaches, similarly to other solid tumours, have shown promising results so far.

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Introduction

Cervical cancer is the fourth most common female malignancy worldwide and represents a major global health challenge.[1] Approximately 90% of the 270 000 cervical cancer deaths in 2015 occurred in low-income and middle-income countries (LMIC) where mortality is 18 times higher than that in developed countries.[2] High-risk subtypes of the human papillomavirus (HPV) cause almost all cervix cancers and HPV screening and vaccination programmes are effective strategies in disease prevention.[3] Squamous cell carcinoma and adenocarcinoma are the most common histological subtypes accounting for approximately 70% and 25% of all cervix cancers, respectively.[4,5] Despite advances in prevention, screening, diagnosis, and treatment during the past decade, substantial regional and global disparities in cervical cancer outcomes have led international gynaecological cancer societies to publish evidence-based management guidelines that aim to improve the quality of care for patients.[6] This Seminar focuses on the epidemiology, pathophysiology, diagnosis, and clinical management of cervical cancer. Important trials are described and unresolved questions regarding management are discussed.

Epidemiology

In 2018, an estimated 569 847 new cases of cervical cancer were diagnosed and 311 365 deaths occurred worldwide due to this malignancy,[1] although incidence and mortality vary widely with geographic location. In high-income countries, cervical cancer incidence and mortality have decreased by more than half over the past 30 years since the introduction of formalised screening programmes.[7] A study of global trends across 38 countries in five continents showed substantial decreases in age-standardised incidence rates in the highest-income countries analysed, whereas these rates have increased or stabilised in lower-resourced settings included in the study.[8] However, decreases in cervical cancer incidence have been observed in LMICs when opportunistic screening has been used.[9]

In 2012, cervical cancer was the 11th most common female malignancy (9·9/100 000 women) and the ninth most common cause of cancer mortality (3·3/100 000 women) in high-income countries;[10] however, in LMICs, cervical cancer was the second most common type of cancer (15·7/100 000 women) and the third most common cause of cancer death (8·3/100 000).[10] In Africa and Latin America, cervical cancer is the leading cause of cancer-specific mortality in women. The lifetime risks (up to age 74 years) of developing cervical cancer were 0·9% for women in high-income countries and 1·6% in LMICs, and the risks of death due to cervical cancer were 0·3% for women in high-income countries and 0·9% in LMICs.

The median age at diagnosis is 47 years in the USA, with almost 50% of cases diagnosed under age 35 years.[11] In South Africa, where cervical cancer is the leading

Search strategy and selection criteria

We searched MEDLINE, Current Contents, and PubMed with the terms "cervical cancer", "radical hysterectomy", "trachelectomy", "lymphadenectomy", "sentinel node", "chemotherapy", "radiation therapy", "targeted therapy", "fertility-sparing management", and "molecular classification" for articles published in English between Jan 1, 1990, and April 30, 2018. We also reviewed the reference lists of articles identified by this search. We focused our search strategy on systematic reviews, meta-analyses, and clinical trials registered on http://clinicaltrials.gov, and selected articles on the basis of their representativeness and relevance. We mostly selected publications from the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant.

Panel 1: Risk factors for cervical cancer

Chronic infection by high-risk oncogenic subtypes of human papilloma virus (HPV) causes almost all cases of cervical cancer[14] and, therefore, risk factors are those associated with acquiring HPV infection, severely impaired immune response to HPV infection, or both.[15,16] These risk factors include:

- early age of sexual debut
- multiple sexual partners or a high-risk sexual partner
- immunosuppression (eg, after organ transplantation or immunodeficiency disorders such as HIV)
- history of sexually-transmitted infection
- history of HPV-related vulvar or vaginal dysplasia
- non-attendance for screening and underscreening in countries with established cervical screening programmes (resulting in an estimated two-thirds of cervical cancers in such countries)[17,18]

Tobacco smoke was found to be a major risk factor for cervical precancer and cancer in the European Prospective Investigation into Cancer and Nutrition cohort study of more than 300 000 women. Smoking status, duration, and amount smoked were associated with double the risk of high-grade dysplasia and carcinoma after adjustment for HPV status.[19] Importantly, smoking cessation was associated with a two-fold risk reduction.

cause of cancer death in women, more than 25% of diagnoses between 2004 and 2012 were in women aged 40 to 49 years.[12] During this time, age-specific mortality increased with increasing age with 70% of deaths occurring in women older than 50 years.[12] In a population-based study of nearly 70 000 cervical cancer cases over a 7-year time period, older women were more likely to be diagnosed with advanced stage disease (16·53% in 21–34 year old women *vs* 42·44% in those aged 70 years).[13]

Cervical cancer risk factors are described in panel 1 and its pathogenesis is shown in figure 1.

Impact of HIV infection

More than 70% of cases of HIV infection occur in sub-Saharan Africa.[21] Women infected with HIV are at increased risk of HPV infection at an early age (13–18 years) and are at high risk of cervical cancer.[22] Compared with non-infected women, HIV positive patients with cervical cancer are diagnosed at an earlier age (15–49 years).[12] An increase in cervical cancer incidence in South Africa between 2001 and 2009 could be explained by the increased number of HIV infections observed during this period due to increased nationwide coverage of anti retroviral therapy in the country that led to improved longevity of people living with HIV or AIDS.[12] Unlike other AIDS-defining diseases (*Pneumocystis jiroveci* pneumonia and other opportunistic infections, [eg, extrapulmonary cryptococcosis and histoplasmosis]),

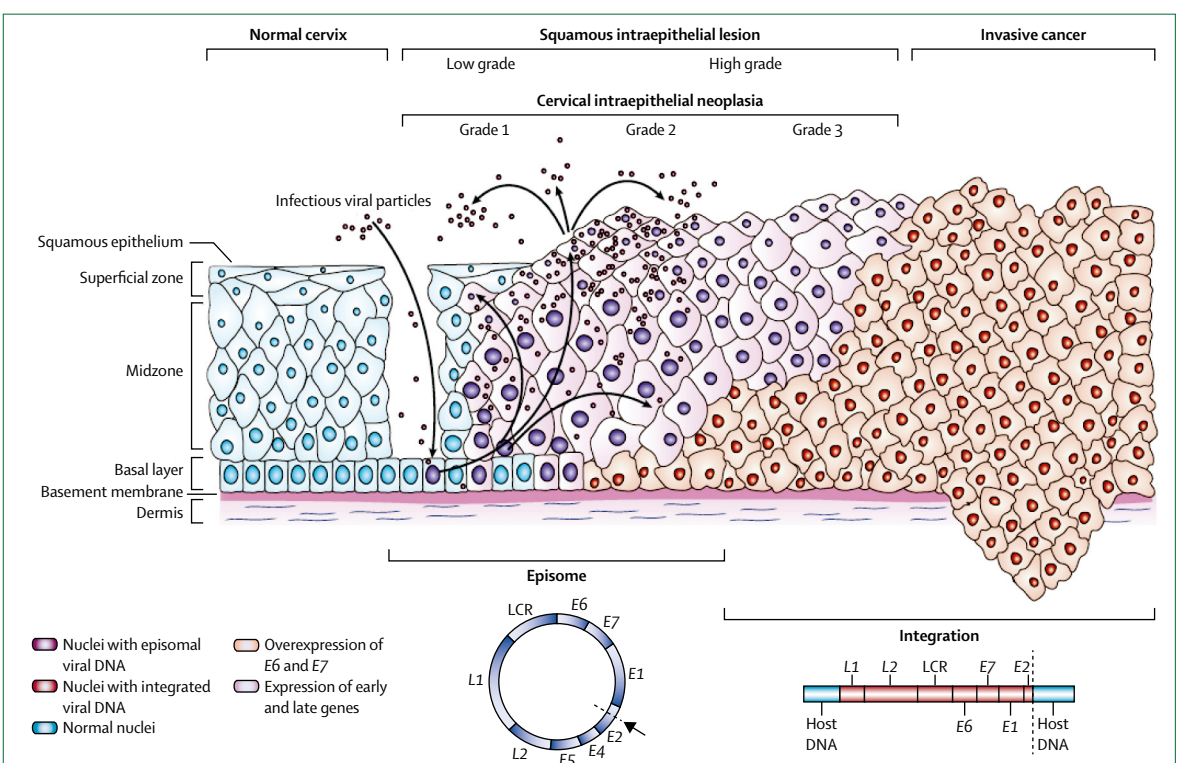

Figure 1: **Pathogenesis of cervical cancer**
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which incidence decreased following the introduction of antiretroviral therapy, cervical cancer incidence remained unchanged because chronic immunosuppression is a risk factor for virus-associated malignancies.[23] HIV infection brings unique challenges to the management of women with cervical cancer; for example, the interaction of tumour and HIV virus can lead to T-cell dysfunction, increased risks of neutropenia and reactivation of latent infections during systemic treatment, difficulties in staging due to non-cancer associated lymphadenopathy, and HIV-related thrombocytopenia that might increase complications of surgery and chemotherapy.[23]

Primary prevention of cervical cancer

Primary prevention of cervical cancer is done through avoidance of HPV infection. Abstaining from sexual activity, mutual monogamy of virgins, or the use of condoms, which do not provide 100% protection, can prevent HPV infection. However, effective primary prevention of cervical cancer relies on HPV vaccination. The first bivalent and quadrivalent HPV vaccines became available in 2006, and each has shown more than 90% efficacy in preventing HPV type 16 and 18, which are associated high-grade cervical dysplasia.[3] In 2018, a nine-valent vaccine has shown efficacy at 6 years in young women aged 16 to 26 years and is being rolled out.[24]

In countries where HPV vaccination programmes have been introduced, substantial decreases in cervical cancer incidence are anticipated but will not be apparent for several years because of the latency period between chronic HPV infection and onset of malignancy.[25] In Australia, the first country to establish an HPV vaccination programme (in 2007) that used the quadrivalent vaccine Gardasil with a more than 70% vaccine coverage in girls and boys aged 12 and 13 years, a 38% reduction in high-grade cervical dysplasia in women under 18 years of age was observed within 3 years of the programme's implementation.[26] In countries where at least 50% of eligible females were vaccinated, HPV 16 and 18 infections decreased by almost 70%.[27] However, in one study of over 900 000 women in the USA, cumulative HPV vaccination coverage of eligible females by 2014 was less than 50% in girls under age 17 years.[28] Efforts to improve adherence to recommended HPV vaccination schedules are essential to achieve sufficient coverage to ensure herd immunity. The introduction of vaccine programmes in LMICs has been restricted by cost, paucity of adolescent health platforms, cultural challenges, and difficulties in reaching the target population.[29]

Secondary prevention

The Papanicolaou smear was the original cervical screening test. In four European randomised controlled trials, HPV-based screening provided greater protection against cervical cancers HPV-based screening was more efficcacious at detecting cervical pre-cancers) compared with cytology.[30] Consistent with these findings, a recent Canadian randomised trial showed that among more than 19 000 women undergoing screening, primary HPV testing was associated with a significantly lower likelihood of CIN3-positive at 48 months compared with cytology.[31] However, participants in both groups underwent HPV testing and cytology at 48 months, and hence the exit intervention was not equivalent to that at study entry. Furthermore, women in rural and remote areas, who are underscreened and have a higher risk of cervical cancer risk compared with women in urban areas, were under-represented and the observed effect might, therefore, have been underestimated.

Essential elements of national cancer screening programmes for implementation in LMICs have been defined and are outlined in panel 2.[32]

Clinical presentation

In its early stages, cervical cancer is often asymptomatic and might be diagnosed following routine screening or pelvic examination. Symptoms include post-coital or abnormal vaginal bleeding.[33] A profuse malodorous vaginal discharge might also be a symptom but is rarely present in isolation.[34] The triad of lower limb oedema, flank pain, and sciatica suggest pelvic sidewall invasion.[35] Passage of urine through the vagina is a symptom of vesicovaginal fistula and suggests invasion of the bladder, whereas passage of faeces through the vagina is a symptom of rectovaginal fistula and suggest invasion of the rectum.

Diagnosis

Diagnosis is based on histopathological assessment of a cervical biopsy. Women with symptoms of cervical cancer require pelvic examination, visualisation of the cervix and vaginal mucosa, and cervical cytology. The cervix and vaginal mucosa should be visualised by speculum examination. The cervix might appear normal when the disease is microinvasive or in the endocervical canal. Cervical cancer can metastasise via lymphatic vessels to pelvic, para-aortic, mediastinal, supraclavicular, and inguinal lymph nodes. Enlarged, indurated inguinal and supraclavicular lymph nodes can be palpable in advanced disease.

A colposcopy and biopsy should be performed in symptomatic patients or women with cytology suggestive of invasion without visible lesions. A cone biopsy is mandatory if malignancy is suspected either clinically or on cervical cytology but is not confirmed on histopathological review of cervical biopsies.[7] The cone should be a type III excision (depth >1·5 cm) in one piece.[7]

Staging

Staging is determined clinically based on tumour size and the degree of pelvic extension (table 1).[36,37] For microscopic lesions, stage is assigned following conisation when tumour dimensions can be determined histologically. Stage should always be assigned at diagnosis and never amended. Clinical staging is

Panel 2: Essential elements of national cancer screening programmes for implementation in low-income and middle-income countries

Policy to be decided before the initiation of screening programme

- Population to be screened
- Organised or opportunistic
- How financed
- The screening process (methods)

Invitation to recruit

- Screening algorithms
- Triaging and referral for positive screens
- Linking screening data to population-based registries
- Data systems and resources to ensure treatment and return to screening programme after treatment

Health systems infrastructure

- Trained screeners (physicians, nurses, and community health workers)
- Screening reminders
- Systems to collect and analyse cytology
- Management structure to ensure operations of screening programme
- Stock of consumables

Monitoring

- Establish frameworks for monitoring and assessment
- Monitoring of programme to assess performance and to improve screening uptake

Implementation research

- Assessment of invitational strategies to screening programme
- Determination of age and screening intervals; identification of high-risk groups
- Strategies to promote participation (understanding barriers and facilitators to participation)

	TNM	FIGO
Primary tumour cannot be assessed	TX	..
No evidence of primary tumour	T0	..
Carcinoma in situ (preinvasive)	Tis	..
Cervical carcinoma confined to the cervix (without extension to uterine corpus)	T1	I
Invasive carcinoma diagnosed only by microscopy, stromal invasion with a maximum depth of 5·0 mm measured from the base of the epithelium, and horizontal spread of 7·0 mm or less; vascular space involvement, venous or lymphatic, does not affect classification	T1a	IA
Measured stromal invasion no greater than 3·0 mm and lateral spread no greater than 7·0 mm	T1a1	IA1
Measured stromal invasion greater than 3·0 mm and no greater than 5·0 mm, and horizontal spread no greater than 7·0 mm	T1a2	IA2
Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a or IA2	T1b	IB
Clinically visible lesion no greater than 4·0 cm in greatest dimension	T1b1	IB1
Clinically visible lesion greater than 4·0 cm in greatest dimension	T1b2	IB2
Cervical carcinoma invades beyond the uterus but not the pelvic wall or lower third of vagina	T2	II
Tumour without parametrial invasion	T2a	IIA
Clinically visible lesion no greater than 4·0 cm in greatest dimension	T2a1	IIA1
Clinically visible lesion greater than 4·0 cm in greatest dimension	T2a2	IIA2
Tumour with parametrial invasion	T2b	IIB
Tumour extends to pelvic wall, involves lower third of vagina, causes hydronephrosis, or a combination of all symptoms, or non-functioning kidney	T3	III
Tumour involves lower third of vagina, without extending to the pelvic wall	T3a	IIIA
Tumour extends to pelvic wall, causes hydronephrosis or non-functioning kidney, or both	T3b	IIIB
Tumour invades mucosa of bladder or rectum, extends beyond the true pelvis, or both (bullous oedema is not sufficient to classify a tumour as T4 or IV)	T4	IV
Tumour invades mucosa of bladder or rectum (bullous oedema is not sufficient to classify a tumour as T4 or IV)	T4a	IVA
Tumour extends beyond the true pelvis	T4b	IVB

TNM is a cancer staging system, where T is associated with the size of the primary tumour, N with the nodal involvment, and M with metastatic disease.

Table 1: **Staging of cervical tumours according to the International Federation of Gynecology and Obstetrics (FIGO) and the American Joint Committee on Cancer (AJCC)**

preferred to surgical staging because it is accessible in LMICs and is accurate in the assessment of locally advanced disease.

Staging combines physical examination, endoscopic procedures, and imaging modalities (panel 3) according to International Federation of Gynecology and Obstetrics (FIGO) guidelines, but it is not always necessary to use all modalities on every patient. The FIGO system does not include lymph node status in contrast to the American Joint Committee on Cancer system.[38] Consequently, the FIGO system might understage patients and a revised FIGO staging system that includes lymph node status is due for publication in 2019. Accurate staging is crucial in treatment planning, counselling patients regarding prognosis, and assessment of eligibilty for research studies.

The role of surgical staging versus non-invasive radiological modalities for diagnosing metastatic paraaortic lymph nodes is controversial.[39] A systematic review of pretreatment assessment of the para-aortic nodes by surgery identified only one randomised study of 61 patients and concluded that evidence for the benefit of pretreatment surgical staging was insufficient and that the procedure might actually be harmful.[40] Pretreatment

surgical staging was not associated with a greater risk of complications, but was associated with shorter progression-free survival and overall survival compared with clinical staging.

In a meta-analysis of 72 studies that included 5042 patients, the sensitivity of PET (figure 2) for detecting involved nodes was 75% and the specificity was 98%, which were superior to MRI (sensitivity of 56% and specificity of 93%) and CT (sensitivity of 58% and specificity of 92%).[41] In a review that included 4 studies of 136 patients, the sensitivity and specificity of PET for detecting involved para-aortic nodes was 84% and 95% compared with 79% and 99% for detection of pelvic nodal metastasis.[42] Such imaging modalities might not be available in LMICs.

A strong association has been found between clinical and surgical staging for stages IIIB and IVA but not for other stages.[43,44] Determination of parametrial and lymph node involvement are not possible by clinical staging without facilities for CT, MRI, or both.

Surgical treatment for cervical cancer

In stage IA1, the risk of lymph node metastasis is less than 1%[45] and treatment can include conisation for women wishing to preserve fertility, or simple extrafascial hysterectomy if fertility is not desired.[46] Stage IA2 cervical cancers have a risk of lymph node involvement of up to 8%.[47] Standard treatment for stage IA2 has been radical hysterectomy (table 2) and bilateral pelvic lymphadenectomy. Radical hysterectomy involves resection of the uterus, cervix, parametria, and cuff of upper vagina.[48,49] Up to one third of patients undergoing radical hysterectomy might have long-term sequelae, including long-term urinary voiding dysfunction, vesicovaginal fistula, lymphocoele formation, and obturator and genitofemoral neuropraxia.[50] Pelvic lymphadenectomy includes resection of the obturator, internal, external, and common iliac nodes. Lower limb lymphoedema was found to affect 47% of patients following pelvic lymphadenectomy in a single centre prospective study of 60 patients.[51]

Stage IA2 cervical cancers have a low risk of parametrial invasion and modified radical hysterectomy, with less parametrium resection and a smaller vaginal cuff, is appropriate.[52] Bladder, bowel, and sexual dysfunction are due to the disruption of autonomic nerve fibres during parametrectomy. With the ability of MRI to delineate tumour extent and the low risk (<1%) of parametrial involvement, some authors have argued that simple hysterectomy and pelvic lymphadenectomy should be the new standard of care.[53] The SHAPE trial (NCT01658930) is an ongoing randomised study that aims to assess the oncologic safety of simple extrafascial hysterectomy and pelvic node dissection versus radical hysterectomy for women with low-risk cervical cancer.

Women younger than 40 years, with stage IA1 disease with lymph-vascular space invasion (LVSI), stage IA2, smaller stage IB1 tumours (<2 cm diameter), without evidence of lymph node metastases on imaging, and evidence of endocervical extension on MRI, wishing to preserve fertility, are appropriate candidates for radical trachelectomy.[54,55] Radical trachelectomy can be performed via laparotomic, vaginal, laparoscopic, or robotic-assisted routes, and involves resection of the entire cervix and 2 to 3 cm of upper vagina and parametrium, and suturing the distal lower uterine segment to the vaginal mucosa to create a so-called neo-cervix, around which a permanent cervical suture (cerclage) is placed.[56–58] Recurrence is similar to that of radical hysterectomy.[55] Risk factors for recurrence include larger lesions, LVSI, and non-squamous non-adenocarcinoma histologies.[59] Risk of first-trimester miscarriage after radical trachelectomy is equivalent to the population risk (up to 20%) but second trimester miscarriage occurs more frequently than in the general population (9·5% *vs* 4%).[60,61]

***Panel 3*: International Federation of Gynecology and Obstetrics (FIGO) cervical cancer staging**

Physical examination

- Pelvic examination: speculum, bimanual, and rectovaginal examination for palpation and inspection of the primary tumour, uterus, vagina, and parametria. The parametria are most accurately assessed by rectovaginal examination.
- Examination for distant metastases: palpation of groin and supraclavicular lymph nodes, examination of the right upper quadrant.

Cervical biopsy

- Colposcopy with directed cervical biopsy or cervical biopsy without colposcopy if visible lesion
- Endocervical curettage
- Conisation

Endoscopy

- Hysteroscopy
- Cystoscopy
- Proctoscopy
- Suspicious lesions should be confirmed by biopsy

Imaging studies

- Intravenous pyelogram to evaluate for urinary tract obstruction
- Chest radiograph and radiograph of the skeleton for skeletal metastases
- CT or MRI can be used instead when available

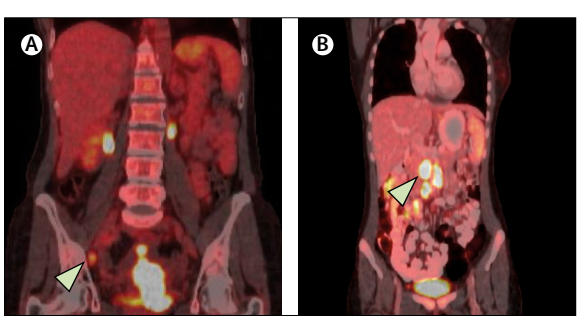

***Figure 2*: PET/CT of patient with cervical cancer with metastases in pelvic and para-aortic lymph nodes**

	Procedures
Piver-Rutledge-Smith classification[48]	
Class 1	Extrafascial hysterectomy: the fascia of the cervix and lower uterine segment is removed with the uterus; the uterine artery is ligated close to uterus; uterosacral and cardinal ligaments are left intact; and the vagina is not resected
Class 2	Modified radical hysterectomy (Wertheim): the ureters are dissected in the paracervical region but not resected from the vesicouterine ligaments; uterine arteries are ligated when they traverse the ureters; uterosacral ligaments are excised midway from their sacral insertion; cardinal ligaments are resected up to their medial half; and the upper third of the vagina is resected
Class 3	Radical hysterectomy: uterine arteries are ligated at their origin from the superior vesical or internal iliac arteries; uterosacral and cardinal ligaments are resected at their attachments to the sacrum and pelvic sidewall; and the upper half of the vagina is resected
Class 4	Radical hysterectomy: ureters are completely dissected from the vesicouterine ligaments; superior vesical arteries are sacrificed; and the proximal three quarters of the vagina are resected
Class 5	Radical hysterectomy: bladder is partially resected, or distal ureter is resected with ureteral reimplantation into the bladder
Querleu Morrow classification[49]	
Type A	Extrafascial hysterectomy: the position of the ureters is determined by palpation or direct vision (after opening of the ureteral tunnels) without freeing the ureters from their beds; the paracervix is transected medial to the ureter, but lateral to the cervix; the uterosacral and vesicouterine ligaments are not transected at a distance from the uterus; and vaginal resection is limited (<10 mm)
Type B	Radical hysterectomy: uterosacral and vesicouterine ligaments are partially resected; the ureter is unroofed and rolled laterally, permitting transection of the paracervix at the level of the ureteral tunnel; the caudal (posterior, deep) neural component of the paracervix caudal to the deep uterine vein is not resected; and at least 10 mm of the vagina from the cervix or tumour is resected
Type C	Radical hysterectomy: the uterosacral ligament is transected at the rectum and vesicouterine ligament at the bladder; the ureter is mobilised completely; and 15 to 20 mm of the vagina from the tumour or cervix and the corresponding paracolpos is resected
Type D	Additional ultraradical procedures, mostly indicated at the time of pelvic exenteration; type D1 is resection of the entire paracervix at the pelvic sidewall along with the hypogastric vessels, exposing the roots of the sciatic nerve; and type D2 is the same as type D1 plus resection of the entire paracervix with the hypogastric vessels and adjacent fascial or muscular structures

Table 2: **Types of radical hysterectomy**

In a review of 200 pregnancies after radical trachelectomy, two-thirds ended in a live birth.[62] Delivery following radical trachelectomy is by caesarean section because of the cerclage.

The prospective CONTESSA-NEOCON-F study will address the safety of neoadjuvant chemotherapy to downsize stage IB1 lesions of more than 2 cm to enable subsequent fertility-sparing surgery.[63]

Radical hysterectomy with pelvic and para-aortic lymphadenectomy is the preferred modality for FIGO stage IB1 cervical tumours. These tumours are generally visible macroscopically and are less than 4 cm in diameter (table 1). Alternatively, primary radiotherapy can be used. Few high-quality studies comparing radical hysterectomy with primary radiotherapy in this setting are available. Surgery offers several advantages compared with radiotherapy, including preservation of vaginal function, shorter duration of treatment, and avoidance of radiation-induced menopause in younger patients, which allows more options for fertility treatments.[64,65]

The risk of ovarian metastases is low[66,67] and conservation of normal appearing ovaries in women younger than 45 years of age is standard practice. Lateral transposition of the ovaries outside of the pelvis might be performed to restrict radiation exposure if this treatment is likely to be used postoperatively. A meta-analysis of 24 studies that included 892 women found that ovarian transposition was associated with preservation of ovarian function and negligible risk for metastases to the transposed ovaries.[68]

Treatment options for stage IB2 cervical cancers include radical hysterectomy, pelvic and para-aortic lymphadenectomy, and adjuvant radiotherapy or chemoradiotherapy (typically cisplatin-based); external beam pelvic radiotherapy and vaginal brachytherapy followed by a simple hysterectomy; or definitive concurrent chemoradiotherapy. Radical hysterectomy and pelvic lymphadenectomy have been used to treat stage IB2 disease, followed by adjuvant radiotherapy given the high risk of recurrence.[11] Combined radical hysterectomy and adjuvant pelvic radiotherapy have a high risk of long-term morbidity.[50] Therefore, some oncologists advocate for primary CCRT-alone or CCRT followed by simple extrafascial hysterectomy. The evidence that simple hysterectomy following CCRT improves survival in women with locally advanced cervical cancers is, however, lacking (ie, evidence has not shown a survival benefit with hysterectomy after radiotherapy, with or without chemotherapy, in women with locally advanced cervical cancer compared with radiotherapy or chemoradiotherapy alone).[69]

Treatment for stages IIB to IVA is non-surgical but depends on local access to radiotherapy facilities. The standard of care is definitive chemoradiotherapy because surgery is unlikely to be curative and the combination of radical surgery and chemoradiotherapy has a high risk of adverse events and chronic morbidity.[50]

Recent surgical developments for stage IA2 and IB1 cervical cancers

Radical hysterectomy can be done via laparotomy or by minimally-invasive surgery (standard laparoscopy or robotic-assisted laparoscopy). A meta-analysis of 26 non-randomised studies that included 4013 patients compared the three surgical routes and found that,

compared with laparotomy, robotic-assisted surgery resulted in less blood loss (weighted mean difference [WMD] 384·3 mL [95% CI 233·7–534·8]), fewer blood transfusions (odds ratio [OR] 0·12 [95% CI 0·06–0·25]), faster time to discharge from hospital (WMD −3·55 [95% CI −5 to −2·10]), less febrile episodes (OR 0·43 [95% CI 0·20–0·89]) and wound infections (OR 0·31 [95% CI 0·13–0·73]), but longer operative time (WMD28.8 min [95% CI 2·15–59·74]).[70] No differences were found in intraoperative complications and lymph node counts. Robotic-assisted surgery was equivalent to laparoscopy in all outcome measures. Cost–benefit was not evaluated.

The findings of a large phase 3 randomised trial of laparoscopic or robotic radical hysterectomy versus abdominal radical hysterectomy in patients with early-stage cervical cancer (stages 1A1 [with lymphovascular invasion],1A2, and 1B1)—the LACC trial—have challenged the perceived oncologic safety of minimally-invasive surgery.[71] The primary endpoint was disease-free survival at 4·5 years and the preliminary findings are already available.[71,72] The study was terminated early on the advice of the data safety monitoring committee after 631 women had been randomised. Patients treated with minimally-invasive surgery had higher recurrence (hazard ratio [HR] 4·26 [95% CI 1·44–12·6], p=0·009) and worse overall survival (6·0 [1·77–20·3], p=0·004) compared with those treated by open abdominal radical hysterectomy. The findings of the LACC trial might change clinical practice. Furthermore, comparative effectiveness of minimally-invasive surgery in women with early stage cervical cancer was investigated in a retrospective cohort of 2221 women treated with radical hysterectomy and showed that minimally-invasive surgery was associated with a higher risk of all-cause mortality compared with laparotomy (4-year survival of 8·4% *vs* 5·8%, HR 1·48 [95% CI 1·10–1·98]).[72]

Sentinel node biopsy (SLN) is an alternative to pelvic lymphadenectomy that can reduce lymphadenectomy-associated morbidity and identify sentinel nodes in unexpected locations. False negative cases have been reported as less than 1% in retrospective series. However, the long-term prognosis of SLN negative patients is unknown and the role of sentinel lymph node mapping in women with early study stage cervical cancer is being investigated in the SENTICOL III trial (NCT03386734), a randomised phase 3 study comparing sentinel nodes with complete lymphadenectomy. The study's co-primary endpoints are disease-free survival and health-related quality of life. SLN biopsy will be done using isotopic detection of a methylene blue dye or indocyanine green.

Adjuvant treatment for patients with stage 1A2–1B2 disease

Following surgery, review of the histopathology by a multidisciplinary team of gynaecological oncology surgeons, radiation and medical oncologists, and radiologists and pathologists, enables the assessment of risk factors for recurrence and decision making regarding adjuvant treatment. Adjuvant treatment is recommended for patients at intermediate or high risk of recurrence. Large tumour diameter, deep stromal invasion, and LVSI are independent prognostic variables for recurrence.[73] The Sedlis criteria (table 3) identified intermediate risk patients using a risk scoring system. The GOG 92 study[74] stratified patients with varying levels of recurrence risk to adjuvant whole pelvic radiation or to observation alone. Radiation therapy was associated with 15% recurrence compared with 28% in those patients who were randomised to no further treatment (relative risk 0·53, p<0·008) without an improvement in overall survival (HR 0·70 [90% CI 0·45–1·05], p=0.074).

Patients at high risk of recurrence include those with involved surgical margins, parametrial invasion, and lymph node metastases (Peters' criteria, table 3).[75] These women have up to a 40% recurrence risk and 50% mortality without adjuvant treatment.[76] In contrast to the Sedlis criteria for intermediate risk factors, where adjuvant treatment consists only of radiotherapy, concurrent chemoradiotherapy should be recommended if the final pathology shows any of Peters' criteria.

Adjuvant radiotherapy for patients with stage 1A2–1B2 disease

Adjuvant pelvic radiotherapy treats sites of occult disease. With the advent of computer-based treatment planning with CT and MRI, soft tissue regions at risk, including parametrial and vaginal tissue and pelvic lymph nodes, can be treated while sparing adjacent tissues such as bladder, small bowel, and rectum, using 3-dimensional conformal treatment or intensity-modulated radiotherapy (IMRT). The whole pelvis is treated in 25 to 28 daily fractions of 1·8 Gy in a total of 45 Gy to 50·4 Gy. MRI and PET/CT, when available, are useful in planning radiotherapy because they facilitate evaluation of the dimensions of the primary tumour, extent of parametrial invasion, and nodal metastases. These anatomic sites might be boosted for additional dose depending on pathological factors such as positive margins or residual disease.

	Clinical–pathological features	Risk of recurrence or death without adjuvant therapy
Intermediate-risk disease: Sedlis' criteria	Presence of LVSI plus deep (outer third) cervical stromal invasion and tumour of any size; presence of LVSI plus middle (one-third) stromal invasion and tumour size ≥2 cm; presence of LVSI plus superficial (inner third) stromal invasion and tumour size ≥5 cm; or no LVSI but deep or middle cervical stromal invasion and tumor size ≥4 cm	Risk of recurrence and death of up to 30% following surgery alone
High-risk disease: Peters' criteria	Positive surgical margins; pathologically-confirmed involvement of the pelvic lymph nodes; or microscopic involvement of the parametrium	Risk of recurrence of approximately 40% and risk of death of up to 50% following surgery alone

LVSI=lymphovascular space involvement.

Table 3: **Criteria for adjuvant therapy in stage IB1 cervical cancer**

Adjuvant concurrent chemoradiotherapy for patients with stage 1A2–1B2 disease

The GOG 109 study[75] randomised women with high-risk disease (according to Peter's criteria) following radical hysterectomy to cisplatin-based chemoradiation alone versus radiotherapy alone. At 4 years, compared with chemoradiotherapy, radiotherapy-alone was associated with reduced progression-free survival (63% *vs* 80%, HR 2·01, p=0·003) and worse overall survival (71% *vs* 81%, HR 1·96, p=0·007). In this trial, chemotherapy might also have worked as adjuvant treatment since patients received cycles 3 and 4 following completion of radiotherapy and achieved the most benefit. To clarify the role of adjuvant chemotherapy in this high-risk group, the RTOG 0724 (NCT00980954) trial is in progress, with the inclusion of patients with positive nodes, involved parametria, or both, to investigate whether adjuvant chemotherapy following chemoradiotherapy will improve overall survival and local recurrence compared with chemoradiotherapy alone.

Prognosis for stage 1 disease

The most important factors that affect survival are stage, status of the lymph nodes, tumour volume, depth of tumour invasion into the cervical stroma, and LVSI.[75]Following radical hysterectomy and removal of the lymph nodes, women with stage IB node-negative disease have a 5-year survival of up to 87%,[76] compared with 73% for those with positive nodes. The prognostic value of LVSI has been questioned in a review of 25 studies in which only three found LVSI to be an independent prognostic factor.[77] The number of metastatic lymph nodes is important with three or more positive nodes associated with higher extra-pelvic recurrence and worse overall survival compared with less than three positive nodes.[78]

Concurrent chemoradiotherapy for locally advanced cervical cancers (stages IIB–IVA)

Locally advanced cervical cancer (stages IIB–IVA) has a worse prognosis compared with stages IA and IB.[73] Treatment of stage IIB disease will depend on local access to radiotherapy services but the treatment of choice is primary chemoradiotherapy because surgery is unlikely to be curative, thus adjuvant treatment will be indicated to avoid disease recurrence, and the combination of radical surgery and chemoradiation has a high risk of adverse events and chronic morbidity.[50]

A Cochrane meta-analysis of 13 practice-changing trials done by the GOG and the Radiation Therapy Oncology Group (RTOG) showed that concurrent chemoradiotherapy was associated with a 6% improvement in 5-year survival compared with radiotherapy alone for women with locally advanced cervical cancers in (HR 0·81, p<0·001).[75,79–81]

In a large prospective randomised trial of 850 women in India, chemoradiotherapy was associated with improved disease-free survival and overall survival in patients with stage IIIB cervical squamous cell carcinoma compared with radiotherapy alone.[82] In a multivariate analysis that adjusted for prognostic factors the HR for relapse or death was 0·81 (95% CI 0·67–0·97, p=0·03).

Intracavitary brachytherapy for locally advanced disease

Brachytherapy uses a radiation source placed in the uterus and vagina, which allows a higher dose of radiation to the cervix compared with external beam radiotherapy, while avoiding toxicity to adjacent tissues. Brachytherapy is commenced during pelvic radiotherapy after maximal reduction in the primary tumour is observed after 2 to 5 weeks of treatment.[83] Brachytherapy can be delivered at a low-dose rate (0·4–2 Gy/h) with caesium-137 given by tandem and ovoids, a pulsed-dose rate (using high-dose rate of iridium-192 and treating only 10–30 min each time), or high-dose rate (>12 Gy/h). High-dose rate and low-dose rate are associated with similar survival and late complication events (ie, toxicity effects).[84,85]

In a large US registry study of women with locally advanced cervical cancers, brachytherapy was associated with a 4-year cancer-specific survival of 64% compared with 52% for women treated with pelvic radiotherapy alone.[86] The authors reported a concerning decrease in the use of brachytherapy in the USA between 1988 and 2009, and emphasised that brachytherapy should be standard of care for such patients based on the survival benefits showed by their results.

CT and MRI scans enable image-guided adaptive brachytherapy (IGABT) to increase the radiation dose to the tumour while minimising radiation delivered to surrounding healthy tissues.[87] IGABT was associated with a 2-year local pelvic control of 70% versus 61% (p=0·001) for conventional brachytherapy and a marked decrease in serious urinary and digestive complications (1% *vs* 14%, p=0.027) in a non-randomised prospective study of women with stage IB1 to IIIB cervical cancers.[88] The EMBRACE II trial (NCT03210428)[89] is an ongoing study that aims to reduce treatment-related toxicity while achieving pelvic and systemic control with the latest brachytherapy and external beam radiotherapy technologies.

Adjuvant chemotherapy for for locally advanced cervical cancers (stages IIB–IVA)

The role of adjuvant chemotherapy following chemoradiotherapy was investigated in a randomised trial of 515 women with stage IIB to IVA cervical cancer.[90] Patients were randomised to treatment with cisplatin and gemcitabine weekly for 6 weeks with concurrent external beam radiotherapy followed by brachytherapy and then two adjuvant cycles of cisplatin plus gemcitabine, or to standard treatment with cisplatin and concurrent radiotherapy followed by brachytherapy. 3-year progression-free survival was significantly improved compared with standard treatment (74·4% *vs* 65·0%,

respectively, p=0·029), as well as overall survival (HR 0·68 [95% CI, 0·49 to 0·95], log-rank p=0·0224), and time to progressive disease (HR 0·54 [95% CI 0·37 to 0·79], log-rank p=0·0012). Grade 3 and 4 toxicities were more frequent in the intervention group (86·5% *vs* 46·3%, p<0·001). Despite these findings, adjuvant chemotherapy has not been widely adopted because whether improved survival was due to the adjuvant chemotherapy, the doublet combination chemotherapy delivered concurrently with radiotherapy, or both was unclear, and because of concerns regarding toxicity. Adjuvant chemotherapy after chemoradiotherapy is being evaluated in the OUTBACK study.[91] The primary aim is to assess whether 4 cycles of carboplatin and paclitaxel chemotherapy after standard cisplatin-based chemoradiotherapy improve overall survival.

Neoadjuvant chemotherapy for stages 1B2–IIB

Neoadjuvant chemotherapy followed by radical hysterectomy was compared with primary chemoradiotherapy in women with stage IB2 to IIB cervical cancer in a single centre randomised trial that enrolled 635 patients (median follow up was 58·5 months).[92] The 5-year disease-free survival in the neoadjuvant chemotherapy plus radical hysterectomy group was 69·3% compared with 76·7% in the primary chemoradiotherapy group (HR 1·38 [95% CI 1·02–1·87], p=0.038), and 5-year overall survival was 75·4% and 74·7% (1·025 [0·752–1·398], p=0·87). The number of neoadjuvant chemotherapy cycles (three), choice of platinum agent (carboplatin or cisplatin), inclusion of patients with stage IIA1 disease, and absence of brachytherapy have been questioned the scientific community.[93,94] Issues included duration and variability between patients of the neoadjuvant treatment; inclusion of stages IB2, IIA, and IIB in the same trial; stage IIA disease should have been subclassified into IIA1 and IIA2; and preoperative brachytherapy was not investigated as a form of neoadjuvant treatment. However, the findings of this trial suggest that the standard of care for patients with locally advanced cervical cancer should be definitive chemoradiotherapy. An European Organisation for Research and Treatment of Cancer phase 3 randomised trial of neoadjuvant chemotherapy followed by surgery versus primary chemoradiotherapy for stage IB2 to IIB cervical cancer (NCT00039338) has completed recruiting and results are expected in 2019. Neoadjuvant chemotherapy before chemoradiotherapy is also being evaluated in the prospective randomised phase 3 multicentre trial INTERLACE (NCT01566240) of paclitaxel 80 mg/m² and carboplatin dose area under the curve 2 (based on drug amount [mg] and the patient's estimated renal function), both administered weekly for 6 weeks before standard chemoradiotherapy (external beam and brachytherapy plus concurrent cisplatin weekly for 5 weeks). The primary endpoint is overall survival and the study aims to recruit 770 participants.

Prognosis for locally advanced cervical cancers

Prognostic factors for locally advanced cervical cancers include age, race, stage, histological type (adenocarcinomas are associated with shorter survival compared with squamous cell carcinomas), grade, lymph node involvement and location (para-aortic involvement is associated with worse outcomes compared with only involved pelvic nodes), tumour volume, performance status, and the treatment received. 5-year overall survival for women with locally advanced cervical cancers is approximately 70% following completion of concurrent chemoradiotherapy.

Treatment of metastatic or recurrent disease

Cervical cancer can recur locally in the pelvis or with metastatic disease. Approaches to patient follow-up and symptom management are summarised in panels 4 and 5. Treatment for recurrent cervical cancer that is confined to the cervix or upper vagina can be curative. Management options will depend on the patient's previous treatment and include hysterectomy or pelvic exenteration (reviewed elsewhere)[94,102] in women who have already received radiotherapy, or radiotherapy in those who have not previously received this treatment or in whom surgery is not indicated because of comorbidities or low probability of complete resection.

Where available, platinum-based chemotherapy combined with the angiogenesis inhibitor bevacizumab is the treatment of choice for metastatic, recurrent, or persistent disease not amenable to curative local therapy. Cisplatin-based chemotherapy had been standard of care for patients with recurrent or metastatic

Panel 4: Follow-up of patients with cervical cancer

The National Comprehensive Cancer Network guidelines recommend review of patients treated for cervical cancer every 3 to 6 months in the first 2 years, and then every 6 months for the next 3 years.[95] These recommendations are based on data showing that most recurrences occur within 36 months after completion of first-line treatment.[96] However, recurrence is seldom diagnosed during routine follow-up and more commonly following unscheduled clinic visits.[97] Patients are often symptomatic at recurrence and symptoms might include vaginal bleeding, low back pain radiating to a leg, and unexplained weight loss.[96] Hence, it is important to counsel patients about these symptoms. The role of vaginal vault or cervical cytology in follow-up is controversial as retrospective studies have shown restricted utility and some experts have argued against its use because cytology detection rates for recurrence in these studies were low (0–17%) and a cytological atypical feature is rarely the only evidence of disease recurrence.[98] If recurrent disease is suspected a biopsy should be performed to confirm recurrence together with imaging such as PET or CT to evaluate the extent of disease and guide treatment.

Panel 5: Quality of life and symptom management

Quality of life, including sexual function, might be adversely affected by treatment for cervical cancer. All treatment modalities can have long-term adverse effects. Autonomic nerves to pelvic viscera might be transected during radical hysterectomy resulting in bladder, bowel, and sexual dysfunction. Radiotherapy can have long-term effects on bladder and bowel function and will lead to loss of ovarian function in premenopausal women. Common physical symptoms include:[99]

- lymphoedema
- altered bowel habit: diarrhoea, faecal urgency, and faecal incontinence or leakage. These symptoms are more common after radiotherapy and in one study by Andreyev and colleagues[100] up to half of patients reported bowel symptoms that negatively affected their quality of life following pelvic radiotherapy
- altered bladder function: urinary urgency and urge incontinence, urinary frequency, pain on micturition due to chronic interstitial cystitis and bladder pain, detrusor instability, urinary retention, and vesicovaginal fistula with continual urinary incontinence
- sexual difficulties including low sexual drive, vaginal dryness, dyspareunia, and vaginal shortening
- psychological morbidity: the effect of a cancer diagnosis and the potential for all the physical sequelae of treatment can lead to depression, anxiety, low self-esteem, fear of recurrence, early and abrupt onset menopause, body image issues, and social isolation

Radiotherapy is associated with worse quality of life and sexual function. 24 (17%) of 142 patients treated with this modality reported lower limb oedema in the GOG 244 study.[101]

cervical cancer but carboplatin and paclitaxel might benefit patients with recurrent or metastatic cervical cancer who have received cisplatin previously.[103] The GOG 240 trial[104] investigated the addition of bevacizumab to platinum-based chemotherapy, which improved median overall survival by 3·5 months compared with chemotherapy alone in patients with metastatic, persistent, or recurrent cervical carcinoma (16·8 *vs* 13·3 months, HR 0·77 [95% CI 0·62–0·95]). Although bevacizumab has shown a survival benefit in patients with advanced disease its cost is prohibitive and because most cervical diagnoses occur in LMICs, the drug is unlikely to improve outcomes globally unless it becomes more affordable.[105]

Immunotherapies

Pembrolizumab inhibits the immune checkpoint programmed cell death 1 protein (PD-1) and has received regulatory approval by the US Food and Drug Administration for use in advanced cervical cancer with progressive disease either during or after chemotherapy, on the basis of the response observed in the KEYNOTE-158 (NCT02628067) trial.[106,107] The effects of the PD-1 inhibitor nivolumab were studied in 19 patients in the phase 1–2 study CheckMate358.[108] The objective response rate was 26·3% (95% CI 9·1–51·2) with a disease control rate of 68·4%. The GOG 3016 (NCT03257267) EMPOWER-Cervical 1 is the first prospective randomised phase 3 trial of a checkpoint inhibitor in the treatment of cervical cancer comparing the PD-1 inhibitor cemiplimab with investigator choice chemotherapy in patients with recurrent, persistent, or metastatic cervical cancer.

Therapeutic vaccines are currently being explored.[109] A phase 3 trial (NCT02853604) of ADXS11–001 (a live-attenuated *Listeria monocytogenes* bacterial vaccine vector) in the adjuvant treatment of high-risk, locally-advanced disease is recruiting patients.

The BEATcc study (NCT03556839) is a randomised phase 3 trial of platinum chemotherapy plus paclitaxel with bevacizumab and the programmed cell death ligand-1 (PD-L1) inhibitor atezolizumab compared with platinum chemotherapy plus paclitaxel and bevacizumab in metastatic, persistent, or recurrent cervical cancer. The trial is recruiting patients.

Complete response in patients with metastatic disease following treatment with HPV-targeted autologous T-cells has been observed[110] and a phase 2 study (NCT03108495) is recruiting patients.

Controversies, uncertainties, and outstanding research questions

One question that remains unanswered is if the addition of chemotherapy after chemoradiotherapy can improve survival. The OUTBACK trial, which has completed accrual, is investigating this question. The randomised phase 3 trial RTOG 0724 (NCT00980954) is addressing a similar question but in patients with high-risk early stage cancer after radical hysterectomy. The potential of IMRT in locally-advanced cervical cancer is also being investigated.[111]

Conventional radiotherapy can have adverse effects on bladder, small bowel, and rectum. IMRT restricts the radiation dose to these tissues and is a strategy to reduce toxicity while allowing an increase in the dose to the tumour.[112,113] Large prospective studies are needed in centres that treat large numbers of patients and that have established quality assurance protocols.[113] The TIME-C trial compared IMRT with 3D conformal radiotherapy in the postoperative setting and showed that pelvic IMRT reduced patient-reported acute gastrointestinal and genitourinary toxicities.[114]

The use of biomarkers for cervical cancer is also being investigated in clinical trials. Somatic mutations in the PI3K/AKT/mTOR pathway and in Erb-B2 receptor tyrosine kinase 3 (ERBB3) offer potentially actionable targets.[113,115] Amplifications and fusions involving the gene *BCAR4* can be targeted indirectly by the dual tyrosine kinase inhibitor lapatinib.[116]

Challenges associated with cervical cancer care and research in LMICs

Numerous challenges are associated with cancer care in LMICs including an insufficient number of appropriately trained health-care personnel and equipment to treat cervical precancers and cancers, including blood products and drugs to deliver safe anaesthesia; limited facilities, including major shortages of linear accelerators to deliver radiotherapy; and geopolitical factors, such as wars, environmental disasters, and lack of sanitation.[29] Challenges differ between the emerging economies of Asia and South America and many African countries. In sub-Saharan Africa, the HIV epidemic has added additional challenges to the care of women with cervical cancer.[29] High quality data regarding outcomes in HIV-infected cervical cancer patients in high-income countries are not available, as HIV infection was an exclusion criterion in large randomised trials, so the knowledge in this patient group has gaps. To date, to our knowledge, no studies are planned in this important patient population.

The findings of the *Lancet* Commission on Global Access to Palliative Care and Pain Relief highlighted the need for resources that could alleviate unnecessary suffering in LMICs.[117] Concerns regarding the addictive potential of opioids have led to legislative barriers that restrict access to analgesia.[118]

The high incidence of cervical cancer in LMICs is directly attributable to the absence of formalised screening programmes. Prevention in LMICs will require wide coverage of the target population at a time when cervical cancer precursors are most likely to be diagnosed and, to be effective, a strong infrastructure is essential.[29] Cervical cancer incidence is increasing in LMICs but health-care systems are unable to respond because of a paucity resources. Establishing population-based cancer and death registries to determine disease prevalence and create reliable death notification protocols and investment in infrastructure are necessary first steps to establish cancer control programmes. Furthermore, the need to develop the infrastructure to offer patients appropriate and timely treatment is pressing, including specialist training and the establishment of multidisciplinary teams. Convincing governments to invest in the health of their nations should be a priority.[29]

The Cervix Cancer Research Network was established by The Gynecologic Cancer Intergroup in 2009 to make clinical trials available to patients in LMICs.[113] The major barrier to LMICs participating in clinical trials is the lack of funding that would allow support for infrastructure development within LMICs.

Conclusions

Fertility-sparing treatment options for women with low-risk early-stage disease are now standard of care and advances in technologies, such as IMRT, have resulted in less treatment-related toxicity for women with locally-advanced disease. Immunotherapies hold promise for women with recurrent and metastatic cervical cancer. Results of ongoing clinical trials in the surgical management of early-stage disease, the adjuvant treatment of locally advanced disease, and in the palliative setting will lead to incremental improvements in patient outcomes. Cervical cancer is, however, a striking example of a global health disparity with about 90% of the disease occurring in LMICs where incidence and disease-specific mortality continue to increase. Ultimately, cervical cancer is preventable through HPV vaccination and screening and it is in LMICs that coordinated efforts must be focused to establish effective prevention programmes.

Contributors

PAC did the initial literature search. AJ, AO, and LD reviewed the literature search and contributed with additional references from the literature. All authors wrote and approved the manuscript.

Declaration of interests

AO was an adviser for Roche, AstraZeneca, Pharmamar, Clovis Oncology, Tesaro, Immunogen, and Genmab; and declares travel grants from Roche, AstraZeneca, Clovis Oncology, Pharmamar, and Tesaro. The remaining authors have nothing to declare.

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