Cancer of the cervix uteri

Ericka Wiebe, Lynette Denny, Gillian Thomas

1. Introduction

Worldwide, cervical cancer is second only to breast cancer as the most common female malignancy in both incidence and mortality, and results in approximately 275,000 deaths annually [1]. More than 85% of new cases are diagnosed in economically disadvantaged people.

1.1. Anatomy

The cervix is the lower aspect of the uterus. It is roughly cylindrical in shape, projects through the superior-anterior vaginal wall, and communicates with the vagina through the endocervical canal, which terminates in the external os located at the top of the vagina. Cancer of the cervix may originate from the mucosa of the surface of the cervix or from within the canal. Carcinoma of the uterine cervix grows locally and may extend in continuity to the uterus and paracervical tissues, and pelvic organs.

Cervical cancer may spread to regional lymph nodes, and only later metastasize hematogenously to distant structures. The cervix is drained into the following first echelon nodal stations: parametral, internal iliac (obturator–hypogastric), external iliac, and presacral, followed by drainage to the common iliac nodes. From the common iliac nodes, lymph drainage goes to the para-aortic nodes. The most common sites of distant spread include the para-aortic, mediastinal and supraclavicular nodes, the lungs, liver, and skeleton.

2. Staging

FIGO staging is based on clinical examination. The FIGO staging guidelines were most recently updated in 2009 (Table 1) [2]. Stage 0 is no longer included in the FIGO 2009 staging.

A thorough pelvic examination is mandatory to provide information for FIGO staging, and this rarely requires anesthesia. When there is doubt as to which stage a particular cancer should be allocated, the earlier stage is mandatory.

The following examinations are permitted for the determination of FIGO staging, as indicated by presenting characteristics (see sections below): palpation, inspection, colposcopy, endocervical curettage, hysterectomy, cystoscopy, proctoscopy, intravenous pyelography, and X-ray examination of the lungs and skeleton. Blood tests should include full blood count, renal and liver functions. Syphilis and HIV serology need to be considered, based on discussion with the patient about risk factors.

2.1. Initial assessment of microinvasive disease

The diagnosis of both Stage IA1 and IA2 should be based on microscopic examination of removed tissue, preferably a cone biopsy, which must include the entire lesion. The depth of invasion should not be >5mm taken from the base of the epithelium, either surface or glandular, from which it originates. The second dimension, the horizontal spread, must not exceed 7mm. Vascular space involvement, either venous or lymphatic, should not alter the staging, but should be specifically recorded because it may affect treatment decisions. Macroscopically obvious lesions, and those with larger dimensions, should be staged as IB. It is impossible to clinically determine if a cancer of the cervix has extended to the corpus. Extension to the corpus should therefore be disregarded for staging purposes.

The diagnosis of Stage IA1 or IA2 disease can only be made on the basis of a cone biopsy with negative margins, or on a trachelectomy or hysterectomy specimen. If the margins of the cone biopsy are positive for cervical intraepithelial neoplasia (CIN) III or invasive cancer, a second cone biopsy should be performed or the patient treated as for Stage IB1 disease [3].

2.2. Initial evaluation of grossly invasive disease

Visible lesions require a biopsy to confirm a diagnosis of cervical carcinoma. A patient with a growth apparently fixed to the pelvic wall by a short and indurated, but not nodular, parametrium should be allotted to Stage IB. Stage III should be defined for cases where the parametrium is nodular to the pelvic wall or if the growth itself extends to the pelvic wall. The presence of hydronephrosis or non-functioning kidney(s) resulting from obstruction of the ureter(s) by cancer also permits a case to be allotted to Stage III.

In cases of grossly invasive disease, a chest X-ray, and evaluation of hydronephrosis (with renal ultrasound, intravenous pyelography, CT, or MRI) are mandatory. The bladder and rectum are evaluated by cystoscopy and sigmoidoscopy only if the patient is clinically symptomatic. Suspected bladder or rectal involvement should be confirmed by biopsy and histologic evidence. The presence of bullous edema, as such, should not permit a case to be allotted to Stage IV.

Imaging evaluation may be of additional benefit to clinical examination in practice areas where resources allow. Imaging may allow for identification of additional prognostic factors and help direct selection of therapy. MRI provides the best radiologic assessment of primary tumors greater than 10mm, but is not mandatory [4–8]. Level of Evidence B
The depth of invasion should not be more than 5mm taken from the base of the epithelium, either surface of glandular, from which it originates. Vascular space invasion should not alter the staging.

Table 1
Cancer of the cervix uteri

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded). IA: Invasive cancer identified only microscopically. (All gross lesions even with superficial invasion are Stage IB cancers.) Invasion is limited to measured stromal invasion with a maximum depth of 5mm and no wider than 7mm. IB: Clinical lesions confined to the cervix, or preclinical lesions greater than stage IA.</td>
</tr>
<tr>
<td>II</td>
<td>The carcinoma extends beyond the uterus, but has not extended onto the pelvic wall or to the lower third of vagina. IIA: Involvement of up to the upper 2/3 of the vagina. No obvious parametrial involvement. IIB: Obvious parametrial involvement but not onto the pelvic sidewall.</td>
</tr>
<tr>
<td>III</td>
<td>The carcinoma has extended onto the pelvic sidewall. On rectal examination, there is no cancer-free space between the tumor and pelvic sidewall. The tumor involves the lower third of the vagina. All cases of hydrenephrosis or non-functioning kidney should be included unless they are known to be due to other causes.</td>
</tr>
<tr>
<td>IV</td>
<td>The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum. IVA: Spread to adjacent pelvic organs. IVB: Spread to distant organs.</td>
</tr>
</tbody>
</table>

a Adapted from FIGO Committee on Gynecologic Oncology [2].

CT and/or MRI and/or positron emission tomography (PET) may provide information on nodal status or systemic spread, but are not mandatory. Compared with CT and MRI, PET-CT is a more accurate imaging method for detecting nodal metastases that are greater than 10mm [5,9–12]. Isolated and unexpected areas of PET accurate imaging method for detecting nodal metastases that are not mandatory. Compared with CT and MRI, PET-CT is a more provide information on nodal status or systemic spread, but are

2.4. Histopathology

All tumors must be microscopically verified. Cases should be classified as carcinomas of the cervix if the primary growth is in the cervix. All histologic types must be included. The histopathologic types are:

- Squamous cell carcinoma (keratinizing; non-keratinizing; verruous).
- Endometrioid adenocarcinoma.
- Clear cell adenocarcinoma.
- Adenosquamous carcinoma.
- Adenoid cystic carcinoma.
- Small cell carcinoma.
- Undifferentiated carcinoma.

Grading by any of several methods is encouraged, but is not a basis for modifying the stage groupings. Histopathologic grades are as follows:

- GX: Grade cannot be assessed.
- G1: Well differentiated.
- G2: Moderately differentiated.
- G3: Poorly or undifferentiated.

When surgery is the primary treatment, the histologic findings permit the case to have pathologic staging, as described above. In this situation, the TNM nomenclature may be used.
3. Cervical cancer screening

Primary prevention of cervical cancer through vaccination, and secondary prevention through the detection of cervical cancer precursors, are both known to be effective preventive measures. Details on cervical cancer screening can be accessed via the FIGO website (www.figo.org).

4. Management of cervical cancer

4.1. Microinvasion

4.1.1. Stage IA1

The recommended management for Stage IA1 is total abdominal hysterectomy, vaginal hysterectomy, or laparoscopic total hysterectomy [22]. Colposcopy of the lower genital tract should be performed preoperatively, and if there is any associated vaginal intraepithelial neoplasia (VIN), an appropriate cuff of vagina should be removed.

If fertility is desired, observation after cone biopsy is appropriate, provided the margins are clear and there is no lymphovascular space invasion. Follow-up with Pap smears at 4 months, 10 months, and then annually for at least 5 years should occur. If smears are all negative, the screening may revert to the screening interval recommended for the particular country [23,24]. Level of Evidence C

4.1.2. Stage IA2

There is a small potential for lymph node metastasis in patients with Stage IA2 disease, indicating a role for pelvic lymphadenectomy in these patients [25,26]. The recommended treatment for Stage IA2 is modified radical hysterectomy (Type 2; i.e. ligation of the uterine artery where it crosses the ureter, although a vaginal cuff is not necessary) and pelvic lymphadenectomy. If there is no lymph vascular space invasion, consideration may be given to extrafascial hysterectomy and pelvic lymphadenectomy. Level of Evidence C

If fertility is desired, options are: (1) large cone biopsy plus extraperitoneal or laparoscopic pelvic lymphadenectomy; or (2) radical trachelectomy and extra peritoneal or laparoscopic pelvic lymphadenectomy [27].

4.1.3. Post-treatment follow-up after microinvasive carcinoma

Post-treatment surveillance should be mainly with Pap smears, and should be annually after 2 normal smears at 4 and 10 months.

4.2. Grossly invasive cervical carcinoma (FIGO Stage IB–IVA)

Five-year survival for stages IB2, IIB, IIB, and IVA are approximately 76%, 66%, 42%, and 22%, respectively [28]. Use of concurrent platinum-based chemotherapy with radiotherapy has improved pelvic control and survival [29]. Where feasible, concurrent chemoradiotherapy should be considered standard of care management for FIGO Stages IIIB and higher, and also for most patients with Stage IB2, to optimize local control and survival.

4.2.1. Trend to lesser surgery for small tumors

Low-risk cases of grossly invasive cervical carcinoma have been defined as FIGO IA2–IB1, with tumor size less than 2 cm, cervical stromal invasion of less than 50%, and node negative on MR/CT imaging. Simple hysterectomy, or trachelectomy, with either pelvic lymph node dissection or sentinel lymph node assessment (SLNB), can be considered for tumors measuring less than 3 cm, to minimize the potential morbidity of surgery. Surgicopathological studies suggest the incidence of parametrial involvement is sufficiently low for tumors less than or equal to 2 cm and no vascular space invasion to consider less radical surgery [54,55]. Level of Evidence D

4.2.1.1. Sentinel lymph node assessment

Identification of sentinel lymph nodes can be accomplished with dual labeling using blue dye and radiocolloid [47,48]. In a multicenter Phase 2 trial of sentinel lymph node biopsy (SLNB) in patients with all stages of cervical cancer, the sensitivity of SLNB to detect involved lymph nodes was low [49]. However, sentinel node procedures are more reliable in early stage cervical cancer, for example FIGO IA and IB1 [50–52]. If lymphovascular space invasion is present, pelvic lymphadenectomy needs to be considered. Level of Evidence C

Sentinel lymph node assessment of pelvic lymph nodes should not be utilized in advanced disease owing to lower lymph node identification rates, and higher false-negative rates [53].

4.2.1.2. Adjuvant radiation/chemotherapy

Primary pelvic exenteration may be considered for Stage IVA disease not extending to the pelvic sidewall and no overt extra-pelvic disease, particularly if a vesicovaginal or rectovaginal fistula is present [33–37]. Level of Evidence C

Theoretical advantages of primary surgical management may include:

- More accurate staging information.
- Removal of the primary tumor, thereby obviating the need for brachytherapy [38].
- In a few cases, surgery allows resection of bulky (2–3 cm) positive lymph nodes that are less likely to be sterilized with primary radiation [39,40].
- Detection of pathologic node involvement, allowing direction of adjuvant therapy.

The disadvantage of primary surgical management is the potential need for postoperative therapy to reduce the risk of local recurrence, such as with positive margins or involvement of parametria or nodes [41,42]. Additional risk factors for local recurrence include lymphovascular space invasion, and deep cervical stromal invasion [41,43,44]. After primary surgical management, 50%-85% of patients with Stages IB2–IIA have indications for adjuvant radiation or chemoradiation [30,42,43]. Morbidity is higher when surgery and radiation are combined [30].

The risk of pelvic lymph node involvement for FIGO IB1 disease is approximately 16% [6,45]. The risk of pelvic node involvement increases with tumor size, from 6% for tumors less than 2 cm [6], to 36% for tumors greater than 4 cm [46]. Primary surgical management is often not recommended for tumors measuring more than 3 cm, to minimize the likelihood of postoperative chemoradiotherapy and its associated toxicity.
Risk of pelvic recurrence is also increased in those with uninvolved nodes but primary associated risk factors: tumor size greater than 4cm, capillary-like space (CLS) involvement, and outer one-third invasion of the cervical stroma [43,44]. Adjuvant whole pelvic irradiation reduces the local failure rate and improves progression-free survival compared with patients treated with surgery alone [43]. **Level of Evidence B**

Adjuvant radiation therapy with and without chemotherapy may be particularly beneficial for patients with adenocarcinoma or adenosquamous histology, given the relatively higher rates of distant failure [42,43]. **Level of Evidence C**

Patients with positive common iliac or para-aortic nodes may be treated by extended field radiation [56,57], with or without chemotherapy. **Level of Evidence C**

Exploration of more conformal radiation techniques (e.g., intensity-modulated radiation therapy; IMRT) in the postoperative setting is ongoing [58]. There is insufficient evidence at the present time to recommend IMRT as a standard of care.

### 4.2.2. Neoadjuvant chemotherapy and surgery

Theoretical rationale for the use of neoadjuvant chemotherapy (NACT) includes the induction of tumor shrinkage to facilitate radical excision, and a possible improvement in outcomes over surgery alone. There is also a possibility of NACT sterilizing nodes and parametria, thereby reducing risk factors for adjuvant therapy after surgery; however, the adequacy of neoadjuvant therapy in this situation is not known.

Meta-analysis of individual patient data from randomized trials of neoadjuvant platinum-based chemotherapy prior to definitive surgery shows that patients treated with NACT have better survival outcomes than those treated with primary radiation alone, given at a relatively low dose [59]. No randomized data compare the results of NACT followed by surgery with concurrent chemoradiation. The European Organization for Research and Treatment of Cancer is currently conducting a Phase 3 study comparing NACT and surgery with definitive chemoradiation in patients with FIGO Stages IB2, IIA2, or IIB cervical cancers.

NACT followed by surgery is commonly used in some countries, but its role is uncertain as a review of available literature suggests no benefit of NACT–surgery over upfront surgery plus adjuvant therapy [60]. Optimal pathologic response, defined as persistent residual disease with less than 3 mm of stromal invasion in the surgical specimen, is the strongest predictor of freedom from local recurrence for patients treated with NACT and surgery [61]. A chemotherapy regimen of paclitaxel, ifosfamide, and cisplatin has higher response rates than ifosfamide and cisplatin for FIGO Stage IB2, although not for Stage IIB [62]. A statistically significant effect on overall survival was not found, although this study was insufficiently powered for overall survival outcomes [62]. Surgery after NACT should consist of radical hysterectomy and pelvic lymphadenectomy.

Many patients randomized to NACT–surgery either were unable to proceed with radical surgery after chemotherapy (40%) or required additional adjuvant therapy after surgery (26%) [63]. NACT–surgery should be carefully considered in patients with larger tumors or adenocarcinoma histology owing to lower response rates. FIGO IIB and higher stages should be preferentially managed with definitive chemoradiation therapy.

NACT obscures the pathologic findings at the time of surgery, complicating evaluation of indications for adjuvant radiotherapy with or without adjuvant chemotherapy. Indications for adjuvant therapy after primary surgery [42,43] are often applied in the setting of NACT–surgery. **Level of Evidence C**

### 4.2.3. Primary radiation management

Chemoradiotherapy is the standard of care for patients with IB2, IIA2, IIB, IIIA, IIIB, and IVA disease. Standard concurrent chemoradiation therapy includes external radiation and intracavitary brachytherapy [64,65]. **Level of Evidence A**

#### 4.2.3.1. Radiation

Standard radiation treatment of cervical carcinoma is external pelvic irradiation plus brachytherapy. Suggested doses of external beam radiation are 45–50 Gy in 180–200 cGy per fraction. Standard radiation planning techniques are outlined in Table 2.

There is no consensus regarding the dose at which midline blocks may be introduced, or the use of nodal and parametrial boost doses. In general, when pelvic doses greater than 45 Gy are to be used in combination with intracavitary brachytherapy, midline blocks may be introduced during the final fractions of external beam radiation. Midline blocks prevent excessive doses adjacent to the brachytherapy dose region, while delivering adequate dose to involved volumes outside of the high-dose brachytherapy region. Total doses of External Beam Radiation Therapy (EBRT) and brachytherapy must be considered in evaluating the need for midline shielding. Care must be taken to avoid shielding common

### Table 2

<table>
<thead>
<tr>
<th>Radiation technique</th>
<th>Targets</th>
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<tbody>
<tr>
<td><strong>Simulation</strong></td>
<td>2D techniques</td>
</tr>
<tr>
<td><strong>Target volumes</strong></td>
<td>Tumor plus uterus, parametrical tissue, and uterosacral ligaments</td>
</tr>
<tr>
<td></td>
<td>Pelvic lymph nodes (internal iliac, external iliac, obturator, and presacral) and lower common iliac lymph nodes</td>
</tr>
<tr>
<td></td>
<td>Margin for microscopic spread of disease</td>
</tr>
<tr>
<td><strong>Field borders</strong></td>
<td>Tumor determined by palpation and CT scan (if available) plus 2 cm margin</td>
</tr>
<tr>
<td></td>
<td>A–P fields:</td>
</tr>
<tr>
<td></td>
<td>Lateral: 2 cm lateral to the bony margin of the pelvis</td>
</tr>
<tr>
<td></td>
<td>Superior: L4/L5 or L5/S1 vertebral interspace</td>
</tr>
<tr>
<td></td>
<td>Inferior: 2 cm below the obturator foramen (or 2 cm below lower extent of clinical tumor)</td>
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<tr>
<td></td>
<td>Anterior: anterior to symphysis pubis, 2 cm anterior to tumor</td>
</tr>
<tr>
<td></td>
<td>Posterior: posterior to sacrum to include potential microscopic disease along the uterosacral ligament</td>
</tr>
<tr>
<td><strong>Energy</strong></td>
<td>Irradiation should be given by an appropriate energy causing a uniform dose distribution (~5% to +7%) within the target volume.</td>
</tr>
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</table>

8 MV generally provides a homogenous dose distribution in the target volume with 4-field techniques. In resource-limited areas, satisfactory pelvic radiation therapy can be achieved with lower energy linacs or cobalt units [67].
lilac and presacral lymph nodes, as well as utero-sacral ligaments, prior to adequate dose delivery to these regions.

An external beam boost to the parametrial tissues should be considered if there is gross involvement of the parametria, or if grossly enlarged pelvic lymph nodes have been identified on imaging. A dose of 60 Gy from a combination EBRT and brachytherapy contributions may be required to control gross involvement of lymph nodes or parametria. Suggestions to achieve adequate parametrial boost doses without undue toxicity include lowering the superior border for boost doses to the level of S2/3, and limiting the external beam portion of the boost dose to 54 Gy [68]. In dosimetric evaluation, midline-blocked parametrial boosts contribute substantial dose to small volumes of rectum, sigmoid, and bladder [69]. Intensity-modulated techniques are being explored as a method to boost bulky pelvic lymph nodes or residual parametrial disease, while improving sparing of proximal critical structures [70,71].

4.2.3.2. Brachytherapy

Brachytherapy is short-range radiotherapy delivered through applicators that are inserted through the cervix into the intrauterine cavity. Optimal applicator placement is essential to provide adequate dose to the tumor volume, optimize local control, and minimize morbidity. Brachytherapy should be carried out by practitioners experienced in intracavitary brachytherapy techniques, including appropriate treatment planning and dosimetric evaluation where possible [72].

In a meta-analysis of 4 studies involving 1265 patients with locally advanced cervical cancer, there were no significant differences between low-dose-rate (LDR) and high-dose-rate (HDR) intracavitary brachytherapy in overall survival (OS), disease-free survival (DFS), recurrence-free survival (RFS) local control rate, recurrence, metastasis, and treatment-related complications [73].

Potential advantages of HDR brachytherapy include outpatient treatment, patient convenience, rigid immobilization, accuracy of source and applicator positioning, and the ability to adjust individual source dwell times to provide greater individualization of treatment plans. Pulse-dose-rate (PDR) is an alternative option for brachytherapy delivery, via short pulses of radiation, typically once an hour in an inpatient setting [74]. PDR offers the dose optimization of an HDR source, and the radio-biologic advantages of LDR brachytherapy [75].

Brachytherapy is conventionally prescribed to a Point A using a Manchester system, where Point A is defined relative to the applicator geometry [76]. A change in practice to MRI-delineated target volumes and volumetric dose prescribing has been proposed [77,78]. A multi-institutional trial of clinical outcomes (EMBRACE) is underway [79].

The relative doses of EBRT and brachytherapy have depended on tumor volume, and institutional preference. In combination with EBRT, equivalent total doses to Point A should be 80–90 Gy. Commonly used HDR dose/fractionation schemes used with external beam doses of 45 Gy in 25 fractions are listed in Table 3. There is often a relative increase in brachytherapy dose compared with the EBRT dose in smaller tumors [80].

### 4.2.3.3. Total treatment time

Timely completion of radiotherapy is essential for optimal outcomes. In retrospective trial data, patients with radiotherapy treatment times of greater than 9–10 weeks had significantly higher rates of pelvic failure, compared with women completing treatment in less than 6–7 weeks [83,84]. It is recommended that all external beam radiotherapy and brachytherapy be completed within 56 days.

### 4.2.3.4. Addition of chemotherapy to radiation

Concurrent chemoradiation confers a significant overall survival benefit compared with the same radiation alone, with a meta-analysis of individual patient data from 13 trials showing a 5-year survival advantage of 6% (Hazard Ratio: 0.81) [29]. Concurrent chemoradiotherapy also reduced local and distant recurrence, and improved disease-free survival. Level of Evidence A

A once-weekly infusion of cisplatin (40 mg/m² weekly with appropriate hydration) for 5–6 cycles, is a commonly used concurrent chemotherapy regimen, and is equally effective and less toxic than combined cisplatin and 5-fluorouracil in a 21-day schedule during external beam therapy [64,85]. For patients who are unable to receive platinum chemotherapy, 5-fluorouracil-based regimens are an acceptable alternative [29,86]. Data on the toxicity associated with concurrent chemotherapy and extended field irradiation are limited [56,57].

Although randomized studies of chemoradiotherapy included patients with FIGO Stage IB2 and above, given the magnitude of the survival benefit, concurrent chemotherapy with a platinum-based regimen is often recommended for any patient considered suitable for radical radiotherapy, if the patient is fit enough.

Additional adjuvant chemotherapy after concurrent chemoradiotherapy is being explored in an international randomized controlled trial (OUTBACK Trial) [87]. A single randomized study suggests possible benefit in progression-free and overall survival with additional chemotherapy, but with more severe toxicity [88]. At present there is insufficient evidence to recommend additional adjuvant chemotherapy as a standard of care.

### 4.2.3.5. Resource-limited practices

Where available, brachytherapy constitutes an essential component of radical radiotherapy or chemoradiotherapy. However, bulky tumors may be curable with external beam radiation alone if brachytherapy and/or chemotherapeutic agents are not readily available [67]. Recognized prognostic factors for probability of cure include lower stage, squamous cell histology, and good performance status.

In situations where brachytherapy is not available, an external beam boost is a reasonable option to achieve local control. A total radiation dose of 54–70 Gy can provide local control rates of 52%, with a median time to recurrence of 2.3 years [89].

### 4.2.3.6. Post-treatment follow-up

The median time to recurrence after treatment is 17 months [90–92]. Routine clinical follow-up after radical treatment is not a sensitive method for detecting recurrent disease, as the majority of patients present with symptomatic recurrences [90,91,93]. An optimal post-treatment follow-up strategy has not been established and clinical practice is variable. Common recommendations include history taking and clinical examination at routine follow-up intervals to detect treatment complications and psychosexual morbidity, as well as to assess for recurrent disease [94]. Level of Evidence D

As isolated central recurrences are potentially curable, closer clinical follow-up in the 2–3 years after treatment may be important. Routine imaging is not indicated. Special circumstances, such as involved high pelvic lymph nodes, may justify interval imaging of the abdomen to assess for potentially curable progression of disease.

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<table>
<thead>
<tr>
<th>Number of high-dose-rate fractions</th>
<th>Dose per fraction (Gy)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>5.4</td>
<td>[72]</td>
</tr>
<tr>
<td>5</td>
<td>5.5–6</td>
<td>[72,80]</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>[81]</td>
</tr>
<tr>
<td>2</td>
<td>9–10</td>
<td>[82]</td>
</tr>
</tbody>
</table>
4.3. Stage IVB/distant metastases

4.3.1. Systemic therapy

Presentation with distant metastatic disease is rare. There has been no randomized comparison of chemotherapy to best supportive care for Stage IVB cervical carcinoma. Few studies have evaluated the impact of systemic therapy on palliative and quality-of-life endpoints [95]. A management plan should consider that the median duration of survival with distant metastatic disease is approximately 7 months.

Despite limited response rates, cisplatin has been the standard chemotherapy used in the setting of distant metastatic disease [96]. Given low response rates to cisplatin alone after concurrent chemoradiation, recent evidence supports the use of platinum doublets over cisplatin alone, although with very modest benefits in response rates. Cisplatin may be combined with taxanes, topotecan, gemcitabine, or vinorelbine [97].

Palliative systemic therapy may be considered for patients with an ECOG (Eastern Cooperative Oncology Group) performance status of 0–2 (Table 4). Discussion of participation in clinical trials should be considered, particularly for patients who have relapsed within 12 months [98].

4.3.2. Palliative radiation for localized symptoms

Local treatment with radiation therapy is indicated to sites of symptomatic involvement in patients with metastatic disease. Alleviation of symptoms with palliative radiation can often be achieved for pain arising from enlarged para-aortic or supraclavicular nodes, skeletal metastases [99], and symptoms associated with cerebral metastases. In view of the short life expectancy of patients with metastatic cervical cancer, palliative radiotherapy should be given via larger fractions over shorter periods of time than conventional radical courses of treatment. There are no data to endorse specific dose/fractionation schemes for soft tissue metastases; commonly used schedules include large single fractions, 20 Gy in 5 fractions, and 30 Gy in 10 fractions.

4.3.3. Comprehensive palliative care

Patients with incurable cervical cancer may develop a range of challenging symptoms and should be managed on an individual basis. Common problems associated with advanced cervical cancer can include: pain, ureteric obstruction causing renal failure, hemorrhage, malodorous discharge, lymphedema, and fistulae. Patients may benefit from a wide range of clinical services to manage these symptoms, as well as psychosocial care and support for patients and their families.

4.4. Recurrent disease

Recurrences may be pelvic, para-aortic, distant, or a combination. The risk of both pelvic and distant failure increases with the bulk of disease [100,101]. The majority of recurrences occur within 2 years of diagnosis, and the prognosis is poor, with most patients dying as a result of uncontrolled disease [102]. Treatment decisions should be based on the performance status of the patient, the site of recurrence and/or metastases, the extent of metastatic disease, and prior treatment [103].

For patients with extensive local disease or distant metastatic disease, the intent of therapy is palliative, and best supportive care is generally the recommended management. For patients with good performance status and limited metastatic disease, a trial of platinum doublet systemic therapy may be justified, understanding the limited benefits with respect to response rate and progression-free survival [96]. Local recurrence that is not salvageable with surgery or radiotherapy has a very poor response to systemic chemotherapy.

4.4.1. Local recurrence

Some patients with locally recurrent disease after definitive therapy (surgery or radiotherapy) are potentially curable. Favorable prognostic factors include an isolated central pelvic recurrence with no sidewall disease, a long disease-free interval, and size of the recurrence less than 3 cm in diameter [36,104].

Relapse in the pelvis following primary surgery may be treated by either radical chemoradiation or pelvic exenteration. Radical irradation (with or without concurrent chemotheraphy) may result in 5-year disease-free survival rates of 45%–74% with isolated pelvic failure after primary surgery [105,106]. The extent of recurrent disease and involvement of pelvic lymph nodes are prognostic factors for survival [107]. Level of Evidence C

The radiation dose and volume should be tailored to the extent of recurrent disease; 45–50 Gy in 180 cGy fractions should be delivered to areas likely to be involved with microscopic disease, and a boost dose of up to 64–66 Gy to the gross tumor volume using field reductions. Concurrent chemotheraphy with either cisplatin and/or 5-fluorouracil may improve outcome [108].

Pelvic exenteration may be a feasible treatment option in selected patients who have recurrence after radiation. Suitable candidates for exenteration after previous surgery or pelvic radiation are patients without evidence of intra-peritoneal or extra pelvic spread, and who have a tumor-free space along the pelvic sidewall [33–37]. Level of Evidence C

Owing to the morbidity of exenteration, its use is confined to those with curative potential, and requires careful patient selection regarding the associated physical and psychological demands. Confirmation of recurrence with a pathologic specimen obtained by biopsy is essential prior to proceeding with exenteration.
A PET/CT is the most sensitive non-invasive test to determine any sites of distant disease, and if possible, should be performed prior to exenteration [13,109–116]. Patient assessment and counseling regarding the implications and ability to manage stoma and ostomy sites must be addressed prior to surgery [117]. Careful selection of patients may yield a 5-year survival with pelvic exenteration in the order of 30%–60% [33,34,36], and an operative mortality of less than 10% [118].

4.4.2. Para-aortic nodal recurrence

After the pelvis, para-aortic lymph nodes are the next most common site of recurrent disease. Possible long-term survival with radical-intent radiotherapy or chemoradiotherapy can be achieved in approximately 30% of patients with isolated para-aortic nodal recurrence [90,119]. Patients with asymptomatic, low volume recurrences that occur greater than 24 months from initial treatment have better outcomes [90,119]. Level of Evidence C

5. Special circumstances

5.1. Incidental cervical cancer

Incidental findings of invasive cervical cancer may occur following simple hysterectomy for a presumed benign condition. A high degree of suspicion for cervical disease should be exercised prior to simple hysterectomy, as survival of cervical cancer is diminished in cases of tumor cut-through leaving residual disease [120].

After identification of invasive cervical cancer, a PET/CT scan if available, or a pelvic and abdominal CT or MRI scan and chest imaging should be performed, to assess the extent of disease. The choice of treatment should be determined by the histologic and the radiologic findings. If margins are positive, or if there is deep stromal infiltration and vascular space invasion, pelvic radiation should be given, with consideration of adding vaginal brachytherapy [120–122]. Level of Evidence C

5.2. Cervical cancer during pregnancy

A multidisciplinary approach with involvement of obstetrician and neonatologist is recommended to formulate an optimal treatment approach for each individual situation. All management plans should include full discussion with the woman (and preferably her partner), and her wishes must be respected. In general, the management of cervical cancer in pregnant women follows the same principles as in non-pregnant women.

Diagnoses made before 16–20 weeks of pregnancy are generally treated without delay with either surgery or chemoradiation owing to concern of detriment to patient survival with treatment delay. From the second trimester onward, surgery and chemotherapy can be used in selected cases while preserving the pregnancy [123]. Level of Evidence C

If the diagnosis is made after 20 weeks, treatment delay appears to be an option for Stages IA2 and IB1, with no apparent impairment of prognosis compared with non-pregnant controls [124–126]. Treatment consisting of classical cesarean delivery and radical hysterectomy is often undertaken when a balance is reached between competing maternal and fetal health risks, usually not later than 34 weeks of pregnancy. Level of Evidence C

For more advanced disease, it is not known whether treatment delay will affect survival. In addition, there is no standard definition on what constitutes significant treatment delay. In practice, the duration of the treatment delay should be influenced by clinical stage and histopathologic findings of the tumor, gestational age at diagnosis, and the parents’ desire regarding their unborn child. If a treatment delay is planned in women with locally advanced disease, neoadjuvant chemotherapy may be considered in an attempt to prevent disease progression [127,128]. Close clinical surveillance is mandatory.

Conflict of interest

Dr Denny has received honoraria form MSD/MERCK and Glaxo-SmithKline for appearing on various speaker forums and has received research funding from both companies. The other authors have no conflicts of interest to declare.

References


