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FIGO CANCER REPORT 2012

Cancer of the cervix uteri

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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: parametrial, 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, hysteroscopy, 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 >5 mm taken from the base of the epithelium, either surface or glandular, from which it originates. The second dimension, the horizontal spread, must not exceed 7 mm. 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 IIB. 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 10 mm, but is not mandatory [4–8]. **Level of Evidence B**

Table 1
Cancer of the cervix uteri[a]

Stage	Description
I	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 5 mm[b] and no wider than 7 mm. IA1 Measured invasion of stroma ≤3 mm in depth and ≤7 mm width. IA2 Measured invasion of stroma >3 mm and <5 mm in depth and ≤7 mm width.
IB	Clinical lesions confined to the cervix, or preclinical lesions greater than stage IA. IB1: Clinical lesions no greater than 4 cm in size. IB2: Clinical lesions >4 cm in size.
II	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. IIA1: Clinically visible lesion ≤4 cm IIA2: Clinically visible lesion >4 cm
IIB	Obvious parametrial involvement but not onto the pelvic sidewall.
III	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 hydronephrosis or non-functioning kidney should be included unless they are known to be due to other causes.
IIIA	Involvement of the lower vagina but no extension onto pelvic sidewall.
IIIB	Extension onto the pelvic sidewall, or hydronephrosis/non-functioning kidney.
IV	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.

[a] Adapted from FIGO Committee on Gynecologic Oncology [2].
[b] The depth of invasion should not be more than 5 mm taken from the base of the epithelium, either surface of glandular, from which it originates. Vascular space invasion should not alter the staging.

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 10 mm [5,9–12]. Isolated and unexpected areas of PET enhancement should be further investigated with tissue diagnosis, if possible, to confirm or exclude the presence of distant metastatic disease [11,13,14]. **Level of Evidence B**

Compared with radiologic evaluation, surgical node dissection is more accurate for assessment of para-aortic nodal disease [15,16]. In patients with advanced disease, laparoscopic staging of para-aortic lymph nodes may be considered to allow treatment according to extent of disease [17]. No impact on survival has been demonstrated; however, surgical exclusion of para-aortic lymph node involvement portends a better prognosis than radiographic exclusion alone [18]. **Level of Evidence B**

In a surgicopathologic staging study, positive para-aortic nodes were identified in 21% of Stage IIB and 31% of Stage III tumors [19].

2.3. Pathologic staging

In cases treated by surgical procedures, the pathologist's findings in the removed tissues can be the basis for accurate statements on the extent of disease. The findings should not be allowed to change the clinical staging, but should be recorded in the manner described for the pathologic staging of disease. The TNM nomenclature is appropriate for this purpose [20]. Unlike FIGO staging criteria, TNM staging accounts for node positivity; however, the FIGO and TNM classifications are otherwise virtually identical in describing the anatomical extent of disease. Clinical staging is essential to select and evaluate therapy, while the pathological stage provides the most precise data from which to estimate prognosis and calculate end results.

Infrequently, hysterectomy may be carried out in the presence of unsuspected invasive cervical carcinoma. Such cases cannot be clinically staged or included in therapeutic statistics, but it is desirable that they be reported separately. If considered appropriate, some of these patients may be offered repeat laparotomy with full parametrectomy and pelvic lymphadenectomy to allow potentially curative surgery and/or determine the need for adjuvant chemoradiation [21].

Staging is determined at the time of the primary diagnosis and cannot be altered, even at recurrence. Only if the rules for clinical staging are strictly observed is it possible to compare results among clinics and by differing modes of therapy.

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; verrucous).
- 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 (VAIN), 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, IIIB, 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 treatment for FIGO Stages IIB and higher, and also for most patients with Stage IB2, to optimize local control and survival.

4.2.1. Surgical management

Outcomes for FIGO Stages IB1–IIA1 are comparable with surgery with or without adjuvant therapy or primary radiation therapy, although toxicity profiles vary [30,31]. **Level of Evidence A**

The treatment of choice will depend on the availability of resources, and tumor- and patient-related factors. If possible, a multidisciplinary consultation should occur to inform patients regarding therapeutic options, associated toxicities, and expected outcomes. The standard surgical treatment of stage IB1–IIA1 is modified radical or radical abdominal hysterectomy and pelvic lymphadenectomy [32]. **Level of Evidence B**

Primary pelvic exenteration may be considered for Stage IVA disease not extending to the pelvic sidewall and no overt extrapelvic 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.

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. 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, has been proposed for low-risk cases as an alternative to radical hysterectomy and pelvic lymph node dissection to decrease 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**

4.2.1.3. Adjuvant radiation/chemotherapy

The risk of recurrence after radical surgery is increased in the presence of positive nodes, positive parametria, or positive surgical margins. Adjuvant concurrent chemoradiation (cisplatin with or without 5-fluorouracil) improves overall survival, progression-free survival, and both local and distant recurrences compared with pelvic irradiation alone in such patients [42]. **Level of Evidence B**

Table 2
External beam radiotherapy technique for cervical cancer

Radiation technique	Targets
Simulation	2D techniques CT simulation
Target volumes	• Tumor plus uterus, parametrial tissue, and uterosacral ligaments • Pelvic lymph nodes (internal iliac, external iliac, obturator, and presacral) and lower common iliac lymph nodes • Margin for microscopic spread of disease
Field borders	Tumor determined by palpation and CT scan (if available) plus 2 cm margin • A–P fields: Lateral: 2 cm lateral to the bony margin of the pelvis Superior: L4/L5 or L5/S1 vertebral interspace Inferior: 2 cm below the obturator foramen (or 2 cm below lower extent of clinical tumor) • Lateral fields: Anterior: anterior to symphysis pubis, 2 cm anterior to tumor Posterior: posterior to sacrum to include potential microscropic disease along the uterosacral ligament In patients with positive common iliac or para-aortic nodes, extended field radiation should be considered [56,57,66].
Energy	Irradiation should be given by an appropriate energy causing a uniform dose distribution (−5% to+7%) within the target volume. 18 MV generally provides a homogeneous 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].

Risk of pelvic recurrence is also increased in those with uninvolved nodes but primary associated risk factors: tumor size greater than 4 cm, 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

iliac 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].

Table 3
Suggested high-dose-rate brachytherapy dose/fraction schemes (with external beam radiation dose of 45 Gy in 25 fractions)

Number of high-dose-rate fractions	Dose per fraction (Gy)	Reference
6	5.4	[72]
5	5.5–6	[72,80]
4	7	[81]
2	9–10	[82]

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/m^2 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.

Table 4
Eastern Cooperative Oncology Group (ECOG) performance status[a]

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

[a] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5(6):649–55.

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 irradiation (with or without concurrent chemotherapy) 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 chemotherapy 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 with or without concurrent chemotherapy 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

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55(2):74–108.
2. FIGO Committee on Gynecologic Oncology. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynecol Obstet 2009;105(2):103–4.
3. Roman LD, Felix JC, Muderspach LI, Agahjanian A, Qian D, Morrow CP. Risk of residual invasive disease in women with microinvasive squamous cancer in a conization specimen. Obstet Gynecol 1997;90(5):759–64.
4. Hricak H, Gatsonis C, Chi DS, Amendola MA, Brandt K, Schwartz LH, et al. Role of imaging in pretreatment evaluation of early invasive cervical cancer: results of the intergroup study American College of Radiology Imaging Network 6651–Gynecologic Oncology Group 183. J Clin Oncol 2005;23(36):9329–37.
5. Bipat S, Glas AS, van der Velden J, Zwinderman AH, Bossuyt PM, Stoker J. Computed tomography and magnetic resonance imaging in staging of uterine cervical carcinoma: a systematic review. Gynecol Oncol 2003;91(1):59–66.
6. Hricak H, Yu KK. Radiology in invasive cervical cancer. AJR Am J Roentgenol 1996;167(5):1101–8.
7. Subak LL, Hricak H, Powell CB, Azizi L, Stern JL. Cervical carcinoma: computed tomography and magnetic resonance imaging for preoperative staging. Obstet Gynecol 1995;86(1):43–50.
8. Kodama J, Mizutani Y, Hongo A, Yoshinouchi M, Kudo T, Okuda H. Optimal surgery and diagnostic approach of stage IA2 squamous cell carcinoma of the cervix. Euro J Obstet Gynecol Reproductive Biol 2002;101(2):192–5.
9. Grigsby PW, Siegel BA, Dehdashti F. Lymph node staging by positron emission tomography in patients with carcinoma of the cervix. J Clin Oncol 2001;19(17):3745–9.
10. Yang WT, Lam WW, Yu MY, Cheung TH, Metreweli C. Comparison of dynamic helical CT and dynamic MR imaging in the evaluation of pelvic lymph nodes in cervical carcinoma. AJR Am J Roentgenol 2000;175(3):759–66.
11. Havrilesky LJ, Kulasingam SL, Matchar DB, Myers ER. FDG-PET for management of cervical and ovarian cancer. Gynecol Oncol 2005;97(1):183–91.
12. Rose PG, Adler LP, Rodriguez M, Faulhaber PF, Abdul-Karim FW, Miraldi F. Positron emission tomography for evaluating para-aortic nodal metastasis in locally advanced cervical cancer before surgical staging: a surgicopathologic study. J Clin Oncol 1999;17(41):41–5.
13. Sakurai H, Suzuki Y, Nonaka T, Ishikawa H, Shioya M, Kiyohara H, et al. FDG-PET in the detection of recurrence of uterine cervical carcinoma following radiation therapy – tumor volume and FDG uptake value. Gynecol Oncol 2006;100(3):601–7.
14. Yen T-C, Ng K-K, Ma S-Y, Chou HH, Tsai CS, Hsueh S, et al. Value of dual-phase 2-fluoro-2-deoxy-d-glucose positron emission tomography in cervical cancer. J Clin Oncol 2003;21(19):3651–8.
15. Hertel H, Köhler C, Elhawary T, Michels W, Possover M, Schneider A. Laparoscopic staging compared with imaging techniques in the staging of advanced cervical cancer. Gynecol Oncol 2002;87(1):46–51.
16. Ramirez PT, Jhingran A, Macapinlac HA, Euscher ED, Munsell MF, Coleman RL, et al. Laparoscopic extraperitoneal para-aortic lymphadenectomy in locally advanced cervical cancer: a prospective correlation of surgical findings with positron emission tomography/computed tomography findings. Cancer 2011;117(9):1928–34.
17. Marnitz S, Köhler C, Roth C, Füller J, Hinkelbein W, Schneider A. Is there a benefit of pretreatment laparoscopic transperitoneal surgical staging in patients with advanced cervical cancer? Gynecol Oncol 2005;99(3):536–44.
18. Gold MA, Tian C, Whitney CW, Rose PG, Lanciano R. Surgical versus radiographic determination of para-aortic lymph node metastases before chemoradiation for locally advanced cervical carcinoma: a Gynecologic Oncology Group Study. Cancer 2008;112(9):1954–63.
19. Heller PB, Maletano JH, Bundy BN, Barnhill DR, Okagaki T. Clinical-pathologic study of stage IIB, III, and IVA carcinoma of the cervix: extended diagnostic evaluation for paraaortic node metastasis – a Gynecologic Oncology Group study. Gynecol Oncol 1990;38(3):425–30.
20. Edge SB, Byrd DR, Compton CC, Faiz AG, Greene FL, Trotti A, eds. Gynecologic Sites. AJCC Cancer Staging Manual. 7th ed. New York, London: Springer; 2010, pp. 395–402.

21. Kinney WK, Egorshin EV, Ballard DJ, Podratz KC. Long-term survival and sequelae after surgical management of invasive cervical carcinoma diagnosed at the time of simple hysterectomy. Gynecol Oncol 1992;44(1):24–7.
22. Ostör AG. Studies on 200 cases of early squamous cell carcinoma of the cervix. Int J Gynecol Pathol 1993;12(3):193–207.
23. Lee SW, Kim Y-M, Son W-S, You HJ, Kim DY, Kim JH, et al. The efficacy of conservative management after conization in patients with stage IA1 microinvasive cervical carcinoma. Acta Obstet Gynecol Scand 2009;88(2):209–15.
24. Mota F. Microinvasive squamous carcinoma of the cervix: treatment modalities. Acta Obstet Gynecol Scand 2003;82(6):505–9.
25. Webb JC, Key CR, Qualls CR, Smith HO. Population-based study of microinvasive adenocarcinoma of the uterine cervix. Obstet Gynecol 2001;97(5 Pt–1):701–6.
26. Elliott P, Coppleson M, Russell P, Liouros P, Carter J, MacLeod C, et al. Early invasive (FIGO stage IA) carcinoma of the cervix: a clinico-pathologic study of 476 cases. Int J Gynecol Cancer 2000;10(1):42–52.
27. Shepherd JH, Spencer C, Herod J, Ind TE. Radical vaginal trachelectomy as a fertility-sparing procedure in women with early-stage cervical cancer-cumulative pregnancy rate in a series of 123 women. BJOG 2006;113(6): 719–24.
28. Quinn MA, Benedet JL, Odicino F, Maisonneuve P, Beller U, Creasman WT, et al. Carcinoma of the cervix uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. Int J Gynecol Obstet 2006;95(Suppl 1):S43–103.
29. Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. J Clin Oncol 2008;26(35):5802–12.
30. Landoni F, Maneo A, Colombo A, Placa F, Milani R, Perego P, et al. Randomised study of radical surgery versus radiotherapy for stage Ib–IIa cervical cancer. Lancet 1997;350(9077):535–40.
31. Eifel PJ, Morris M, Wharton JT, Oswald MJ. The influence of tumor size and morphology on the outcome of patients with FIGO stage IB squamous cell carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys 1994;29(1):9–16.
32. Landoni F, Maneo A, Cormio G, Perego P, Milani R, Caruso O, et al. Class II versus class III radical hysterectomy in stage IB–IIA cervical cancer: a prospective randomized study. Gynecol Oncol 2001;80(1):3–12.
33. Shingleton HM, Soong SJ, Gelder MS, Hatch KD, Baker VV, Austin JM Jr. Clinical and histopathologic factors predicting recurrence and survival after pelvic exenteration for cancer of the cervix. Obstet Gynecol 1989;73(6):1027–34.
34. Rutledge FN, Smith JP, Wharton JT, O'Quinn AG. Pelvic exenteration: analysis of 296 patients. Am J Obstet Gynecol 1977;129(8):881–92.
35. Morley GW, Hopkins MP, Lindenauer SM, Roberts JA. Pelvic exenteration, University of Michigan: 100 patients at 5 years. Obstet Gynecol 1989;74(6): 934–43.
36. Estape R, Angioli R. Surgical management of advanced and recurrent cervical cancer. Semin Surg Oncol 1999;16(3):236–41.
37. Benn T, Brooks RA, Zhang Q, Powell MA, Thaker PH, Mutch DG, et al. Pelvic exenteration in gynecologic oncology: a single institution study over 20 years. Gynecol Oncol 2011;122(1):14–8.
38. Boronow RC. The bulky 6-cm barrel-shaped lesion of the cervix: primary surgery and postoperative chemoradiation. Gynecol Oncol 2000;78(3 Pt 1): 313–7.
39. Hacker NF, Wain GV, Nicklin JL. Resection of bulky positive lymph nodes in patients with cervical carcinoma. Int J Gynecol Cancer 1995;5(4):250–6.
40. Kupets R, Thomas GM, Covens A. Is there a role for pelvic lymph node debulking in advanced cervical cancer? Gynecol Oncol 2002;87(2):163–70.
41. van Bommel PF, van Lindert AC, Kock HC, Leers WH, Neijt JP. A review of prognostic factors in early-stage carcinoma of the cervix (FIGO I B and II A) and implications for treatment strategy. Eur J Obstet Gynecol Reprod Biol 1987; 26(1):69–84.
42. Peters WA, Liu PY, Barrett RJ, Stock RJ, Monk BJ, Berek JS, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol 2000;18(8):1606–13.
43. Rotman M, Sedlis A, Piedmonte MR, Bundy B, Lentz SS, Muderspach LI, et al. A phase III randomized trial of postoperative pelvic irradiation in Stage IB cervical carcinoma with poor prognostic features: follow-up of a gynecologic oncology group study. Int J Radiat Oncol Biol Phys 2006;65(1):169–76.
44. Sedlis A, Bundy BN, Rotman MZ, Lentz SS, Muderspach LI, Zaino RJ. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: a Gynecologic Oncology Group Study. Gynecol Oncol 1999;73(2):177–83.
45. Follen M, Levenback CF, Iyer RB, Grigsby PW, Boss EA, Delpassand ES, et al. Imaging in cervical cancer. Cancer 2003;98(9 Suppl):2028–38.
46. Piver MS, Chung WS. Prognostic significance of cervical lesion size and pelvic node metastases in cervical carcinoma. Obstet Gynecol 1975;46(5):507–10.
47. Levenback C, Coleman RL, Burke TW, Lin WM, Erdman W, Deavers M, et al. Lymphatic mapping and sentinel node identification in patients with cervix cancer undergoing radical hysterectomy and pelvic lymphadenectomy. J Clin Oncol 2002;20(3):688–93.
48. Hauspy J, Beiner M, Harley I, Ehrlich L, Rasty G, Covens A. Sentinel lymph nodes in early stage cervical cancer. Gynecol Oncol 2007;105(2):285–90.
49. Altgassen C, Hertel H, Brandstädt A, Köhler C, Dürst M, Schneider A. Multicenter validation study of the sentinel lymph node concept in cervical cancer: AGO Study Group. J Clin Oncol 2008;26(18):2943–51.
50. Martínez-Palones JM, Gil-Moreno A, Pérez-Benavente MA, Roca I, Xercavins J. Intraoperative sentinel node identification in early stage cervical cancer using a combination of radiolabeled albumin injection and isosulfan blue dye injection. Gynecol Oncol 2004;92(3):845–50.
51. van de Lande J, Torrenga B, Raijmakers PG, Hoekstra OS, van Baal MW, Brölmann HA, et al. Sentinel lymph node detection in early stage uterine cervix carcinoma: a systematic review. Gynecol Oncol 2007;106(3):604–13.
52. Gortzak-Uzan L, Jimenez W, Nofech-Mozes S, Ismiil N, Khalifa MA, Dubé V, et al. Sentinel lymph node biopsy vs. pelvic lymphadenectomy in early stage cervical cancer: is it time to change the gold standard? Gynecol Oncol 2010; 116(1):28–32.
53. Barranger E, Coutant C, Cortez A, Uzan S, Darai E. Sentinel node biopsy is reliable in early-stage cervical cancer but not in locally advanced disease. Ann Oncol 2005;16(8):1237–42.
54. Coutant C, Cordier AG, Guillo E, Ballester M, Rouzier R, Daraï E. Clues pointing to simple hysterectomy to treat early-stage cervical cancer. Oncol Rep 2009; 22(4):927–34.
55. Frumovitz M, Sun CC, Schmeler KM, Deavers MT, Dos Reis R, Levenback CF, et al. Parametrial involvement in radical hysterectomy specimens for women with early-stage cervical cancer. Obstet Gynecol 2009;114(1):93–9.
56. Varia MA, Bundy BN, Deppe G, Mannel R, Averette HE, Rose PG, et al. Cervical carcinoma metastatic to para-aortic nodes: extended field radiation therapy with concomitant 5-fluorouracil and cisplatin chemotherapy: a Gynecologic Oncology Group study. Int J Radiat Oncol Biol Phys 1998;42(5):1015–23.
57. Grigsby PW, Lu JD, Mutch DG, Kim RY, Eifel PJ. Twice-daily fractionation of external irradiation with brachytherapy and chemotherapy in carcinoma of the cervix with positive para-aortic lymph nodes: Phase II study of the Radiation Therapy Oncology Group 92-10. Int J Radiat Oncol Biol Phys 1998;41(4):817–22.
58. Small W, Mell LK, Anderson P, Creutzberg C, De Los Santos J, Gaffney D, et al. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer. Int J Radiat Oncol Biol Phys 2008;71(2):428–34.
59. Tierney JF, Vale C, Symonds P. Concomitant and neoadjuvant chemotherapy for cervical cancer. Clin Oncol (R Coll Radiol) 2008;20(6):401–16.
60. Rydzewska L, Tierney J, Vale CL, Symonds PR. Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer. Cochrane Database Syst Rev 2010; (1):CD007406.
61. Gadducci A, Cosio S, Zola P, Tisi G, Ferrero A, Piovano E, et al. Pretreatment platelet and hemoglobin levels are neither predictive nor prognostic variables for patients with locally advanced cervical cancer treated with neoadjuvant chemotherapy and radical hysterectomy: a retrospective Italian study. Int J Gynecol Cancer 2010;20(8):1399–404.
62. Buda A, Fossati R, Colombo N, Fei F, Floriani I, Gueli Alletti D, et al. Randomized trial of neoadjuvant chemotherapy comparing paclitaxel, ifosfamide, and cisplatin with ifosfamide and cisplatin followed by radical surgery in patients with locally advanced squamous cell cervical carcinoma: the SNAP01 (Studio Neo-Adjuvante Portio) Italian Collaborative Study. J Clin Oncol 2005;23(18):4137–45.
63. Benedetti-Panici P, Greggi S, Colombo A, Amoroso M, Smaniotto D, Giannarelli D, et al. Neoadjuvant chemotherapy and radical surgery versus exclusive radiotherapy in locally advanced squamous cell cervical cancer: results from the Italian multicenter randomized study. J Clin Oncol 2002;20(1):179–88.
64. Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 1999;340(15):1144–53.
65. Whitney CW, Sause W, Bundy BN, Malfetano JH, Hannigan EV, Fowler WC Jr, et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB–IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. J Clin Oncol 1999;17(5):1339–48.
66. Morris M, Eifel PJ, Lu J, Grigsby PW, Levenback C, Stevens RE, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med 1999;340(15):1137–43.
67. Lei ZZ, He FZ. External cobalt 60 irradiation alone for stage IIB carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys 1989;16(2):339–41.
68. Ferrigno R, dos Santos Novaes PE, Pellizzon AC, Maia MA, Fogarolli RC, Gentil AC, et al. High-dose-rate brachytherapy in the treatment of uterine cervix cancer. Analysis of dose effectiveness and late complications. Int J Radiat Oncol Biol Phys 2001;50(5):1123–35.
69. Fenkell L, Assenholt M, Nielsen SK, Haie-Meder C, Pötter R, Lindegaard J, et al. Parametrial boost using midline shielding results in an unpredictable dose to tumor and organs at risk in combined external beam radiotherapy and

brachytherapy for locally advanced cervical cancer. Int J Radiat Oncol Biol Phys 2011;79(5):1572–9.
70. Kochanski JD, Mell LK, Roeske JC, Mundt AJ. Intensity-modulated radiation therapy in gynecologic malignancies: current status and future directions. Clin Adv Hematol Oncol 2006;4(5):379–86.
71. Kavanagh BD, Schefter TE, Wu Q, Tong S, Newman F, Arnfield M, et al. Clinical application of intensity-modulated radiotherapy for locally advanced cervical cancer. Semin Radiat Oncol 2002;12(3):260–71.
72. Nag S, Erickson B, Thomadsen B, Orton C, Demanes JD, Petereit D. The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the cervix. Int J Radiat Oncol Biol Phys 2000;48(1):201–11.
73. Wang X, Liu R, Ma B, Yang K, Tian J, Jiang L, et al. High dose rate versus low dose rate intracavity brachytherapy for locally advanced uterine cervix cancer. Cochrane Database Syst Rev 2010;(7):CD007563.
74. Rath GK, Sharma DN, Julka PK, Subramani V, Bahl A, Haresh KP. Pulsed-dose-rate intracavitary brachytherapy for cervical carcinoma: the AIIMS experience. Am J Clin Oncol 2010;33(3):238–41.
75. Rogers Cl, Freel JH, Speiser BL. Pulsed low dose rate brachytherapy for uterine cervix carcinoma. Int J Radiat Oncol Biol Phys 1999;43(1):95–100.
76. Tod MC, Meredith WJ. A dosage system for use in the treatment of cancer of the uterine cervix. Br J Radiol 1938;11:809–24.
77. Haie-Meder C, Pötter R, Van Limbergen E, Briot E, De Brabandere M, Dimopoulos J, et al. Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. Radiother Oncol 2005;74(3):235–45.
78. Pötter R, Haie-Meder C, Van Limbergen E, Barillot I, De Brabandere M, Dimopoulos J, et al. Recommendations from gynaecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. Radiother Oncol 2006;78(1):67–77.
79. Haie-Meder C, Mazeron R, Verezesan O, Dumas I, Monnier L, Vieillot S, et al. [Three-dimensional brachytherapy optimization techniques in the treatment of patients with cervix cancer]. Cancer Radiother 2009;13(6–7):520–4. In French.
80. Viswanathan AN, Creutzberg CL, Craighead P, McCormack M, Toita T, Narayan K, et al. International brachytherapy practice patterns: a survey of the Gynecologic Cancer Intergroup (GCIG). Int J Radiat Oncol Biol Phys 2012;82(1):250–5.
81. Pötter R, Knocke TH, Fellner C, Baldass M, Reinthaller A, Kucera H. Definitive radiotherapy based on HDR brachytherapy with iridium 192 in uterine cervix carcinoma: report on the Vienna University Hospital findings (1993–1997) compared to the preceding period in the context of ICRU 38 recommendations. Cancer Radiother 2000;4(2):159–72.
82. Sharma DN, Rath GK, Thulkar S, Kumar S, Subramani V, Julka PK. High-dose rate interstitial brachytherapy using two weekly sessions of 10 Gy each for patients with locally advanced cervical carcinoma. Brachytherapy 2011;10(3):242–8.
83. Perez CA, Grigsby PW, Castro-Vita H, Lockett MA. Carcinoma of the uterine cervix. I. Impact of prolongation of overall treatment time and timing of brachytherapy on outcome of radiation therapy. Int J Radiat Oncol Biol Phys 1995;32(5):1275–88.
84. Lanciano RM, Pajak TF, Martz K, Hanks GE. The influence of treatment time on outcome for squamous cell cancer of the uterine cervix treated with radiation: a patterns-of-care study. Int J Radiat Oncol Biol Phys 1993;25(3):391–7.
85. Kim YS, Shin SS, Nam JH, Kim YT, Kim YM, Kim JH, et al. Prospective randomized comparison of monthly fluorouracil and cisplatin versus weekly cisplatin concurrent with pelvic radiotherapy and high-dose rate brachytherapy for locally advanced cervical cancer. Gynecol Oncol 2008;108(1):195–200.
86. Lanciano R, Calkins A, Bundy BN, Parham G, Lucci JA 3rd, Moore DH, et al. Randomized comparison of weekly cisplatin or protracted venous infusion of fluorouracil in combination with pelvic radiation in advanced cervix cancer: a Gynecologic Oncology Group study. J Clin Oncol 2005;23(33):8289–95.
87. National Cancer Institute. Clinical Trials Home Page: Web site: www.cancer.gov/clinicaltrials
88. Dueñas-González A, Zarbá JJ, Patel F, Alcedo JC, Beslija S, Casanova L, et al. Phase III, open-label, randomized study comparing concurrent gemcitabine plus cisplatin and radiation followed by adjuvant gemcitabine and cisplatin versus concurrent cisplatin and radiation in patients with stage IIB to IVA carcinoma of the cervix. J Clin Oncol 2011;29(13):1678–85.
89. Barraclough LH, Swindell R, Livsey JE, Hunter RD, Davidson SE. External beam boost for cancer of the cervix uteri when intracavitary therapy cannot be performed. Int J Radiat Oncol Biol Phys 2008;71(3):772–8.
90. Hong JH, Tsai CS, Lai CH, Chang TC, Wang CC, Chou HH, et al. Recurrent squamous cell carcinoma of cervix after definitive radiotherapy. Int J Radiat Oncol Biol Phys 2004;60(1):249–57.
91. Bodurka-Bevers D, Morris M, Eifel PJ, Levenback C, Bevers MW, Lucas KR, et al. Posttherapy surveillance of women with cervical cancer: an outcomes analysis. Gynecol Oncol 2000;78(2):187–93.
92. Lim KC, Howells RE, Evans AS. The role of clinical follow up in early stage cervical cancer in South Wales. BJOG 2004;111(12):1444–8.
93. Wolfson AH, Wu X, Takita C, Shao H, Luo C, Watzich M, et al. A novel applicator for low-dose-rate brachytherapy of gynecological cancers. Int J Gynecol Cancer 2003;13(4):532–40.
94. Elit L, Fyles AW, Devries MC, Oliver TK, Fung-Kee-Fung M. Follow-up for women after treatment for cervical cancer: a systematic review. Gynecol Oncol 2009;114(3):528–35.
95. Monk BJ, Huang HQ, Cella D, Long HJ 3rd. Quality of life outcomes from a randomized phase III trial of cisplatin with or without topotecan in advanced carcinoma of the cervix: a Gynecologic Oncology Group Study. J Clin Oncol 2005;23(21):4617–25.
96. Moore DH, Blessing JA, McQuellon RP, Thaler HT, Cella D, Benda J, et al. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. J Clin Oncol 2004;22(15):3113–9.
97. Monk BJ, Sill MW, McMeekin DS, Cohn DE, Ramondetta LM, Boardman CH, et al. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: a Gynecologic Oncology Group study. J Clin Oncol 2009;27(28):4649–55.
98. Long HJ, Bundy BN, Grendys EC, Benda JA, McMeekin DS, Sorosky J, et al. Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group Study. J Clin Oncol 2005;23(21):4626–33.
99. Chow E, Zeng L, Salvo N, Dennis K, Tsao M, Lutz S. Update on the systematic review of palliative radiotherapy trials for bone metastases. Clin Oncol (R Coll Radiol) 2012;24(2):112–24
100. Eifel PJ, Jhingran A, Brown J, Levenback C, Thames H. Time course and outcome of central recurrence after radiation therapy for carcinoma of the cervix. Int J Gynecol Cancer 2006;16(3):1106–11.
101. Fagundes H, Perez CA, Grigsby PW, Lockett MA. Distant metastases after irradiation alone in carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys 1992;24(2):197–204.
102. van Nagell JR, Rayburn W, Donaldson ES, Hanson M, Gay EC, Yoneda J, et al. Therapeutic implications of patterns of recurrence in cancer of the uterine cervix. Cancer 1979;44(6):2354–61.
103. Eralp Y, Saip P, Sakar B, Kucucuk S, Aydiner A, Dincer M, et al. Prognostic factors and survival in patients with metastatic or recurrent carcinoma of the uterine cervix. Int J Gynecol Cancer 2003;13(4):497–504.
104. Friedlander M, Grogan M, U.S. Preventative Services Task Force. Guidelines for the treatment of recurrent and metastatic cervical cancer. Oncologist 2002;7(4):342–7.
105. Grigsby PW. Radiotherapy for pelvic recurrence after radical hysterectomy for cervical cancer. Radiat Med 2005;23(5):327–30.
106. Haasbeek CJ, Uitterhoeve AL, van der Velden J, González DG, Stalpers LJ. Long-term results of salvage radiotherapy for the treatment of recurrent cervical carcinoma after prior surgery. Radiother Oncol 2008;89(2):197–204.
107. Piura B, Rabinovich A, Friger M. Recurrent cervical carcinoma after radical hysterectomy and pelvic lymph node dissection: a study of 32 cases. Eur J Gynaecol Oncol 2008;29(1):31–6.
108. Lee YS, Kim YS, Kim JH, Ahn SD, Lee SW, Shin SS, et al. Feasibility and outcome of concurrent chemoradiotherapy for recurrent cervical carcinoma after initial surgery. Tumori 2010;96(4):553–9.
109. Sun SS, Chen TC, Yen RF, Shen YY, Changlai SP, Kao A. Value of whole body ^{18}F-fluoro-2-deoxyglucose positron emission tomography in the evaluation of recurrent cervical cancer. Anticancer Res 2001;21(4B):2957–61.
110. Husain A, Akhurst T, Larson S, Alektiar K, Barakat RR, Chi DS. A prospective study of the accuracy of 18Fluorodeoxyglucose positron emission tomography (18FDG PET) in identifying sites of metastasis prior to pelvic exenteration. Gynecol Oncol 2007;106(1):177–80.
111. Unger JB, Ivy JJ, Connor P, Charrier A, Ramaswamy MR, Ampil FL, et al. Detection of recurrent cervical cancer by whole-body FDG PET scan in asymptomatic and symptomatic women. Gynecol Oncol 2004;94(1):212–6.
112. Havrilesky LJ, Wong TZ, Secord AA, Berchuck A, Clarke-Pearson DL, Jones EL. The role of PET scanning in the detection of recurrent cervical cancer. Gynecol Oncol 2003;90(1):186–90.
113. Chung HH, Jo H, Kang WJ, Kim JW, Park NH, Song YS, et al. Clinical impact of integrated PET/CT on the management of suspected cervical cancer recurrence. Gynecol Oncol 2007;104(3):529–34.
114. Pallardy A, Bodet-Milin C, Oudoux A, Campion L, Bourbouloux E, Sagan C, et al. Clinical and survival impact of FDG PET in patients with suspicion of recurrent cervical carcinoma. Eur J Nucl Med Mol Imaging 2010;37(7):1270–8.
115. Mittra E, El-Maghraby T, Rodriguez CA, Quon A, McDougall IR, Gambhir SS, et al. Efficacy of 18F-FDG PET/CT in the evaluation of patients with recurrent cervical carcinoma. Eur J Nucl Med Mol Imaging 2009;36(12):1952–9.
116. Kitajima K, Murakami K, Yamasaki E, Domeki Y, Kaji Y, Sugimura K. Performance of FDG-PET/CT for diagnosis of recurrent uterine cervical cancer. Eur Radiol 2008;18(10):2040–7.
117. Ruth-Sahd LA, Zulkosky KD. Cervical cancer: caring for patients undergoing total pelvic exenteration. Crit Care Nurse 1999;19(1):46–57.
118. Höckel M, Dornhöfer N. Pelvic exenteration for gynaecological tumours: achievements and unanswered questions. Lancet Oncol 2006;7(10):837–47.

119. Niibe Y, Kenjo M, Kazumoto T, Michimoto K, Takayama M, Yamauchi C, et al. Multi-institutional study of radiation therapy for isolated para-aortic lymph node recurrence in uterine cervical carcinoma: 84 subjects of a population of more than 5,000. Int J Radiat Oncol Biol Phys 2006;66(5):1366–9.
120. Uzan C, Vincens E, Balleyguier C, Gouy S, Pautier P, Duvillard P, et al. Outcome of patients with incomplete resection after surgery for stage IB2/II cervical carcinoma with chemoradiation therapy. Int J Gynecol Cancer 2010;20(3):379–84.
121. Chen SW, Liang JA, Yang SN, Lin FJ. Postoperative radiotherapy for patients with invasive cervical cancer following treatment with simple hysterectomy. Jpn J Clin Oncol 2003;33(9):477–81.
122. Hopkins MP, Peters WA, Andersen W, Morley GW. Invasive cervical cancer treated initially by standard hysterectomy. Gynecol Oncol 1990;36(1):7–12.
123. Amant F, Brepoels L, Halaska MJ Gziri MM, Calsteren KV. Gynaecologic cancer complicating pregnancy: an overview. Best Pract Res Clin Obstet Gynaecol 2010;24(1):61–79.
124. Duggan B, Muderspach LI, Roman LD, Curtin JP, d'Ablaing G 3rd, Morrow CP. Cervical cancer in pregnancy: reporting on planned delay in therapy. Obstet Gynecol 1993;82(4 Pt 1):598–602.
125. Nevin J, Soeters R, Dehaeck K, Bloch B, Van Wyk L. Advanced cervical carcinoma associated with pregnancy. Int J Gynecol Cancer 1993;3(1):57–63.
126. Hunter MI, Tewari K, Monk BJ. Cervical neoplasia in pregnancy. Part 2: current treatment of invasive disease. Am J Obstet Gynecol 2008;199(1):10–8.
127. Tewari K, Cappuccini F, Gambino A, Kohler MF, Pecorelli S, DiSaia PJ. Neoadjuvant chemotherapy in the treatment of locally advanced cervical carcinoma in pregnancy: a report of two cases and review of issues specific to the management of cervical carcinoma in pregnancy including planned delay of therapy. Cancer 1998;82(8):1529–34.
128. Boyd A, Cowie V, Gourley C. The use of cisplatin to treat advanced-stage cervical cancer during pregnancy allows fetal development and prevents cancer progression: report of a case and review of the literature. Int J Gynecol Cancer 2009;19(2):273–6.