



CERVICAL CANCER

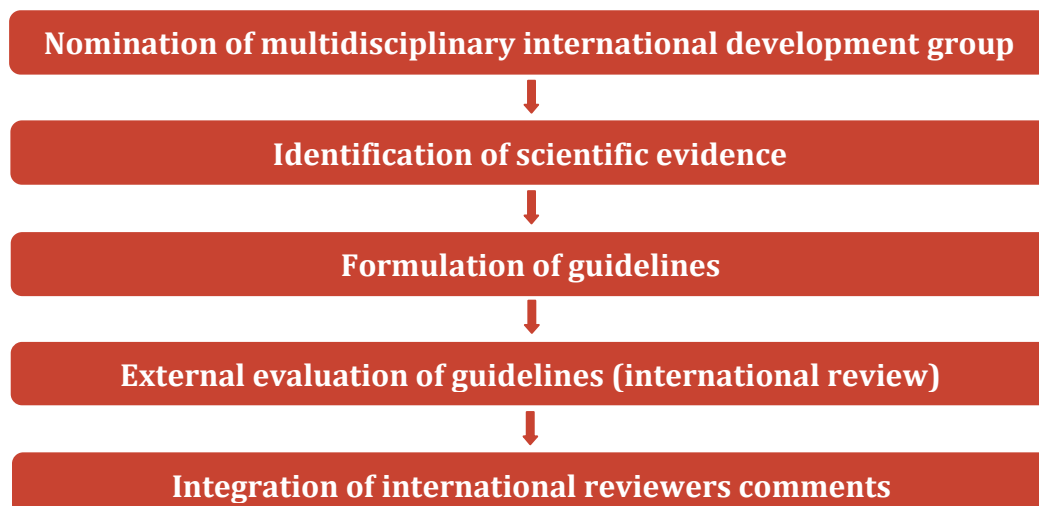
GUIDELINES



Despite significant advances in the screening, detection and treatment of preinvasive cervical lesions, invasive cervical cancer is the fifth most common cancer in European women. There are large disparities in Europe and worldwide in the incidence, management and mortality of cervical cancer¹.

The European Society of Gynaecological Oncology (ESGO), the European Society for Radiotherapy and Oncology (ESTRO), and the European Society of Pathology (ESP) jointly developed clinically relevant and evidence-based guidelines covering comprehensively cervical cancer staging, management and follow-up for patients with cervical. Management includes fertility sparing treatment, stage T1a, T1b1/T2a1, clinically occult cervical cancer diagnosed after simple hysterectomy, locally advanced cervical cancer, primary distant metastatic disease, cervical cancer in pregnancy, and recurrent disease. Principles of radiotherapy and pathological evaluation were also defined.

A five-step development process was followed:



The objectives of the guidelines are to improve and to homogenize the management of patients with cervical cancer within a multidisciplinary setting. These guidelines are intended for use by gynaecological oncologists, general gynaecologists, surgeons, radiation oncologists, pathologists, medical and clinical oncologists, radiologists, general practitioners, palliative care teams, and allied health professionals.

These guidelines exclude the management of neuroendocrine carcinoma, sarcomas, and other rare histologic sub-types. They also do not include any economic analysis of the strategies. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment.

¹ Ferlay, J., *et al.* Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer* **49**, 1374-1403 (2013)

To ensure that the statements were evidence based, the current literature was reviewed and critically appraised. A comprehensive literature review of the studies published between January 1997 and January 2017 was carried out.

If an approach was judged to be acceptable but was not unanimously recognized as a criterion-standard clinical approach, indication was given that it was still subject to discussion and/or evaluation. In the absence of any clear scientific evidence, judgment was based on the professional experience and consensus of the development group.

This guideline has five different “strength of guideline” ratings (SIGN grading system²):

A At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or

A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results

B A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or

Extrapolated evidence from studies rated as 1++ or 1+

C A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or

Extrapolated evidence from studies rates as 2++

D Evidence level 3 or 4; or

Extrapolated evidence from studies rated as 2+

✓ Recommended best practice based on the clinical experience of the guideline development group

1++ high quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias, 1+ well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias, 2++ high quality systematic reviews of case control or cohort studies/high quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal, 2+ well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal, 3 non-analytic studies, eg case reports, case series, 4 expert opinion

² <http://www.sign.ac.uk/guidelines/fulltext/50/annexoldb.html>

GENERAL RECOMMENDATIONS

- ✓ Treatment planning should be made on a multidisciplinary basis (generally at a tumour board meeting) and based upon the comprehensive and precise knowledge of prognostic and predictive factors for oncological outcome, morbidity and quality of life.
- ✓ Patients should be carefully counseled on the suggested treatment plan, and potential alternatives, including risks and benefits of all options.
- ✓ Treatment should be undertaken by a dedicated team of specialists in the diagnosis and management of gynaecological cancers.

STAGING

FIGO staging and TNM classification

- ✓ Patients with cervical cancer should be staged according to the TNM classification. Clinical staging (FIGO) should also be documented (*Table 1*).
- C** TNM should be based on a correlation of various modalities (integrating physical examination, imaging and pathology) after discussion in a multidisciplinary forum.
- ✓ The method used to determine tumour status (T), lymph node status (N) and systemic status (M) i.e. clinical (c), imaging (i) and/or pathological (p) should be recorded.
- ✓ Lymph node metastases should be classified according to the TNM classification (see Principles of pathological evaluation).

Table 1. FIGO staging and TNM classification

T category ³	FIGO stage ⁴	Definition
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Cervical carcinoma confined to the uterus (extension to corpus should be disregarded)
T1a	IA	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less; vascular space involvement, venous or lymphatic, does not affect classification.
T1a1	IA1	Measured stromal invasion of 3.0 mm or less in depth and 7.0 mm or less in horizontal spread
T1a2	IA2	Measured stromal invasion of more than 3.0 mm and not more than 5.0 mm, with a horizontal spread of 7.0 mm or less
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a2/IA2. Includes all macroscopically visible lesions, even those with superficial invasion.
T1b1	IB1	Clinically visible lesion 4.0 cm or less in greatest dimension
T1b2	IB2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2	II	Cervical carcinoma invading beyond the uterus but not to the pelvic wall or to lower third of the vagina
T2a	IIA	Tumor without parametrial invasion
T2a1	IIA1	Clinically visible lesion 4.0 cm or less in greatest dimension
T2a2	IIA2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2b	IIB	Tumor with parametrial invasion
T3	III	Tumor extending to the pelvic sidewall* and/or involving the lower third of the vagina and/or causing hydronephrosis or nonfunctioning kidney
T3a	IIIA	Tumor involving the lower third of the vagina but not extending to the pelvic wall
T3b	IIIB	Tumor extending to the pelvic wall and/or causing hydronephrosis or nonfunctioning kidney
T4	IVA	Tumor invading the mucosa of the bladder or rectum and/or extending beyond the true pelvis (bullous edema is not sufficient to classify a tumor as T4)
	IVB	Tumor invading distant organs

* the pelvic sidewall is defined as the muscle, fascia, neurovascular structures, and skeletal portions of the bony pelvis.

³ Union for International Cancer Control (UICC). 8th edition of the UICC TNM classification of malignant tumours (2016).

⁴ Pecorelli, S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet* **105**, 103-104 (2009).

Pecorelli, S., Zigliani, L. & Odicino, F. Revised FIGO staging for carcinoma of the cervix. *Int J Gynaecol Obstet* **105**, 107-108 (2009).

Pecorelli, S. Corrigendum to "Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet* **108**, 176 (2010).

Prognostic factors

- A** Proper documentation of the following major tumour related prognostic factors is recommended:
- TNM and FIGO stage, including a maximum tumour size and detailed description of extracervical tumour extension and nodal involvement (number, size, location).
 - Pathological tumour type.
 - Depth of cervical stromal invasion and a minimum thickness of uninvolved cervical stroma.
 - Presence or absence of lymphovascular space involvement (LVSI).
 - Presence or absence of distant metastases.

Local clinical and radiological diagnostic work-up

- ✓ Pelvic examination and biopsy +/- colposcopy are mandatory components to diagnose cervical cancer.
- B** Mandatory initial work-up for assessment of pelvic tumour extent and to guide treatment options is pelvic magnetic resonance imaging (MRI).
- ✓ Endovaginal/transrectal ultrasound is an option if performed by a properly trained sonographer.
- ✓ Cystoscopy or rectoscopy may be considered to provide a biopsy if suspicious lesions in the urinary bladder or rectum are documented on MRI or ultrasound.

Nodal/distant diagnostic work-up

- B** In early stage (T1a, T1b1, T2a1), surgical/pathological staging of pelvic lymph nodes is the gold standard to assess the prognosis and guide treatment (except of T1a1 and no LVSI).
- B** In locally advanced cervical cancer (T1b2 and higher (except T2a1)) or in early stage disease with suspicious lymph nodes on imaging, positron emission tomography-computed tomography (PET-CT) or chest/abdomen computed tomography (CT) is recommended for assessment of nodal and distant disease.
- B** PET-CT is the preferred option for treatment planning before chemoradiotherapy with curative intent.
- C** Paraaortic lymph node dissection, at least up to inferior mesenteric artery, may be considered in locally advanced cervical cancer with negative paraaortic lymph nodes on imaging for staging purposes.
- ✓ Equivocal extrauterine disease is to be considered for biopsy to confirm or rule out metastatic disease and to avoid inappropriate treatment. Tru-cut (core-cut) biopsy is the preferred option than fine-needle aspiration biopsy, since it allows histological assessment of the tissue.

MANAGEMENT OF STAGE T1a

Diagnosis of stage T1a disease

- ✓ Diagnosis of T1a cancer should be based on a conisation (or excision) specimen examined by an expert pathologist. Management must be based on an expert pathology review, with accurate measurement of the maximum horizontal two dimensions, depth of invasion, margin status, coexisting pathology and reliable assessment of LVSI.
- ✓ Loop or laser conisation are preferable to cold-knife conisation in women desiring fertility preservation. Maximum care should be taken to provide an intact (unfragmented) specimen with minimal thermal artefact. The cone specimen should be oriented for the pathologist.
- C Surgical margins of the cone specimen should be clear of both invasive and preinvasive disease (except for preinvasive disease in ectocervix).

Management of stage T1a1 disease

- ✓ Management of patients with stage T1a1 disease should be individualized depending on the age, the desire for fertility preservation and the presence or absence of LVSI.
- ✓ In case of positive margins (except for preinvasive disease in ectocervix), a repeat conisation should be performed to rule out more extensive invasive disease.
- B Lymph node staging is not indicated in T1a1 LVSI-negative patients but can be considered in T1a1 LVSI-positive patients. Sentinel lymph node biopsy (without additional pelvic lymph node dissection) is an acceptable method of lymph node staging.
- C Conisation can be considered a definitive treatment as hysterectomy does not improve the outcome.
- C Radical surgical approaches such as radical hysterectomy or parametrectomy represent overtreatment for patients with T1a1 disease.

Management of stage T1a2 disease

- C In patients with stage T1a2 disease, conisation alone or simple hysterectomy is an adequate treatment.
- C Parametrial resection is not indicated.
- B Lymph node staging can be considered in LVSI-negative patients but should be performed in LVSI-positive patients. Sentinel lymph node biopsy alone (without additional pelvic lymph node dissection) appears to be an acceptable method of LN staging.
- ✓ Routine completion of hysterectomy is not recommended after conservative management of stage T1a disease.

MANAGEMENT OF STAGES T1b1/T2a1

General recommendation

- B** Treatment strategy should aim for the avoidance of combining radical surgery and radiotherapy due to the highest morbidity after combined treatment.

Negative lymph nodes on radiological staging

Surgical treatment

- B** Radical surgery by a gynaecological oncologist is the preferred treatment modality. Minimal invasive approach is favored.
- B** The standard lymph node staging procedure is systematic pelvic lymphadenectomy. Sentinel node biopsy before pelvic lymphadenectomy is strongly recommended. Combination of blue dye with radiocolloid or use of indocyanine green alone are the recommended techniques.
- ✓ Lymph node assessment should be performed as the first step of surgical management. Intraoperative assessment of lymph node status (frozen section) is recommended. All sentinel nodes from both sides of the pelvis and/or any suspicious lymph nodes should be sent for frozen section. If sentinel node is not detected, intraoperative assessment of the pelvic lymph nodes should be considered.
- ✓ If intraoperative lymph node assessment is negative or it is not done, systematic pelvic lymph node dissection should be performed. At present, sentinel node biopsy alone cannot be recommended outside prospective clinical trials. Systematic lymph node dissection should include the removal of lymphatic tissue from regions with the most frequent occurrence of positive lymph nodes (sentinel nodes) including obturator fossa, external iliac regions, common iliac regions bilaterally, and presacral region. Distal external iliac lymph nodes (so called circumflex iliac lymph nodes) should be spared if they are not macroscopically suspicious.
- ✓ The type of radical hysterectomy (extent of parametrial resection, Type A-C2) should be based upon the presence of prognostic risk factors identified preoperatively (*Table 2*). Major prognostic factors for oncological outcome as tumour size, maximum stromal invasion, LVSI are used to categorize patients at high, intermediate and low risk for treatment failure. Complete description of the template used for radical hysterectomy should be present in the surgical report. The 2017 modification of the Querleu-Morrow classification is recommended as a tool (*Table 3*).



Ovarian preservation should be offered to premenopausal patients with squamous cell carcinoma and usual-type (human papillomavirus (HPV)-related) adenocarcinoma. Bilateral salpingectomy should be considered.

C

If lymph node involvement is detected intraoperatively including macrometastases or micrometastases, further pelvic lymph node dissection and radical hysterectomy should be avoided. Patients should be referred for definitive chemoradiotherapy. Para-aortic lymph node dissection, at least up to inferior mesenteric artery, may be considered for staging purposes.

C

If a combination of risk factors is known at diagnosis, which would require an adjuvant treatment, definitive radiochemotherapy and brachytherapy can be considered without previous radical pelvic surgery. Pelvic lymph node dissection should be avoided. Para-aortic lymph node dissection, at least up to inferior mesenteric artery, may be considered in patients with negative para-aortic lymph node on imaging.

Table 2. Risk groups according to prognostic factors: suggested type(s) of radical hysterectomy

Risk group	Tumour size	LVSI	Stromal invasion	Type of radical hysterectomy*
Low risk	< 2 cm	Negative	Inner 1/3	B1 (A)
Intermediate risk	≥ 2 cm	Negative	Any	B2 (C1)
	< 2 cm	Positive	Any	
High risk	≥ 2 cm	Positive	Any	C1 (C2)

* according to the Querleu-Morrow classification (see table 3)

Table 3. Querleu-Morrow classification⁵

Type of radical hysterectomy	Paracervix or lateral parametrium	Ventral parametrium	Dorsal parametrium
Type A	Halfway between the cervix and ureter (medial to the ureter-ureter identified but not mobilized)	Minimal excision	Minimal excision
Type B1	At the ureter (at the level of the ureteral bed-ureter mobilized from the cervix and lateral parametrium)	Partial excision of the vesicouterine ligament	Partial resection of the rectouterine-rectovaginal ligament and uterosacral peritoneal fold
Type B2	Identical to B1 plus paracervical lymphadenectomy without resection of vascular/nerve structures	Partial excision of the vesicouterine ligament	Partial resection of the rectouterine-rectovaginal ligament and uterosacral fold
Type C1	At the iliac vessels transversally, caudal part is preserved	Excision of the vesicouterine ligament (cranial to the ureter) at the bladder. Proximal part of the vesicovaginal ligament (bladder nerves are dissected and spared)	At the rectum (hypogastric nerve is dissected and spared)
Type C2	At the level of the medial aspect of iliac vessels completely (including the caudal part)	At the bladder (bladder nerves are sacrificed)	At the sacrum (hypogastric nerve is sacrificed)
Type D	At the pelvic wall, including resection of the internal iliac vessels and/or components of the pelvic sidewall	At the bladder. Not applicable if part of exenteration	At the sacrum. Not applicable if part of exenteration

Alternative treatment options

C Definitive radiotherapy including brachytherapy represents effective alternative treatment (see Principles of radiotherapy). It can be considered in particular in case of unfavorable prognostic and predictive factors for oncological and morbidity outcome.

✓ For high risk and intermediate risk, preoperative brachytherapy followed by surgery (Type A) is used in a limited number of centres. It is an acceptable alternative option only in teams experienced in this approach.

C Neoadjuvant chemotherapy followed by surgery is not recommended.

⁵ Querleu, D., Cibula, D. & Abu-Rustum, N.R. 2017 Update on the Querleu-Morrow Classification of Radical Hysterectomy. *Ann Surg Oncol* (2017)

Positive pelvic lymph nodes on radiological staging

C In patients with unequivocally involved pelvic lymph nodes on imaging, definitive chemoradiotherapy is recommended (see Principles of radiotherapy). Paraaortic lymph node dissection, at least up to inferior mesenteric artery, may be considered in patients with negative paraaortic lymph nodes on imaging.

✓ Debulking of suspicious pelvic lymph nodes may be considered.

Adjuvant treatment

B Adjuvant radiotherapy should be considered in the presence of combination of risk factors at final pathology such as tumour size, LVSI, and depth of stromal invasion.

✓ When in these situations an adequate type of radical hysterectomy has been performed (*Table 3*), observation is an alternative option, especially in teams experienced in this approach.

B After primary radical surgery, adjuvant chemoradiotherapy is indicated in the following groups of patients (see Principles of radiotherapy):

- metastatic involvement of pelvic lymph nodes, including the presence of macrometastases pN1 or micrometastases pN1(mi) in either sentinel node or any other pelvic lymph nodes detected by intraoperative or final pathologic assessment ⇒ chemoradiotherapy
- positive surgical margins (vagina/parametria) ⇒ chemoradiotherapy, brachytherapy boost may be considered
- parametrial involvement ⇒ chemoradiotherapy

Cervical stump cancer

✓ Management of cervical stump cancer follows the recommendations for patients without previous subtotal hysterectomy. Adaptation of radiotherapy may be necessary, in particular for brachytherapy.

FERTILITY SPARING TREATMENT

- ✓ Before starting fertility sparing treatment (FST), consultation at a fertility centre is recommended.
- ✓ FST should exclusively be undertaken in gynaecological-oncological centres with comprehensive expertise in this kind of oncologic therapy.
- ✓ For patients who consider FST, prognostic factors, clinical staging and preoperative work-up do not differ from those who do not consider this (see above).
- ✓ Every woman with a desire to spare fertility and histologically proven squamous cell carcinoma or usual-type (HPV-related) adenocarcinoma ≤ 2 cm of the largest diameter should be counseled about the possibility of FST. This consultation should encompass the risk of FST abandonment if positive margins or lymph node involvement, oncologic and obstetric risks related to this type of management.
- ✓ FST should not be recommended for rare histological subtypes of cervical cancer including neuroendocrine carcinomas and non HPV-related adenocarcinomas (except for adenoid basal carcinoma) which tend to exhibit aggressive behaviour.
- ✓ Expert sonography and/or pelvic MRI are recommended imaging tests to measure remaining (after cone biopsy) cervical length and non-involved cervical length. However, no imaging system can exactly predict the extent of necessary local resection in order to reach sound margins with adequate safety distance.
- B** Negative pelvic lymph node status is the precondition for any FST. Therefore pelvic lymph node (sentinel lymph node) staging should always be the first step in each FST procedure. Identification of sentinel lymph node and its ultrastaging is highly recommended since it increases staging accuracy, namely the identification of micrometastases and small macrometastases. The involvement of suspicious lymph nodes should be confirmed by histology. Intraoperative assessment of lymph node status is highly recommended. All sentinel lymph nodes from both sides of the pelvis or any suspicious lymph nodes should be sent for frozen section. If bilateral sentinel lymph node is not detectable, intraoperative assessment of pelvic lymph nodes should be considered (see management of stages T1b1/T2a1). Lymph node staging is not indicated in stage T1a1 LVSI negative.
- ✓ In case of intraoperatively proven lymph node involvement, fertility sparing surgery should be abandoned and the patient referred to definitive chemoradiotherapy (see above). The specific aim of fertility sparing surgery must be the resection of invasive tumour with adequate free margins and preservation of upper part of the cervix. Intraoperative frozen section is a reliable way of assessing the upper resection margin in trachelectomy specimen and should be considered.
- B** Conisation or simple trachelectomy are adequate fertility sparing procedures for stage T1a1 and T1a2, lymph node negative, LVSI-negative patients.

B

Radical trachelectomy (type A) can be considered for stage T1a1 and T1a2, lymph node negative, LVSI-positive patients. Conisation or simple trachelectomy is an option.

B

Radical trachelectomy (type B) should be performed for patients with cervical cancer stage T1b1 \leq 2 cm of the largest diameter, lymph node negative, LVSI \pm .

✓

Intraoperative placement of permanent cerclage should be performed during simple or radical trachelectomy.

✓

FST in patients with tumours $>$ 2 cm cannot be recommended and is considered as an experimental approach.

✓

In more advanced cases, different propositions for fertility preservation should be discussed. The goal of the fertility preservation should be to offer the most efficient approach related to the legal aspects of the country while not increasing the oncological risk.

✓

Any pregnancy following FST should be considered as a high risk pregnancy and delivery should be performed in a perinatal centre. Following simple or radical trachelectomy with its inherent placement of a permanent cerclage delivery can be performed only by caesarean section.

✓

Routine hysterectomy after finishing fertility plans is not necessary.

CLINICALLY OCCULT CERVICAL CANCER DIAGNOSED AFTER SIMPLE HYSTERECTOMY

General recommendations

- ✓ Management of occult disease should be based on expert pathology review and discussed in a multidisciplinary tumour board.
- ✓ Prior to making further management decisions, optimal imaging to evaluate the local and regional (nodal) disease status is necessary. Optimal imaging follows the same recommendations as that for non-occult disease (see above).
- B** In general, management of occult disease follows the same principles as that of non-occult disease. Treatment strategy should aim for the avoidance of combining radical surgery and radiotherapy due to the highest morbidity after combined treatment.

Management of patients with pT1a1, LVSI ± and pT1a2 LVSI-negative, with clear margins

- ✓ In patients with tumour stage pT1a1 regardless of LVSI status and pT1a2 LVSI-negative with clear margins in the hysterectomy specimen, no additional treatment is recommended.

Management of patients with pT1a2 LVSI-positive or pT1b1 or pT2a1, with clear margins

- ✓ In patients with tumour stage pT1a2 LVSI-positive or pT1b1 or pT2a1 after simple hysterectomy, potential disease in the parametria and lymph nodes has to be addressed.
- D** Radiotherapy or chemoradiotherapy is recommended as an effective treatment option which avoids further surgery. In absence of residual tumour on imaging (including suspicious lymph nodes) radiotherapy alone is recommended. In case of residual tumour on imaging, including suspicious lymph nodes, chemoradiotherapy is recommended.
- C** Paraaortic lymph node dissection, at least up to inferior mesenteric artery, may be considered in patients without suspicious paraaortic nodes on imaging for staging purposes.
- ✓ Debulking of suspicious pelvic lymph nodes may be considered.

Management of patients with pT1a2 LVSI-positive or pT1b1 or pT2a1, with clear margins (continued)

- D** Radical surgery is an option in patients without lymph node involvement on imaging and in the absence of an upfront indication for adjuvant radiotherapy (combination of negative prognostic factors).
- ✓ Pelvic lymph node dissection should be performed as the first step of the surgery. Intraoperative assessment of pelvic lymph nodes may be considered. If intraoperative lymph node assessment is negative or it is not performed, radical parametrectomy with the resection of the upper vagina should be performed preferably using minimal invasive techniques. The type of radical parametrectomy (extent of parametrial resection) should be tailored to the presence of prognostic risk factors of the primary tumour as described above (*Table 2*).
- ✓ Complete description of the template used for radical parametrectomy should be present in the operative report.
- ✓ The 2017 modification of the Querleu-Morrow classification is recommended as a tool (*Table 3*).
- D** If lymph node involvement, including macrometastases or micrometastases, is detected intraoperatively, further surgery (pelvic lymph node dissection and radical parametrectomy) should be avoided and chemoradiotherapy is recommended.
- C** Paraaortic lymph node dissection, at least up to inferior mesenteric artery, may be considered for staging purposes.
- ✓ Debulking of suspicious nodes may be considered.

Management of patients with stage pT1b2 and higher or involved surgical margins or residual tumour including involved lymph node on imaging

- ✓ In patients with stage pT1b2 and higher, involved surgical margins or in those with residual tumour including involved lymph node on imaging, chemoradiotherapy is recommended and further surgery should be avoided.
- C** Paraaortic lymph node dissection, at least up to inferior mesenteric artery, may be considered for staging purposes in patients with negative paraaortic lymph nodes on imaging.
- ✓ Debulking of suspicious pelvic lymph nodes may be considered.

MANAGEMENT OF LOCALLY ADVANCED CERVICAL CANCER

Stage T1b2/T2a2 and negative lymph nodes on radiological staging

- B** Treatment strategy should aim for avoiding the combination of radical surgery and postoperative external radiotherapy, due to the significant increase of morbidity and no evident impact on survival.
- A** Definitive platinum-based chemoradiotherapy and brachytherapy is the preferred treatment (see Principles of radiotherapy).
- C** Paraaortic lymph node dissection, at least up to inferior mesenteric artery, may be considered before chemoradiotherapy and brachytherapy. Pelvic lymph node dissection is not required.
- ✓** Radical surgery is an alternative option, in particular in patients without negative risk factors (combinations of tumour size, LVSI, and/or depth of stromal invasion). Quality of surgery, both parametrectomy and lymph node dissection is, however, of key importance in the management of large tumours. Intraoperative assessment of lymph node status (frozen section) is recommended as the first step. If lymph node involvement is detected intraoperatively, including macrometastases or micrometastases, further pelvic lymph node dissection and radical hysterectomy should be avoided and patients should be referred for definitive chemoradiotherapy and brachytherapy. Paraaortic lymph node dissection, at least up to inferior mesenteric artery, may be considered for staging purposes. If intraoperative lymph node assessment is negative or it is not done, systematic pelvic lymph node dissection should be performed. Type C2 radical hysterectomy is recommended.
- C** Neoadjuvant chemotherapy followed by radical surgery is a controversial alternative. The benefit of tumour downsizing with regards to prognosis has not been proven.

Stage T1b2/T2a2 and involved lymph nodes on radiological staging

- A** Definitive chemoradiotherapy and brachytherapy is recommended in patients with unequivocally involved pelvic lymph nodes on imaging (see Principles of radiotherapy).
- C** An additional radiation boost to the involved lymph nodes should be applied (see principles of radiotherapy).
- C** Paraaortic lymph node dissection, at least up to inferior mesenteric artery, may be considered before treatment for staging purposes in patients with negative paraaortic lymph node on imaging.
- ✓** Debulking of suspicious pelvic lymph nodes may be considered.

Stages T2b, T3a/b, T4a

- A** Definitive platinum based chemoradiotherapy and brachytherapy is recommended (see Principles of radiotherapy).
- C** An additional radiation boost to the involved lymph nodes should be applied (see principles of radiotherapy).
- C** Paraaortic lymph node dissection, at least up to inferior mesenteric artery, may be considered before treatment in patients with negative paraaortic lymph nodes on imaging.
- ✓ Debulking of suspicious pelvic lymph nodes may be considered. Pelvic exenteration is an option in selected cases with stage T4N0M0 disease.

Cervical stump cancer

- ✓ Management of cervical stump cancer follows the recommendations for patients without previous subtotal hysterectomy. Adaptation of radiotherapy may be necessary, in particular for brachytherapy.

DISTANT METASTATIC DISEASE AT PRESENTATION

- ✓ Patients with distant metastatic disease at presentation should have a full diagnostic work up (see staging) to assess extent of disease, suitability for active treatment and treatment modality including best supportive care.
- B** In medically fit patients with widespread distant metastatic disease at presentation (visceral +/- nodal) combination chemotherapy is recommended. Carboplatin/paclitaxel or cisplatin/paclitaxel are preferred regimens in the first line treatment.
- B** Addition of Bevacizumab to standard chemotherapy is recommended in patients with good performance status and where the risk of significant gastrointestinal/genitourinary toxicity has been carefully assessed and discussed with the patient.
- D** Patients with limited distant metastatic disease at presentation, confined to the paraaortic lymph node, should be treated with curative intent with definitive extended field chemoradiotherapy including brachytherapy. Treatment algorithm may also include surgical debulking of enlarged lymph node and additional chemotherapy.
- ✓ Patients with supraclavicular lymph node as only site of distant disease can be considered for chemoradiotherapy with curative intent. Treatment algorithm may include additional chemotherapy.
- C** Adjuvant chemotherapy may be considered in cases carrying a high risk of recurrence such as positive margins, positive lymph node, or LVSI-positive tumours.
- ✓ The role of radiotherapy in palliating symptoms such as bleeding and pain must be considered especially in radiotherapy naive patients.

RECURRENT DISEASE

Curative intent treatment

- ✓ Treatment of recurrent disease with curative intent requires centralisation and involvement of a broad multidisciplinary team including gynaecological oncologist, radiation oncologist, radiologist, pathologist, medical oncologist, urologist and plastic surgeon. A structured programme for multidisciplinary diagnostic work-up, treatment and follow-up must be present in centres responsible for the treatment.
- ✓ Each centre involved in the primary treatment of cervical cancer should have an established network for discussion of difficult cases and willingness for referring patients with recurrence for treatment to highly specialised units.
- ✓ Participation in clinical trials is encouraged to improve the clinical evidence for the effect of curative treatment of recurrent disease.

Diagnostic work-up

- ✓ The aim of the diagnostic work up is to exclude distant metastases and locoregional tumour extension beyond curative treatment.
- ✓ The recurrence should be confirmed by histological examination.
- ✓ Patients with multiple nodal/distant metastases or multifocal local disease with extensive pelvic wall involvement are usually not considered candidates for curative treatment. The prognostic factors should be carefully evaluated and balanced in relation to the major morbidity caused by the treatment.
- ✓ A full diagnostic package consisting of relevant imaging is recommended to establish the status of the disease locally, regionally and systemically (see staging).
- ✓ Patient should be carefully counselled regarding not only treatment options but also the involved risks and consequences.

Central pelvic recurrence after primary surgery

- D** Definitive chemoradiotherapy combined with image guided adaptive brachytherapy is the treatment of choice (see Principles of radiotherapy). The use of boost by external beam techniques to replace brachytherapy is not recommended.
- ✓ For brachytherapy, small superficial lesions (i.e. < 5 mm thickness) in the vagina may be treated using a vaginal cylinder, ovoids or mould, while other lesions usually require combined intracavitary - interstitial techniques.

Pelvic sidewall recurrence after primary surgery

- D** Definitive chemoradiotherapy is the preferred option.
- ✓ Extended pelvic surgery may be considered in highly selected patients provided that the tumour does not invade extensively into the pelvic side wall.
- D** Combined operative-radiotherapy procedures using intraoperative radiotherapy or brachytherapy is an option if free surgical margins are not achievable.
- ✓ Definitive radiotherapy or chemoradiotherapy followed by a stereotactic ablative boost / image guided interstitial brachytherapy / particle beam therapy are emerging options.

Central pelvic or pelvic sidewall recurrence after radiotherapy or chemoradiotherapy

- D** Pelvic exenteration is recommended for central pelvic recurrence where there is no involvement of the pelvic side-wall and extra-pelvic nodes.
- ✓ Laterally extended endopelvic resection may be considered for a recurrence that extends close to or involves the pelvic side-wall.
- ✓ Reirradiation with image guided adaptive brachytherapy for central recurrences is an alternative option especially in patients unfit for or refusing exenteration surgery which should be restricted to highly supercentralised centres.

Role of chemotherapy

- ✓ If further surgery or radiotherapy is considered, no more than 2-4 courses of combination chemotherapy should be given to avoid unnecessary long interval before definitive treatment. Locoregional recurrences, which at diagnosis appear incurable should be reassessed for the possibility of radical treatment if major response is obtained.
- ✓ Suitable candidates for adjuvant chemotherapy are patients who recover well within 2 months after primary treatment for recurrence.

Nodal and oligo-metastatic recurrences

- ✓ Localised para-aortic, mediastinal and/or peri-clavicular recurrences above previously irradiated fields may be treated by radical external beam radiotherapy (EBRT) if possible in combination with concomitant chemotherapy. It is recommended to electively irradiate the immediate regional nodal stations below and up-stream.
- ✓ The therapeutic effect of nodal resection/debulking is unclear and should if possible always be followed by radiotherapy.
- ✓ The management of isolated organ metastases (lung, liver etc.) should be discussed in a multidisciplinary team involved in the treatment of the specific organ affected by the metastasis and should be treated according to the preferred method for that organ involving local resection, radiofrequency ablation, interventional brachytherapy or stereotactic ablative radiotherapy according to size and anatomical position.

Palliative treatment

- ✓ Recommendations for palliative treatment should only be made after a thorough review of the case by a specialist multidisciplinary team and taking into account the performance status, co-morbidities, patient's symptoms and wishes of the patient. The palliative care specialist should be actively involved.
- B** Palliative taxane/ platinum combination chemotherapy with /without bevacizumab is the preferred option.
- ✓ There is currently no standard second line chemotherapy and such patients should be considered for clinical trials.
- ✓ In symptomatic patients, palliative treatment should be tailored according to clinical situations.
- D** In patients with disseminated disease at presentation, radiotherapy (usually a fractionated course) should be considered for effective palliation.
- D** Palliative radiotherapy (single fraction / short course) to control bleeding, discharge and pain due to pelvic disease or bone metastases should be considered.
- ✓ For spinal cord compression due to bone metastases, neuro-surgical intervention or short course fractionated radiotherapy schedule should be considered.
- ✓ Surgical interventions including diversion stoma and / or stenting should be considered as appropriate e.g. in case of obstructive symptomatic disease.

FOLLOW-UP

General recommendations

- ✓ Primary objectives of follow-up for patients with cervical cancer should include:
 - Early detection of recurrent disease
 - Patient education and support
 - Cancer rehabilitation with the goal to prevent and reduce psychosocial, physical, social and existential consequences of cancer and its treatment starts at time of diagnosis. The efforts should optimize the physical abilities and quality of life of women affected by cervical cancer, and include family members/care givers. Several professions for counseling should be available e.g. psychologist, sexual therapist, physiotherapist, and dietitian
 - Assessment of long-term outcome of novel treatment strategies
 - Quality control of care
- ✓ Each visit should be composed of the following:
 - Patient history (including elicitation of relevant symptoms)
 - Physical examination (including a speculum examination and bimanual pelvic examination)
 - Physician assessment of adverse events using validated scales (e.g. Common Terminology Criteria for Adverse Events)
 - Prevention and management of cancer- and treatment-related side-effects e.g. sexual dysfunction (e.g. counseling, vaginal lubricants, local estrogen)
- ✓ In case of the appearance of treatment-related symptoms, a referral to a dedicated specialist (e.g. gastroenterologist, uro/gynaecologist) should be considered.
- ✓ Patients should be educated about symptoms of potential recurrence and potential long-term and late effects of treatment. Patients should also be counseled on sexual health, life-style adaptation, nutrition, exercise, obesity and cessation of smoking.
- C** Follow-up schemes may be individualized taking into account prognostic factors, treatment modality and estimated risk and/or occurrence of side-effects. In general, follow-up intervals of 3 to 4 (6) months for the first 2 years, and then 6 to 12 months up to five years are recommended.
- D** Prescription of hormonal replacement treatment to cervical cancer survivors with premature menopause is advocated, and should be according to regular menopausal recommendation. Combined estrogen and progestin replacement therapy should be prescribed if uterus is in situ (including after definitive radiotherapy). Monotherapy with estrogen is recommended after hysterectomy.
- ✓ Imaging and laboratory tests should be performed based on symptoms or findings suspicious for recurrence or morbidity.



In symptomatic women, MRI or CT should be considered to assess potential clinical recurrence. If positive, whole-body PET-CT should be performed in patients in whom salvage therapy (surgery or radiotherapy) is being considered. Similarly, for suspected recurrence PET-CT can be added when other imaging finding is equivocal.



Pathologic confirmation of any persistent or recurrent tumour should be considered. If a lesion is located deeply in the endocervix (in case of conservative treatment or definitive chemoradiotherapy), ultrasound guided tru-cut biopsy is the preferred method. For any disease beyond the primary tumour site, ultrasound or CT-guided methods can be used to achieve pathologic confirmation. In case of clinically or radiologically suspicious disease, a negative biopsy may not be conclusive.

Follow-up after fertility sparing treatment



All women remain at risk of tumour recurrence following FST and must be carefully followed-up. Follow-up should be carried out by a provider with specific expertise in detection of lower genital tract dysplasia (e.g. gynaecological oncologist, colposcopy expert).



Follow-up intervals should be 3 to 4 months for the first 2 years postoperatively, and then 6 to 12 months up to five years. Thereafter the patient may return to population-based screening. The duration of follow-up may however be individualized depending on the risk of recurrence or persistence of treatment-related complications.



Follow-up should include HPV testing (with or without cytology). Colposcopy in combination with HPV testing in parallel performed by an experienced colposcopist is an option. The incorporation of high-risk HPV testing at 6, 12 and 24 months after treatment is advocated. If HPV testing is negative, then every 3-5 years as long as follow-up is indicated.

Follow-up after simple or radical hysterectomy

- ✓ Follow-up should be carried out by physician experienced with follow-up care after surgery following the general recommendations (see above.). The vaginal vault cytology is not recommended.

Follow-up after definitive chemoradiotherapy

- ✓ The same imaging method should be used for evaluation of tumour response as was used at baseline.

- ✓ Imaging should be performed not earlier than 3 months following completion of treatment. In dubious cases, a re-evaluation should be performed not before 8 weeks thereafter.

- B** For re-evaluation purposes, the optimal diagnostic work-up for local extent is pelvic MRI, and for distant spread it is chest/abdomen CT or PET-CT (preferred after definitive chemoradiotherapy or in high risk patients).

- ✓ Follow-up should be performed by a physician experienced with follow-up care after radiotherapy. Cytology is not recommended in these patients.

- ✓ Providers should inform and educate on sexual and vaginal health since vaginal stenosis and dryness may occur. Vaginal dilation should be offered, as well as vaginal lubricants and local estrogen.

CERVICAL CANCER IN PREGNANCY

✓ Every patient diagnosed with cervical cancer in pregnancy (CCIP) must be counselled by an multidisciplinary team. This team should consist of experts in the fields of gynaecological oncology, neonatology, obstetrics, anesthesiology, radiation oncology, medical oncology, psychooncology and, if requested, theology or ethics.

✓ Given the large spectrum of described therapeutic options the multidisciplinary team recommends an individual consensual treatment plan according to patients intention, tumour stage and gestational age of pregnancy at cancer diagnosis. Primary aims of recommended treatment plan are oncological safety of the pregnant woman as well as survival without additional morbidity of the fetus.

✓ Treatment of patients with CCIP should exclusively be done in gynaecological oncology centres associated with a highest level perinatal centre with expertise in all aspects of oncologic therapy in pregnancy and intensive medical care of premature neonates. Due to the low incidence of CCIP, centralisation in a few well equipped facilities is compulsory.

D Besides clinical examination and histologic verification of invasive cervical cancer preferred imaging modalities for clinical staging in patients with CCIP include MRI or expert ultrasound. Due to limited experience and inherent radioactivity PET-CT (PET-MRI) should only be indicated under very selected circumstances.

✓ Tumour involvement of suspicious nodes should be verified histologically due to its prognostic significance and the impact on the management up to 24th week of gestation (fetal viability), preferable by minimal invasive approach.

D Depending on tumour stage and gestational week of pregnancy following treatment options have to be discussed with the patient including risks and benefits of individual approaches:

- Adapted surgery including removal of the tumour: conisation, trachelectomy and lymph node staging (see above) according to the stage of the disease with the intent to preserve the pregnancy.
- Radical surgery or definitive chemoradiation as recommended for the stage of the disease without preservation of the pregnancy, with or without previous pregnancy termination.
- Delay of oncological treatment until fetal maturity (if possible >32 week of gestation) and beginning of cancer specific treatment immediately after delivery by caesarean section.
- Chemotherapy until fetal maturity and beginning of cancer specific treatment immediately after delivery by caesarean section. Treatment after delivery must consider application of previous chemotherapy. In patients with locally advanced stage or with residual tumour after conisation that cannot be completely excised (risk of premature rupture of membranes and/or cervical insufficiency) platinum-based chemotherapy can be considered starting earliest at 14 weeks of gestation.

D

Spontaneous delivery seems to have negative prognostic impact in patients with CCIP. Thus, caesarean section after 32th week of gestation (if possible) is the recommended mode of delivery. At the time of or following caesarean section definitive stage adjusted oncologic therapy has to be performed corresponding to that of non pregnant women taking into account therapy which has already been given during pregnancy.

PRINCIPLES OF RADIOTHERAPY

Definitive chemoradiotherapy and brachytherapy: general aspects

Definitive management (without tumour related surgery) consists of concomitant pelvic chemoradiotherapy (platinum based) and brachytherapy or pelvic EBRT alone and brachytherapy.

Overall treatment time for the definitive treatment should not exceed 7-8 weeks.

Delay of treatment and/or treatment interruptions have to be avoided.

Definitive chemoradiotherapy

EBRT is recommended minimum as 3D conformal radiotherapy. The preferred treatment is intensity-modulated radiotherapy (IMRT) due to the more conformal dose distribution that maximizes sparing of organs at risk.

EBRT can be applied as concomitant chemoradiotherapy with total dose of 45-50 Gy (1.8 Gy per fraction) and single agent radio-sensitizing chemotherapy, preferably cisplatin (weekly 40mg/m²) so that definitive radiotherapy is not compromised. If cisplatin is not applicable, alternative treatment options are fluorouracil (5FU) or carboplatin. EBRT may also be applied without concomitant chemotherapy according to treatment selection (i.e. patients unfit for any chemotherapy). In such cases regional hyperthermia may be considered.

Tumour and lymph node related target volume for IMRT includes the primary cervical tumour and the adjacent tissues such as parametria, uterine corpus, upper vagina and the pelvic lymph nodes (obturator, internal, external and common iliac, pre-sacral). In case of pelvic lymph node involvement indicating an increased risk of para-aortic lymph node spread, EBRT may include the paraaortic region up to the renal vessels (45 Gy). In case of paraaortic lymph node involvement, target volume includes minimum the region up to the renal vessels.

A reduced target volume for EBRT resulting in a small pelvic field not including the common iliac nodes may be considered in low and intermediate risk T1b1 patients with negative lymph nodes on imaging and no LVSI.

Boost treatment for involved lymph node(s) may be applied as simultaneous integrated boost within the IMRT treatment or as sequential boost. The total dose including the contribution from brachytherapy should be 55-60 Gy (equi-effective dose to 2 Gy per fraction (EQD2)). An alternative treatment option is surgical debulking of enlarged nodes.

Image guided radiotherapy (IGRT) is recommended for IMRT to ensure safe dose application in the tumour related targets, to account for motion uncertainties, to reduce margins and to achieve reduced doses to organs at risk.

Overall treatment time for EBRT should not exceed 5-6 weeks.

Definitive brachytherapy

Image guided adaptive brachytherapy (IGABT) is recommended, preferably using MRI at the time of brachytherapy. IGABT is delivered in large tumours towards the end of or after concomitant chemoradiotherapy. Repeated gynaecological examination is mandatory and alternative imaging modalities such as CT and ultrasound may be used.

The tumour related targets for brachytherapy include the residual gross tumour volume (GTV-T_{res}) after chemoradiotherapy, the adaptive high risk clinical target volume (CTV-T_{HR}) including the whole cervix and residual adjacent pathologic tissue and the intermediate risk clinical target volume (CTV-T_{IR}).

Intracavitary and combined intracavitary/interstitial brachytherapy should be performed under anaesthesia.

The brachytherapy applicator should consist of a uterine tandem and a vaginal component (ovoids/ring/mould/combined ring/ovoid). Combined intracavitary/interstitial brachytherapy for adjusting the application further to the individual target should be considered. The vaginal component carries holes for straight or oblique needle guidance into the parametria.

In case of significant residual disease in the parametrium (as in any extra-cervical area, e.g. vagina, uterine corpus, adjacent organ) this should become part of the CTV-T_{HR}. The brachytherapy application should be a combined intracavitary/interstitial approach in order to achieve a sufficiently high radiation dose in the whole CTV-T_{HR}.

In IGABT the planning aim should be to deliver a brachytherapy dose of 40-45 Gy (EQD2) to reach a total EBRT+ brachytherapy dose of $\geq 85-90$ Gy EQD2 (D90) (assuming 45 Gy through EBRT) to the CTV-T_{HR}, ≥ 60 Gy (D98) to the CTV-T_{IR}, and ≥ 90 Gy (D98) to the GTV-T_{res}. 3D and 2D dose volume and point constraints for rectum, bladder, vagina, sigmoid and bowel are recommended and they have to be based on the published clinical evidence.

Point A dose normalization should be used as starting point for step-wise treatment plan optimization, although point A dose reporting and prescription has been extended by the volumetric approach.

Brachytherapy should be delivered in several fractions as high dose rate (usually 3-4) or in 1-2 fractions as pulse dose rate brachytherapy.

In large tumours brachytherapy should be delivered within 1-2 weeks towards the end of or after chemoradiotherapy. In limited size tumours brachytherapy may start earlier during chemoradiotherapy.

For the tumour related targets (GTV-T_{res}, CTV-T_{HR}, CTV-T_{IR}) the use of external beam therapy for giving extra dose (e.g. parametrial boost, cervix boost) is discouraged, even when using advanced EBRT technology such as stereotactic radiotherapy. The use of a midline block for boosting the parametrium is discouraged when applying advanced image guided radiotherapy, in particular beyond 45 to 50 Gy.

Care should be taken to optimize patient comfort during (fractionated) brachytherapy. Preferably this includes a multidisciplinary approach.

Adjuvant radiotherapy or chemoradiotherapy

Adjuvant radiotherapy or chemoradiotherapy follows analogue principles for target selection and dose and fractionation as outlined for definitive treatment.

The application of IMRT and IGRT is to be considered as treatment related morbidity may be reduced.

Adjuvant (additional) brachytherapy should only be considered, if a well-defined limited area - accessible through a brachytherapy technique - is at high risk of local recurrence (e.g. vagina, parametrium). Such adjuvant brachytherapy should follow the major principles outlined above for image guided brachytherapy.

Definitive 3D conformal EBRT or chemoradiotherapy and radiography based brachytherapy

3D conformal radiotherapy alone or as definitive concomitant chemoradiotherapy (platinum based) ± paraaortic radiotherapy and/or 2D radiography based brachytherapy is recommended, if IMRT and/or IGABT are not available.

In case of 3D conformal radiotherapy and/or radiography based brachytherapy the recommendations for EBRT and IGABT as outlined above in regard to target, dose, fractionation and overall treatment time have to be respected as much as possible.

A sequential lymph node boost is applied as appropriate after completion of 3D EBRT.

Planning aim for brachytherapy should be based on point A. Dose to point A should be ≥ 75 Gy (EQD2) in limited width adaptive CTV-T_{HR} (≤ 3 cm) and should aim at higher doses in large width adaptive CTV-T_{HR} (>4 cm). In addition, dose for the maximum width of the adaptive CTV-T_{HR} should be reported. Radiography based dose point constraints - plus 3D dose volume constraints as available - for rectum, bladder, vagina, sigmoid and bowel are recommended and they have to be based on the published clinical evidence.

PRINCIPLES OF PATHOLOGICAL EVALUATION

Requirements for specimen submitted for pathological evaluation

Patient information, previous cervical cytology, histological specimens, clinical, and radiological data and colposcopic findings need to be included on the specimen request form.

Details of cytology, biopsy and surgical specimen (cone/loop specimen, trachelectomy, type of hysterectomy, presence of ovaries and fallopian tubes, presence of lymph nodes and designation of the lymph node sites, presence of vaginal cuff, and presence of parametria) need to be itemized in the specimen request form.

Biopsies and surgical specimens should be sent to the pathology department in a container with liquid fixative ("clamping" of the specimen on cork may be done).

Cytology specimens should be sent to the pathology department either as a smear preparation (exfoliative cytology on a clearly designated and identifiable slide with patient's name and birth date) or as liquid based cytology. The latter is necessary when an HPV test is requested.

Cone/loop specimen should ideally be sent intact with a suture to identify the 12 o'clock position.

Specimen grossing and sampling

Small biopsy specimens should be enumerated and measured.

The diameter (two dimensions) and depth of cone/loop specimens should be measured. It should be recorded if the specimen is complete or fragmented. If more than one piece of tissue is received, every piece should be measured in three dimensions and entirely examined.

Inking of the surgical margins of cone/loop specimens is optional.

Dissection of cone/loop specimens should be performed in an appropriate fashion. All the pieces submitted should be in consecutive numerical order. This is important since if tumour is present in more than one piece, it needs to be known whether these are consecutive pieces and thus a single tumour or represents multifocal tumour. It is recommended to place only one piece of tissue in each cassette. There are also techniques which allow embedding of more than one piece in a cassette if they are small enough. In cases which do not comprise intact cone/loops, serial radial sectioning and placing of each slice of tissue in a single cassette should be performed.

The description of the specimen (hysterectomy, trachelectomy, presence of ovaries and fallopian tubes, presence of lymph nodes and indication of the lymph node sites, presence of vaginal cuff, presence of parametria) should be recorded and checked for consistency with the description given in the specimen request form.

The presence of any gross abnormality in any organ should be documented.

The dimensions of the uterus for a hysterectomy specimen and the cervix for a trachelectomy specimen should be documented.

The minimum and maximal length of the vaginal cuff should be documented.

The size of the parametria should be documented in two dimensions (vertical and horizontal).

Gross tumour involvement of the parametrium, vagina, uterine corpus or other organs should be documented. The relationship of the cervical tumour to the vaginal and parametrial margins (and upper margin in case of a trachelectomy specimen) should be measured and appropriate sections taken to demonstrate this.

Parametrial and vaginal margins should be inked.

Parametria should be submitted totally for histological examination.

The upper surgical margin of a trachelectomy specimen should be inked.

The upper margin of a trachelectomy specimen should be sampled in its entirety in a way that demonstrates the distance of the tumour to the margin. The vaginal margin should be examined totally as radial sections if no tumour is seen grossly.

When the tumour is small (or with tumours which cannot be identified macroscopically), the cervix should be separated from the corpus, opened and processed as for a cone/loop specimen.

In the case of a large tumour, the hysterectomy or trachelectomy specimen should be opened in the sagittal plane.

The description of the cervix and measurement of any gross tumour mass should be documented.

Gross tumours should be measured in three dimensions, namely two measurements of horizontal extent and the depth of invasion.

The tumour site within the cervix should be documented.

The cervical tumour should be sampled in order to demonstrate the maximum depth of invasion, the relationship of the tumour with the surgical borders and the extension to other organs.

If visible, the site of a previous cone biopsy should be documented.

At least one block per centimeter of the greatest tumour dimension for large tumours should be taken.

Additional blocks including the cervix adjacent to the tumour should be taken in order to demonstrate precursor lesions.

The whole cervix should be sampled in the case of a small tumour or where no macroscopic tumour is identified.

The uterine corpus, vagina and adnexa should be sampled according to standard protocols if not involved by tumour. If the uterine corpus and/or adnexa are grossly involved, additional blocks should be sampled.

The entire vaginal margin should be blocked.

All the lymph nodes should be submitted for histological examination. If the lymph nodes are grossly involved, representative samples are sufficient. If grossly uninvolved, each node should be sliced at 2 mm intervals and totally embedded. From each block haematoxylin and eosin (H&E) sections should be taken. Lymph nodes should be submitted in separate cassettes according to the site recorded on the specimen request form.

Pathological analysis of sentinel lymph node

Intraoperative assessment should be performed on a grossly suspicious sentinel node and may be performed on a “non-suspicious” sentinel lymph node(s) since the confirmation of tumour involvement will result in abandoning a hysterectomy or trachelectomy.

For intraoperative evaluation the sentinel lymph node(s) need to be sent to the pathology department in a container without liquid fixative.

Intraoperative analysis requires gross dissection of the resected adipose tissue by the pathologist with the selection of the lymph node(s).

For a lymph node with obvious gross tumour, a single section is adequate for frozen section.

Frozen section may be combined with imprint cytology.

Any non-suspicious sentinel node should be bisected (if small) or sliced at 2 mm thickness and entirely frozen.

From each sample, histological sections should be cut and stained by H&E.

After frozen section analysis the tissue should be put into a cassette, fixed in liquid fixative and subsequently processed and embedded in paraffin.

Sentinel lymph node(s) tissue blocks should be entirely analysed by examining multiple serial sections at different levels with H&E stains. Cytokeratin stains should be performed on all blocks.

The detection of micrometastases and isolated tumour cells should be improved by immunohistochemistry with pancytokeratin antibodies (e.g. AE1/AE3). Different procedures have been published and there is no standard method. Cytokeratin positive cells should always be correlated with the morphology. Müllerian inclusions (endosalpingiosis, endometriosis) and mesothelial cells may rarely be present in pelvic and para-aortic lymph nodes and be cytokeratin positive.

Requirements for pathology report

Description of the specimen(s) submitted for histological evaluation.

Macroscopic description of specimen(s) (biopsy, loop/cone, trachelectomy, hysterectomy) including specimen dimensions (three dimensions), number of tissue pieces for loop/cones, maximum and minimum length of vaginal cuff and the parametria in two dimensions.

Macroscopic tumour site(s), if the tumour is visible grossly, in trachelectomy and hysterectomy specimens.

Tumour dimensions including two measurements of horizontal extent and depth of invasion or thickness (tumour dimension should be based on a correlation of the gross and histological features). When multifocal separate tumours are present, each should be described and measured separately and the largest used for tumour staging. Specimens from prior conisation and subsequent conisation, trachelectomy or hysterectomy should be correlated for estimation of the tumour size. This is of importance since different specimens may have been reported at different institutions. It should also be recognized that simply adding together the maximum tumour size in separate specimens may significantly overestimate the maximum tumour dimension.

Histological tumour type and tumour grade.

The presence or absence of LVSI.

Coexisting pathology (squamous intraepithelial lesion/cervical intraepithelial neoplasia, adenocarcinoma in situ, stratified mucin-producing intra-epithelial lesion).

Minimum distance of uninvolved cervical stroma.

Margin status (invasive and preinvasive diseases). Specify the margin(s).

Lymph node status including sentinel lymph node status, the total number of nodes found and the number of positive lymph nodes and the presence of extranodal extension (list for all separate sites). Micrometastasis (greater than 0.2 mm and up to 2 mm) are reported as pN1(mi). Isolated tumour cells no greater than 0.2 mm in regional nodes should be reported as pN0 (i+).

Pathologically confirmed distant metastases.

Provisional pathological staging pre-tumour board/multidisciplinary team meeting (AJCC 8th edition).

Items to be included on pathology report of carcinomas of the cervix

CLINICAL/SURGICAL	MACROSCOPIC	MICROSCOPIC
Specimen(s) submitted	<p>Specimen dimensions</p> <ul style="list-style-type: none"> • Number of tissue pieces (for loops/cones). • Tissue piece dimensions (for loops/cones). <ul style="list-style-type: none"> ○ Diameter of ectocervix (two measurements). ○ Depth of specimen. • Vaginal cuff. <ul style="list-style-type: none"> ○ Minimum length. ○ Maximum length. • Size of parametria in two dimensions (vertical and horizontal). <p>Macroscopic tumour site(s)</p>	<p>Tumour dimensions*</p> <ul style="list-style-type: none"> • Horizontal extent (two measurements). • Depth of invasion or thickness. <p>Histological tumour type</p> <p>Histological tumour grade</p> <p>LVSI</p> <p>Coexisting pathology</p> <ul style="list-style-type: none"> • Squamous intraepithelial lesion/cervical intraepithelial neoplasia. • Adenocarcinoma in situ. • Stratified mucin-producing intraepithelial lesion. <p>Minimum distance of uninvolved cervical stroma</p> <p>Margin status (invasive and preinvasive diseases). Specify the margin(s)</p> <p>Lymph nodes status (sentinel lymph node status, number involved/number retrieved and presence of extra-nodal extension)</p> <p>Pathologically confirmed distant metastases</p> <p>Pathological staging pre-tumour board/multidisciplinary team meeting (TNM category)</p>
* Tumour dimension should be based on a correlation of the gross and histological features		

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