



CERVICAL CANCER

GUIDELINES

- Complete report -

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1 Introduction

Cervical cancer is uncommon in Europe but still represents a major public health problem¹. The estimated number of new cervical cancer cases in Europe in 2012 was 58 348 with 24 397 deaths². Five-year relative survival for European women diagnosed with cervical cancer in 2000-2007 was 62%, ranging from 57% in Eastern Europe to 67% in Northern Europe. Survival was particularly low (<55%) in Bulgaria, Latvia and Poland and highest in Norway (71%)³. The large geographic variation in cervical cancer rates reflects differences in the availability of screening and in human papillomavirus (HPV) infection prevalence. In countries with a low incidence of cervical cancer, the prevalence of chronic HPV is approximately two folds lower than in high-incidence countries. Other epidemiologic risk factors associated with cervical cancer are notably a history of smoking, parity, oral contraceptive use, early age of onset of coitus, larger number of sexual partners, history of sexually transmitted disease, certain autoimmune diseases, and chronic immunosuppression. Squamous cell carcinomas account for approximately 80% of all cervical cancers and adenocarcinoma accounts for approximately 20%.

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 gynecologic oncologists, general gynaecologists, surgeons, radiation oncologists, pathologists, medical and clinical oncologists, radiologists, general practitioners, palliative care teams, and allied health professionals. The guidelines aim at covering comprehensively staging, management, and follow-up for patients with cervical cancer. Management includes fertility sparing treatment (FST); stage T1a, T1b1/T2a1, clinically occult cervical cancer diagnosed after simple hysterectomy; early and locally advanced cervical cancer (LACC); primary distant metastatic disease; cervical cancer in pregnancy (CCIP); and recurrent disease. Algorithms presenting guidelines for the management of patients with cervical cancer are available online at the Web sites of the European Society of Gynaecological Oncology, the European Society for Radiotherapy and Oncology, and the European Society of Pathology. These guidelines exclude the management of neuroendocrine carcinomas, sarcomas, and other rare histologic subtypes. 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.

2 Acknowledgements

The European Society of Gynaecological Oncology (ESGO) would like to thank the European Society for Radiotherapy and Oncology (ESTRO), the European Society of Pathology (ESP), and the international development group for their constant availability, work, and for making possible the development of these guidelines for the management of patients with cervical cancer. ESGO also wishes to express sincere gratitude to the Institut national du cancer (France) for providing the main funding for this work.

3 Method

The guidelines were developed using a five-step process (see Figure 1). The strengths of the process include creation of a multidisciplinary international development group, use of scientific evidence and/or international expert consensus to support the guidelines, and use of an international external review process (physicians and patients). This development process involved three meetings of the international development group, chaired by Professor David Cibula (Charles University Hospital, Prague, Czech Republic), Professor Richard Poetter (Vienna General Hospital, Vienna, Austria) and Professor Maria Rosaria Raspollini (University Hospital, Careggi - Florence, Italy).

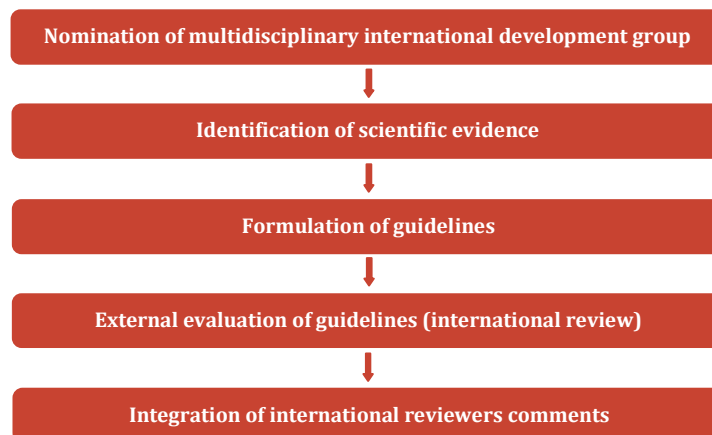


Figure 1. Development process

3.1 Nomination of multidisciplinary international development group

The ESGO/ESTRO/ESP nominated practicing clinicians that are involved in the management of cervical cancer patients and have demonstrated leadership in clinical management of patients through research, administrative responsibilities, and/or committee membership to serve on the expert panel. The objective was to assemble a multidisciplinary panel. It was therefore essential to include professionals from relevant disciplines (surgery, medical oncology, pathology, radiology, gynaecology, radiation oncology) to contribute to the validity and acceptability of the guidelines. The list of the development group is available in Appendix 1.

3.2 Identification of scientific evidence

To ensure that the statements were evidence based, the current literature was reviewed and critically appraised. A systematic literature review of relevant studies published between January 1997 and January 2017 was carried out using the MEDLINE database. This search used indexing terms as follows: 5-fluorouracil (5-FU), abdominal trachelectomy, abdominal radical trachelectomy, advanced cervical cancer, advanced cervical disease, advanced disease, advanced stage, biomarker, bleomycin, cancer antigen 125 (CA 125), cancer antigen 15-3 (CA 15-3), carboplatin, carcinoembryonic antigen (CEA), cervical cancer, cervix cancer, circulating immune complexes (CIC), cisplatin, cis-diamminedichloroplatinum, cis-platinum, clinical staging, clinically occult carcinoma, cold knife conisation (CKC), complications, computed tomography (CT), cone biopsy, cone resection, cone resection margins, conisation, cryopreservation, cytokeratin fragment 21-1 (CYFRA 21-1), destructive techniques, excisional techniques, external beam radiotherapy (EBRT), fertility, fertility outcome, fertility preservation, fertility sparing, fertility sparing management, fertility sparing surgery (FSS), Fédération Internationale de Gynécologie et d'Obstétrique (FIGO), FIGO staging system, follow-up, follow-up protocols, frozen sections, FST, gestation, high sensitivity C-reactive protein (hsCRP), HPV testing, hysterectomy, image guided adaptive brachytherapy (IGABT), image guided radiotherapy (IGRT), imaging, imaging modalities, immunosuppressive acidic protein (IAP), intensity modulated radiotherapy (IMRT), intensive care, intensive care unit, interleukin 6 (IL-6), LACC, laparoscopic staging, laparoscopy, laparotomy, large loop excision of the transformation zone (LLETZ), laser ablation, laser ablation-destruction, laser conisation, laser conisation-excision, laser destruction, length of stay, LACC, locally advanced cervical disease, locally advanced disease, locally advanced stage, loop electrosurgical excision procedure (LEEP), lymphadenectomy, lymph node (LN), LN assessment, LN dissection, LN staging, lymphovascular space involvement (LVSI), magnetic resonance imaging (MRI), metastatic disease, microinvasive cancer, microinvasive cervical cancer, mortality rate, mortality analysis, multivariate analysis, neoadjuvant chemotherapy (NACT), neonatal intensive care unit

(NICU) admission, nerve-sparing radical surgery, nerve-sparing robotic radical hysterectomy, nodal involvement, obstetric outcomes, occult carcinoma, occult invasive carcinoma, occult invasive cervical cancer, oncologic outcome, ovarian preservation, ovarian transplantation, ovarian transposition (OT), oxaliplatin, paclitaxel, para-aortic lymphadenectomy, para-aortic lymph node (PALN) assessment, para-aortic lymph node dissection (PALND), pathology, pathology report, pathology report adequacy, pelvic lymph node (PLN) assessment, pelvic lymph node dissection (PLND), pelvic lymphadenectomy, perioperative care, physical examination, platinum, positron emission tomography (PET), positron emission tomography-computed tomography (PET-CT), postoperative care, postoperative complications, postoperative recurrence, pregnancy, preterm spontaneous rupture of membranes (pPROM), preoperative brachytherapy, pregnancy, pregnancy rate, pregnant patient, preoperative care, preoperative workup, prognosis, prognostic factor, quality of health care, quality of life, radical abdominal trachelectomy, radical surgery, radical trachelectomy, radical vaginal trachelectomy, recurrence, recurrent disease, reoperation, reproduction, reproductive techniques, residual disease, residual tumour, restaging, risk factors, robotic radical hysterectomy, sensitivity, sentinel lymph node (SLN), SLN procedure, sentinel node (SN), serum biomarker, serum marker, specificity, simple trachelectomy, squamous cell carcinoma antigen (SCC-Ag), staging, staging procedures, surgery, surgical management, surgical outcome, surgical outcome criteria, surgical procedures, surgical resection, surveillance, survival rate, survival analysis, tissue polypeptide antigen (TPA), TNM classification, total laparoscopic radical trachelectomy, trachelectomy, transplantation, transposition, treatment outcome, tumour-associated trypsin inhibitor (TATI), tumour necrosis factor alpha (TNF- α), ultrastaging, ultrasound (US), upstaging, uterine cervix cancer, uterine transplantation, vaginal radical trachelectomy, vaginal trachelectomy, vascular space involvement, vascular endothelial growth factor (VEGF), vincristine.

The literature search was limited to publications in English. Priority was given to high-quality systematic reviews, meta-analyses, and randomized controlled trials (RCTs) but lower levels of evidence were also evaluated. The search strategy excluded editorials, letters, and *in vitro* studies. The reference list of each identified article was reviewed for other potentially relevant papers. The bibliography was also supplemented by additional references provided by the international development group. Another bibliographic search was carried out to identify previous initiatives using a systematic literature search in MEDLINE database (no restriction in the search period, indexing terms: clinical practice guidelines, evidence-based medicine, guidelines, methodology, recommendations, cervical cancer) and a bibliographic search using selected websites (see Appendix 2). After the selection and critical appraisal of the articles, a summary of the scientific evidence was developed.

3.3 Formulation of guidelines

The development group developed guidelines for staging, FST, management (stage T1a, T1b1/T2a1, clinically occult cervical cancer diagnosed after simple hysterectomy, LACC, primary distant metastatic disease, CCIP, and recurrent disease), and follow-up for patients with cervical cancer. The guidelines were retained if they were supported by sufficient high level scientific evidence and/or when a large consensus among experts was obtained. If an approach is judged to be acceptable but is not unanimously recognized as a criterion-standard clinical approach, indication is given that it is 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 (expert agreement). The reliability and quality of the evidence given throughout this document has been graded following the Scottish intercollegiate guidelines network (SIGN) grading system (see Appendix 3). Principles of radiotherapy and principles of pathological evaluation were also defined.

3.4 External evaluation of the guidelines - International review

The ESGO/ESTRO/ESP consulted a large panel of practicing clinicians that are involved in the management of cervical cancer patients. Cervical cancer patients were also included. The objective was to assemble a multidisciplinary panel. The 159 international reviewers were independent from the

development group. International reviewers were asked to evaluate each guideline according to their relevance and feasibility in clinical practice (only physicians). Quantitative and qualitative evaluations of the guidelines were performed. Patients were asked to qualitatively evaluate each guideline (according to their experience, preferences, feelings, etc.). The list of international reviewers is available in Appendix 1.

3.5 Integration of international reviewers comments

Responses of the 159 external reviewers were pooled and discussed by the development group to finalize the guidelines.

4 Management of conflicts of interest

The experts of the multidisciplinary international development group were required to complete a declaration of interest form, and to promptly inform the ESGO council if any change in the disclosed information occurred during the course of this work.

5 Summary of guidelines

5.1 General recommendations

- ✓ Treatment planning should be made on a multidisciplinary basis (generally at a tumor board meeting) and based on 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 gynecologic cancers.

5.2 Staging

5.2.1 TNM classification and FIGO

- ✓ Patients with cervical cancer should be staged according to the TNM classification. Clinical staging (FIGO) should also be documented (Figure 2).
- 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 tumor status (T), lymph node status (N), and systemic status (M), that is, clinical (c), imaging (i), and/or pathological (p) should be recorded.
- ✓ LN metastases should be classified according to the TNM classification (see Principles of pathological evaluation).

5.2.2 Prognostic factors

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

5.2.3 Local clinical and radiological diagnostic workup

- ✓ Pelvic examination and biopsy +/- colposcopy are mandatory components to diagnose cervical cancer.
- B Mandatory initial workup for assessment of pelvic tumor extent and to guide treatment options is pelvic MRI.
- ✓ Endovaginal/transrectal US 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 US.

5.2.4 Nodal/distant diagnostic workup

B

In early stage (T1a, T1b1, T2a1), surgical/pathological staging of PLNs is the criterion standard to assess the prognosis and guide treatment (except of T1a1 and no LVSI).

B

In LACC (T1b2 and higher (except T2a1)) or in early-stage disease with suspicious LNs on imaging, PET-CT, or chest/abdomen 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

PALN dissection, at least up to inferior mesenteric artery, may be considered in LACC with negative PALNs 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 because it allows histological assessment of the tissue.

Figure 2. FIGO staging and TNM classification

T category ⁴	FIGO stage ⁵⁻⁷	Definition
TX		Primary tumour cannot be assessed
T0		No evidence of primary tumour
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	Tumour 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	Tumour with parametrial invasion
T3	III	Tumour extending to the pelvic sidewall* and/or involving the lower third of the vagina and/or causing hydronephrosis or nonfunctioning kidney
T3a	IIIA	Tumour involving the lower third of the vagina but not extending to the pelvic wall
T3b	IIIB	Tumour extending to the pelvic wall and/or causing hydronephrosis or nonfunctioning kidney
T4	IVA	Tumour invading the mucosa of the bladder or rectum and/or extending beyond the true pelvis (bullous edema is not sufficient to classify a tumour as T4)
	IVB	Tumour invading distant organs

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

5.3 Management of stage T1a

5.3.1 Diagnosis of stage T1a disease

- ✓ Diagnosis of T1a cancer should be based on a conization (or excision) specimen examined by an expert pathologist. Management must be based on an expert pathology review, with accurate measurement of the maximum horizontal 2 dimensions, depth of invasion, margin status, coexisting pathology, and reliable assessment of LVSI.
- ✓ Loop or laser conization is preferable to CKC in women desiring fertility preservation. Maximum care should be taken to provide an intact (unfragmented) specimen with minimal thermal artifact. 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).

5.3.2 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 conization should be performed to rule out more extensive invasive disease.
- B LN staging is not indicated in T1a1 LVSI-negative patients but can be considered in T1a1 LVSI-positive patients. SLN biopsy (without additional PLN dissection) is an acceptable method of LN staging.
- C Conization 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.

5.3.3 Management of stage T1a2 disease

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

5.4 Management of stages T1b1/T2a1

5.4.1 General recommendation

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

5.4.2 Negative lymph nodes on radiological staging

5.4.2.1 *Surgical treatment*

B Radical surgery by a gynecologic oncologist is the preferred treatment modality. Minimally invasive approach is favored.

B The standard LN staging procedure is systematic pelvic lymphadenectomy. SN biopsy before pelvic lymphadenectomy is strongly recommended. Combination of blue dye with radiocolloid or use of indocyanine green alone is the recommended technique.

✓ LN assessment should be performed as the first step of surgical management. Intraoperative assessment of LN status (frozen section) is recommended. All SNs from both sides of the pelvis and/or any suspicious LNs should be sent for frozen section. If SN is not detected, intraoperative assessment of the PLNs should be considered.

✓ If intraoperative LN assessment is negative or not done, systematic PLN dissection should be performed. At present, SN biopsy alone cannot be recommended outside prospective clinical trials. Systematic LN dissection should include the removal of lymphatic tissue from regions with the most frequent occurrence of positive LNs (SNs) including obturator fossa, external iliac regions, common iliac regions bilaterally, and presacral region. Distal external iliac LNs (so-called circumflex iliac LNs) should be spared if they are not macroscopically suspicious.

✓ The type of radical hysterectomy (extent of parametrial resection, type A-C2) should be based on the presence of prognostic risk factors identified preoperatively (Figure 3). Major prognostic factors for oncological outcome as tumor size, maximum stromal invasion, and LVSI are used to categorize patients at high, intermediate, and low risk of 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 (Figure 4).

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

C If LN involvement is detected intraoperatively including macrometastases or micrometastases, further PLN dissection and radical hysterectomy should be avoided. Patients should be referred for definitive chemoradiotherapy. PALN 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. PLN dissection should be avoided. PALN dissection, at least up to inferiormesenteric artery, may be considered in patients with negative PALN on imaging.

Figure 3. 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 Figure 4)

Figure 4. Querleu-Morrow classification⁸

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

5.4.2.2 *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 centers. It is an acceptable alternative option only in teams experienced in this approach.

C NACT followed by surgery is not recommended.

5.4.3 Positive pelvic lymph nodes on radiological staging

C

In patients with unequivocally involved PLNs on imaging, definitive chemoradiotherapy is recommended (see Principles of radiotherapy). PALN dissection, at least up to inferior mesenteric artery, may be considered in patients with negative PALNs on imaging.

✓

Debulking of suspicious PLNs may be considered.

5.4.4 Adjuvant treatment

B

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

✓

When in these situations an adequate type of radical hysterectomy has been performed (Figure 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 PLNs, including the presence of macrometastases pN1 or micrometastases pN1(mi) in either SN or any other PLNs detected by intraoperative or final pathologic assessment ⇒ chemoradiotherapy
- positive surgical margins (vagina/parametria) ⇒ chemoradiotherapy, brachytherapy boost may be considered
- parametrial involvement ⇒ chemoradiotherapy

5.4.5 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.

5.5 Fertility sparing treatment

✓

Before starting FST, consultation at a fertility center is recommended.

✓

FST should exclusively be undertaken in gynecologic-oncological centers with comprehensive expertise in this kind of oncologic therapy.

✓

For patients who consider FST, prognostic factors, clinical staging, and preoperative workup 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 equal to or less than 2 cm of the largest diameter should be counseled about the possibility of FST. This consultation should encompass the risk of FST abandonment if there are positive margins or LN involvement and 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 behavior.

✓

Expert sonography and/or pelvic MRI are recommended imaging tests to measure remaining (after cone biopsy) cervical length and noninvolved 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 PLN status is the precondition for any FST. Therefore, PLN (SLN) staging should always be the first step in each FST procedure. Identification of SLN and its ultrastaging is highly recommended because it increases staging accuracy, namely, the identification of micrometastases and small macrometastases. The involvement of suspicious LNs should be confirmed by histology. Intraoperative assessment of LN status is highly recommended. All SLNs from both sides of the pelvis or any suspicious LNs should be sent for frozen section. If bilateral SLN is not detectable, intraoperative assessment of PLNs should be considered (see Management of stages T1b1/T2a1). LN 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 tumor with adequate free margins and preservation of the 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 Conization and simple trachelectomy are adequate fertility sparing procedures for stages T1a1 and T1a2, LN-negative, LVSI-negative patients.

B Radical trachelectomy (type A) can be considered for stages T1a1 and T1a2, LN-negative, LVSI-positive patients. Conization or simple trachelectomy is an option.

B Radical trachelectomy (type B) should be performed for patients with cervical cancer stage T1b1 equal to or less than 2 cm of the largest diameter, LN-negative, LVSI ±.

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

✓ FST in patients with tumors greater than 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 center. Following simple or radical trachelectomy with its inherent placement of a permanent cerclage delivery can be performed only by cesarean section.

✓ Routine hysterectomy after finishing fertility plans is not necessary.

5.6 Clinically occult cervical cancer diagnosed after simple hysterectomy

5.6.1 General recommendations

✓ Management of occult disease should be based on expert pathology review and discussed in a multidisciplinary tumor 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 nonoccult disease (see above).

B In general, management of occult disease follows the same principles as that of nonoccult disease. Treatment strategy should aim for the avoidance of combining radical surgery and radiotherapy because of the highest morbidity after combined treatment.

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



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

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



In patients with tumor stage pT1a2 LVSI positive or pT1b1 or pT2a1 after simple hysterectomy, potential disease in the parametria and LNs has to be addressed.



Radiotherapy or chemoradiotherapy is recommended as an effective treatment option that avoids further surgery. In absence of residual tumor on imaging (including suspicious LNs), radiotherapy alone is recommended. In case of residual tumor on imaging, including suspicious LNs, chemoradiotherapy is recommended.



PALN dissection, at least up to inferior mesenteric artery, may be considered in patients without suspicious para-aortic nodes on imaging for staging purposes.



Debulking of suspicious PLNs may be considered.



Radical surgery is an option in patients without LN involvement on imaging and in the absence of an upfront indication for adjuvant radiotherapy (combination of negative prognostic factors).



PLN dissection should be performed as the first step of the surgery. Intraoperative assessment of PLNs may be considered. If intraoperative LN assessment is negative or is not performed, radical parametrectomy with the resection of the upper vagina should be performed preferably using minimally invasive techniques. The type of radical parametrectomy (extent of parametrial resection) should be tailored to the presence of prognostic risk factors of the primary tumor as described above (Figure 3).



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 (Figure 4).



If LN involvement, including macrometastases or micrometastases, is detected intraoperatively, further surgery (PLN dissection and radical parametrectomy) should be avoided, and chemoradiotherapy is recommended.



PALN dissection, at least up to inferior mesenteric artery, may be considered for staging purposes.



Debulking of suspicious nodes may be considered.

5.6.4 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 tumor including involved lymph node on imaging, chemoradiotherapy is recommended, and further surgery should be avoided.



PALN dissection, at least up to inferior mesenteric artery, may be considered for staging purposes in patients with negative PALNs on imaging.



Debulking of suspicious PLNs may be considered.

5.7 Management of locally advanced cervical cancer

5.7.1 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 because of the significant increase in morbidity and no evident impact on survival.
- A** Definitive platinum-based chemoradiotherapy and brachytherapy are the preferred treatment (see Principles of radiotherapy).
- C** PALN dissection, at least up to inferior mesenteric artery, may be considered before chemoradiotherapy and brachytherapy. PLN dissection is not required.
- ✓ Radical surgery is an alternative option, in particular in patients without negative risk factors (combinations of tumor size, LVSI, and/or depth of stromal invasion). Quality of surgery, both parametrectomy and LN dissection, is, however, of key importance in the management of large tumors. Intraoperative assessment of LN status (frozen section) is recommended as the first step. If LN involvement is detected intraoperatively, including macrometastases or micrometastases, further PLN dissection and radical hysterectomy should be avoided, and patients should be referred for definitive chemoradiotherapy and brachytherapy. PALN dissection, at least up to inferior mesenteric artery, may be considered for staging purposes. If intraoperative LN assessment is negative or is not done, systematic PLN dissection should be performed. Type C2 radical hysterectomy is recommended.
- C** NACT followed by radical surgery is a controversial alternative. The benefit of tumor downsizing with regard to prognosis has not been proven.

5.7.2 Stage T1b2/T2a2 and involved lymph nodes on radiological staging

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

5.7.3 Stage T2b, T3a/b, T4a

- A** Definitive platinum-based chemoradiotherapy and brachytherapy are recommended (see Principles of radiotherapy).
- C** An additional radiation boost to the involved LNs should be applied (see Principles of radiotherapy).
- C** PALN dissection, at least up to inferior mesenteric artery, may be considered before treatment in patients with negative PALNs on imaging.
- ✓ Debulking of suspicious PLNs may be considered. Pelvic exenteration is an option in selected cases with stage T4 N0 M0 disease.

5.7.4 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.

5.8 Distant metastatic disease at presentation



Patients with distant metastatic disease at presentation should have a full diagnostic workup (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 and 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 PALN region, should be treated with curative intent with definitive extended field chemoradiotherapy including brachytherapy. Treatment algorithm may also include surgical debulking of enlarged LN and additional chemotherapy.



Patients with supraclavicular LN as the 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 LN, or LVSI-positive tumors.



The role of radiotherapy in palliating symptoms such as bleeding and pain must be considered especially in radiotherapy naive patients.

5.9 Recurrent disease

5.9.1 Curative intent treatment



Treatment of recurrent disease with curative intent requires centralization and involvement of a broad multidisciplinary team including gynecologic oncologist, radiation oncologist, radiologist, pathologist, medical oncologist, urologist, and plastic surgeon. A structured program for multidisciplinary diagnostic workup, treatment, and follow-up must be present in centers responsible for the treatment.



Each center 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 specialized units.



Participation in clinical trials is encouraged to improve the clinical evidence for the effect of curative treatment of recurrent disease.

5.9.1.1 *Diagnostic workup*

- ✓ The aim of the diagnostic workup is to exclude distant metastases and locoregional tumor 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 counseled regarding not only treatment options but also the involved risks and consequences.

5.9.1.2 *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 (ie, < 5-mm thickness) in the vagina may be treated using a vaginal cylinder, ovoids, or mold, whereas other lesions usually require combined intracavitary-interstitial techniques.

5.9.1.3 *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 tumor does not invade extensively into the pelvic sidewall.
- D Combined operative-radiotherapy procedures using intraoperative radiotherapy or brachytherapy are 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 is an emerging option.

5.9.1.4 *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 sidewall and extrapelvic nodes.
- ✓ Laterally extended endopelvic resection may be considered for a recurrence that extends close to or involves the pelvic sidewall.
- ✓ 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 specialized centers.

5.9.1.5 *Role of chemotherapy*

- ✓ If further surgery or radiotherapy is considered, no more than 2 to 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.

5.9.1.6 *Nodal and oligometastatic recurrences*

- ✓ Localized para-aortic, mediastinal, and/or periclavicular recurrences above previously irradiated fields may be treated by radical EBRT if possible in combination with concomitant chemotherapy. It is recommended to electively irradiate the immediate regional nodal stations below and upstream.
- ✓ 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.

5.9.2 **Palliative treatment**

- ✓ Recommendations for palliative treatment should be made only after a thorough review of the case by a specialist multidisciplinary team and taking into account the performance status, comorbidities, 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, neurosurgical intervention or short-course fractionated radiotherapy schedule should be considered.
- ✓ Surgical interventions including diversion stoma and/or stenting should be considered as appropriate, for example, in case of obstructive symptomatic disease.

5.10 Follow-up

5.10.1 General recommendations

- ✓ Primary objectives of follow-up for patients with cervical cancer should include the following:
 - 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, for example, 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 (eg, Common Terminology Criteria for Adverse Events)
 - Prevention and management of cancer- and treatment-related adverse effects, for example, sexual dysfunction (eg, counseling, vaginal lubricants, local estrogen)
- ✓ In case of the appearance of treatment-related symptoms, a referral to a dedicated specialist (eg, gastroenterologist, urologist/gynecologist) 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, lifestyle 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 adverse 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 5 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 suggestive of 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 tumor 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 tumor 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.

5.10.2 Follow-up after fertility sparing treatment



All women remain at risk of tumor 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 (eg, gynecologic oncologist, colposcopy expert).

C

Follow-up intervals should be 3 to 4 months for the first 2 years postoperatively, and then 6 to 12 months up to 5 years. Thereafter the patient may return to population-based screening. The duration of follow-up, however, may be individualized depending on the risk of recurrence or persistence of treatment-related complications.

C

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 to 5 years as long as follow-up is indicated.

5.10.3 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.

5.10.4 Follow-up after definitive chemoradiotherapy



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



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

B

For re-evaluation purposes, the optimal diagnostic workup 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 because vaginal stenosis and dryness may occur. Vaginal dilation should be offered, as well as vaginal lubricants and local estrogen.

5.11 Cervical cancer in pregnancy



Every patient diagnosed with CCIP must be counseled by a multidisciplinary team. This team should consist of experts in the fields of gynecologic 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 patient's intention, tumor 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 gynecologic oncology centers associated with a highest level perinatal center with expertise in all aspects of oncologic therapy in pregnancy and intensive medical care of premature neonates. Because of the low incidence of CCIP, centralization in a few well-equipped facilities is compulsory.



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. Because of limited experience and inherent radioactivity PET-CT (PET-MRI) should be indicated only under very selected circumstances.



Tumor involvement of suspicious nodes should be verified histologically because of its prognostic significance and the impact on the management up to 24th week of gestation (fetal viability), preferably by minimally invasive approach.



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

- Adapted surgery including removal of the tumor: conization, 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 weeks of gestation) and beginning of cancer-specific treatment immediately after delivery by cesarean section.
- Chemotherapy until fetal maturity and beginning of cancer specific treatment immediately after delivery by cesarean section. Treatment after delivery must consider application of previous chemotherapy. In patients with locally advanced stage or with residual tumor after conization that cannot be completely excised (risk of premature rupture of membranes (PROM) and/or cervical insufficiency), platinum-based chemotherapy can be considered starting earliest at 14 weeks of gestation.



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

6 Principles of radiotherapy

6.1 Definitive chemoradiotherapy and brachytherapy: general aspects

Definitive management (without tumor 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 to 8 weeks.

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

6.2 Definitive chemoradiotherapy

EBRT is recommended minimum as 3-dimensional (3D) conformal radiotherapy. The preferred treatment is IMRT because of the more conformal dose distribution that maximizes sparing of organs at risk⁹.

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

Tumor and LN-related target volume for IMRT includes the primary cervical tumor and the adjacent tissues such as parametria, uterine corpus, upper vagina, and the PLNs (obturator, internal, external and common iliac, presacral). In case of PLN involvement indicating an increased risk of PALN spread, EBRT may include the para-aortic region up to the renal vessels (45 Gy). In case of PALN involvement, target volume includes at a 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 LNs on imaging and no LVSI.

Boost treatment for involved LN(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 to 60 Gy (equi-effective dose to 2 Gy per fraction (EQD2)). An alternative treatment option is surgical debulking of enlarged nodes.

IGRT is recommended for IMRT to ensure safe dose application in the tumor-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 to 6 weeks.

6.3 Definitive brachytherapy

IGABT is recommended, preferably using MRI at the time of brachytherapy. IGABT is delivered in large tumors toward the end of or after concomitant chemoradiotherapy. Repeated gynecologic examination is mandatory, and alternative imaging modalities such as CT and ultrasound may be used.

The tumor-related targets for brachytherapy include the residual gross tumor 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})¹⁰⁻¹².

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

The brachytherapy applicator should consist of a uterine tandem and avaginal component (ovoids/ring/mold/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 extracervical area, eg, 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 to 45 Gy (EQD2) to reach a total EBRT + brachytherapy dose of equal to or greater than 85 to 90 Gy EQD2 (D90) (assuming 45 Gy through EBRT) to the CTV-T_{HR}, equal to or greater than 60 Gy (D98) to the CTV-T_{IR}, and equal to or greater than 90 Gy (D98) to the GTV-T_{res}. Three dimensional 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 evidence¹⁰⁻¹².

Point A dose normalization should be used as starting point for stepwise treatment plan optimization, although point A dose reporting and prescription have been extended by the volumetric approach¹⁰⁻¹².

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

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

For the tumor-related targets (GTV-T_{res}, CTV-T_{HR},CTV-T_{IR}), the use of external beam therapy for giving extra dose (eg, 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 IGRT, in particular beyond 45 to 50 Gy.

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

6.4 Adjuvant radiotherapy or chemoradiotherapy based on intensity modulated radiotherapy and image guided radiotherapy

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

6.5 Definitive 3D conformal external beam radiotherapy or chemoradiotherapy and radiography-based brachytherapy

Three-dimensional conformal radiotherapy alone or as definitive concomitant chemoradiotherapy (platinum based) ± para-aortic 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 LN 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 equal to or greater than 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 evidence¹⁰⁻¹².

6.6 Comment of the radiation oncology subgroup of the development group

The radiation oncology subgroup of the multidisciplinary international development group designed this section on principles of radiotherapy. This chapter on principles of radiotherapy is mainly based on the progress achieved in chemoradiotherapy, brachytherapy and external beam radiotherapy during the last two decades. Progress in chemoradiotherapy has been driven through several phase III trials and meta-analyses providing level 1 evidence which resulted in grade A recommendations (see 13.1.5). The progress in brachytherapy and external beam radiotherapy has followed the classical pathways of technology innovations and developments in clinical settings and is ongoing.

MRI image guidance, applicator development and adaptive treatment planning for brachytherapy have played a major role in the development of image guided adaptive brachytherapy and started from mono-institutional innovations. Several mono-institutional evaluations at various clinical departments in Europe and beyond could prove the new method of image guided brachytherapy to be feasible, reproducible, reliable and clinically valuable. The European Gyn GEC ESTRO group has become the major driving force in this development, providing essential recommendations to guide this treatment as early as 2005 and 2006. This group also started large multi-center retrospective and prospective clinical trials and evaluations of image guided adaptive brachytherapy (RetroEMBRACE, EMBRACE I (2008-2015) and EMBRACE II (since 2016)) benchmarking these innovations in a multicentre clinical setting¹³. In parallel, the International Commission of Radiation Units finished a revision on their recommendations from 1985 (ICRU report 38) in 2016 (ICRU report 89) which was based on the Gyn GEC ESTRO Recommendations. Therefore, at present there is a methodology for image guided brachytherapy available, agreed upon on the international level, how to treat cervical cancer through an advanced adaptive approach. The method is comprehensively described in ICRU report 89 and additionally allows to integrate recent volumetric (3D/4D) and traditional (2D, point A) treatment approaches. In addition, there is major high quality clinical evidence coming up from scientific reports on large cohorts of the EMBRACE clinical trial experience in regard to patient, tumour and treatment parameters and oncological, morbidity and quality of life outcomes. This ongoing increasing evidence (see 13.1.4) makes image guided brachytherapy to become the new clinical standard of care in a large growing number of centers in Europe and in many centers and countries all over the world. Therefore, the radiotherapy subgroup decided - in agreement with a large amount of radiation oncology reviewers of this guideline - to make this new method and the clinical evidence achieved so far to become the backbone of these guidelines and to declare this new paradigm the new standard of care for cervix cancer brachytherapy in Europe.

Image guided external beam radiotherapy using advanced imaging as well as advanced hard and software technology for radiation application (IMRT, IGRT) also has entered the field of gynaecologic radiation therapy for cervical cancer. IMRT and IGRT provide several advantages in dose distribution in regard to sparing of organs at risk without compromising clinical outcome compared to traditional 3D conformal radiotherapy. In addition, IMRT and IGRT are increasingly spread in Europe and all over the world. For these reasons advanced methodology for external beam radiotherapy application was selected to form the

basis for these European guidelines, although there is at present much “work in progress” and the clinical evidence for dose and volume prescription for IMRT and IGRT including lymph node boosting is limited. The radiotherapy subgroup took the decision - again in agreement with a large amount of radiation oncology reviewers of this guideline - to allocate IMRT with IGRT including simultaneous lymph node boosting to represent the “preferred treatment” for external beam radiotherapy.

7 Principles of pathological evaluation

The pathology report represents a key component in the management of cancer patients. The completeness and accuracy of the pathology report derives from several factors. Pre-analytical steps must be carried out in an optimal way to allow for adequate pathological evaluation. The inclusion of informative clinical and surgical data on the pathology request form and accurate sampling and processing of the specimens are the basis for a correct histological diagnosis and the provision of information on tumour staging and prognosis.

The pathology report should be comprehensive of all the features which allow a cervical carcinoma patient to be placed into a risk group which ensures the appropriate management. It should include all the parameters impinging on tumour staging and patient management. The histological subtype is important since some uncommon tumour types are associated with aggressive (e.g. high grade neuroendocrine carcinoma, small cell or large cell neuroendocrine carcinoma) or favourable (e.g. adenoid-basal carcinoma) behaviour and may be considered for different treatment. Histological tumour grade is generally reported in squamous cell carcinomas and adenocarcinomas but in general this does not affect the treatment and the prognosis, especially since there is no validated grading system for cervical squamous cell carcinomas or adenocarcinomas. Accurate tumour measurement, which often requires correlation of the gross and microscopic features, is important for substaging of tumours (for example IA1 versus IA2 versus IB1, IB1 versus IB2). The presence or absence of LVSI, the LN status (number of nodes retrieved, number involved, presence of extracapsular extension), involvement of extracervical tissues and the margin status, including the distance of tumour and preinvasive disease to various margins is also critical for patient management.

The use of immunohistochemical markers in a prognostic and/or predictive role is not currently established but this may change in the future. However, pathologists often use immunohistochemical stains as a diagnostic tool.

Intraoperative evaluation of a sentinel (or other) LN with obvious gross tumour may be done with a single section to confirm the presence of metastasis. Frozen section examination is optional for non-suspicious SNs. At frozen section, there is no evidence for the exact number of histological sections to be examined, but the number should be adequate to pick up macro- and micrometastasis since the presence of metastatic tumour within a LN changes the management with abandonment of surgery and instigation of chemoradiotherapy. Full pathological examination of SNs (outside of the intraoperative setting) involves serial sectioning of the LN(s) with multiple levels, sometimes with the performing of immunohistochemical staining with pancytokeratin antibodies (e.g. AE1/AE3) if tumour is not identified on examination of routinely stained sections. To rule out micrometastasis, which measure from greater than 0.2 mm to 2 mm it is useful to cut the node grossly into 2 mm sections and to perform serial sectioning on each block at 200 µm levels. Immunohistochemistry with cytokeratin antibodies is useful to confirm metastasis which are uncertain on haematoxylin and eosin (H&E) stained sections. Immunohistochemistry also helps to detect isolated tumour cells (up to 0.2 mm in diameter). These are regarded as node negative and pN0(i+) but their clinical impact has not yet been determined.

7.1 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 LNs and designation of the LN 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.

7.2 Specimen grossing and sampling

Small biopsy specimens should be enumerated and measured.

The diameter (2 dimensions) and depth of cone/loop specimens should be measured. It should be recorded if the specimen is complete or fragmented. If more than 1 piece of tissue is received, every piece should be measured in 3 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 because if tumor is present in more than 1 piece, it needs to be known whether these are consecutive pieces and thus a single tumor or represents multifocal tumor. It is recommended to place only 1 piece of tissue in each cassette. There are also techniques that allow embedding of more than 1 piece in a cassette if they are small enough. In cases that 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 LNs and indication of the LN 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 2 dimensions (vertical and horizontal).

Gross tumor involvement of the parametrium, vagina, uterine corpus, or other organs should be documented. The relationship of the cervical tumor 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 away that demonstrates the distance of the tumor to the margin. The vaginal margin should be examined totally as radial sections if no tumor is seen grossly.

When the tumor is small (or with tumors that 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 tumor, the hysterectomy or trachelectomy specimen should be opened in the sagittal plane.

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

Gross tumors should be measured in 3 dimensions, namely, 2 measurements of horizontal extent and the depth of invasion.

The tumor site within the cervix should be documented.

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

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

At least 1 block per centimeter of the greatest tumor dimension for large tumors should be taken.

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

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

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

The entire vaginal margin should be blocked.

All the LNs should be submitted for histological examination. If the LNs 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, H&E sections should be taken. LNs should be submitted in separate cassettes according to the site recorded on the specimen request form.

7.3 Pathological analysis of sentinel lymph node

Intraoperative assessment should be performed on a grossly suspicious SN and may be performed on a “nonsuspicious” SLN(s) because the confirmation of tumor involvement will result in abandoning a hysterectomy or trachelectomy.

For intraoperative evaluation, the SLN(s) needs 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 LN(s).

For a LN with obvious gross tumor, a single section is adequate for frozen section.

Frozen section may be combined with imprint cytology.

Any nonsuspicious SN 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.

SLN(s) tissue blocks should be entirely analyzed 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 tumor 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 their morphology. Müllerian inclusions (endosalpingiosis, endometriosis) and mesothelial cells may rarely be present in PLNs and PALNs and be cytokeratin positive.

7.4 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 (3 dimensions), number of tissue pieces for loop/cones, and maximum and minimum length of vaginal cuff and the parametria in 2 dimensions.

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

Tumor dimensions including 2 measurements of horizontal extent and depth of invasion or thickness (tumor dimension should be based on a correlation of the gross and histological features). When multifocal separate tumors are present, each should be described and measured separately, and the largest used for tumor staging. Specimens from prior conization and subsequent conization, trachelectomy, or hysterectomy should be correlated for estimation of the tumor size. This is of importance because different specimens may have been reported at different institutions. It should also be recognized that simply adding the maximum tumor size in separate specimens may significantly overestimate the maximum tumor dimension.

Histological tumor type and tumor grade.

The presence or absence of LVSI.

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

Minimum distance of uninvolved cervical stroma.

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

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

Pathologically confirmed distant metastases.

Provisional pathological staging pretumor board/multidisciplinary team meeting (American Joint Committee on Cancer, eighth edition).

7.5 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 tumor site(s)</p>	<p>Tumour dimensions*</p> <ul style="list-style-type: none"> • Horizontal extent (two measurements). • Depth of invasion or thickness. <p>Histological tumor type Histological tumor grade LVI Coexistent 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 Margin status (invasive and preinvasive diseases). Specify the margin(s) LNs status (SLN status, number involved/number retrieved and presence of extranodal extension) Pathologically confirmed distant metastases Pathological staging pretumour board/multidisciplinary team meeting (TNM category⁴)</p>
* Tumor dimension should be based on a correlation of the gross and histological features		

8 Staging

8.1 Summary of available scientific evidence

8.1.1 Prognostic factors

Many studies¹⁴⁻¹¹⁸ have pointed out since the last four decades the independent prognostic significance of LN involvement, stage, histological type, tumour size, LVSI, stromal invasion, parametrial invasion, grade, and/or age in patients with cervical cancer. The LN involvement appears as the most powerful prognostic factors^{14-53,83,86,87,93,96-102,105,108,109,112-114,118} influencing survival rate. An early stage is associated with an improvement of survival rates^{18,28,32,33,42,43,45,54-63,86,87,89,92,95-97,101,103-105,107,109,110,115}. The presence of a large tumour (especially tumour size > 4 cm)^{14,17-21,23,25,26,30,34,39,55,59,63-69,84,88,91,96,97,101,106,114-116,118}, LVSI^{16,18,19,22,30,36,39,47,52,59,62,64,66,70-73,82,83,90,112}, stromal invasion depth^{19,39,44,56,62,66,70,74-76}, parametrial invasion^{19,22,36,39,40,44,47,62,77,78,90,94,99}, and a high grade^{15,39,42,60,65,67,71,85,87,90,97,104} are independent factors in decreasing survival rates. Prognostic significance of age for survival remains controversial. The majority of identified studies^{23,46,54,55,57,65,68,73,79,80,83,85,89,109,116} reporting the prognostic significance of age in patients with cervical cancer reported that the young patient age at presentation is an independent factor in improving survival. But other identified studies^{20,45,48,60} observed that the young age is independently associated with a higher risk of death.

LoE 1+

8.1.2 Detection of advanced disease (FIGO stage ≥ IIB)

Using the technique of meta-analysis, Thomeer *et al.*¹¹⁹ assessed the diagnostic performance of clinical examination (sixteen studies¹²⁰⁻¹³⁵) and MRI (twenty studies^{121-123,127-143}) in detecting advanced stage disease (FIGO stage ≥ IIB). Authors showed that MRI is significantly better than clinical examination in ruling out advanced disease in patients with cervical carcinoma (Table 1). It should be noted that (1) three included studies had a sensitivity of 0% and specificity of 100%, which was mainly because most patients were not operated on when advanced disease was clearly present during clinical examination, (2) different technical aspects of MRI influenced the summary results, (3) the prevalence of disease in the studies had a significant effect on the summary results on clinical examination, (4) the presence of verification bias had a negative effect on the summary results of MRI, (5) the use of anaesthesia had a positive effect on the summary results of clinical examination, and (6) the use of a fast spin echo sequence, higher magnetic field and an additional coil had a significant positive influence on the summary results of MRI.

LoE 1-

One study¹⁴⁴ not included in the meta-analysis¹¹⁹ mentioned above was identified and presents consistent findings with those previously reported.

LoE 2-

8.1.3 Detection of parametrial invasion

Thomeer *et al.*¹¹⁹ assessed also the diagnostic performance of clinical examination (seven studies^{120,123,127,128,131,145,146}) and MRI (twenty-nine studies^{122,123,127,128,131,135-142,145-160}) in detecting parametrial invasion in patients with cervical carcinoma. Their analyses revealed that MRI has a higher sensitivity than clinical examination for staging cervical carcinoma and the both tests have comparably high specificity (Table 1). It should be noted that (1) details of the examination were often not reported in studies, with the exception of the three largest studies^{120,121,125} (62% of the patients) where most details were described, (2) in most of the studies it was not evident whether the results of MRI and clinical examination data influenced each other, (3) different technical aspects of MRI influenced the summary results, (4) the prevalence of disease in the included studies had a significant effect on the summary results of

LoE 1-

MRI concerning parametrial invasion, (5) the presence of verification bias has a negative effect on the summary results of MRI concerning parametrial invasion and advanced disease, (6) the use of an fast spin echo sequence, higher magnetic field and an additional coil had a significant positive influence on the summary results of MRI for both parametrial invasion and the detection of advanced disease, (7) the use of a slice thickness of 5 mm or smaller also had a significant positive effect on the evaluation of parametrial invasion with MRI, (8) other parameters were not significant or not interpretable because of the low number of studies included, and (9) even with inclusion of studies with old MRI sequences the data are significantly favourable for MRI in comparison to clinical examination.

Six original studies¹⁶¹⁻¹⁶⁶ not included in the meta-analysis¹¹⁹ mentioned above were identified. A study¹⁶¹ comparing these two techniques confirmed the superiority of MRI on clinical examination for detection of parametrial invasion. Three small studies¹⁶²⁻¹⁶⁴ confirmed the reliability of MRI in detecting parametrial invasion. In the fifth identified original study¹⁶⁵, there was agreement between MRI and histopathology for parametrial infiltration in 75% of cases, with a tendency towards underestimation in 21% of cases. Discordant findings were reported in the sixth identified study¹⁶⁶ indicating that the best diagnostic results in terms of sensitivity and specificity were achieved by clinical examination. Authors also evaluated CT and found that clinical examination was also better than CT. It should be noted that all patients included in this sixth identified study¹⁶⁶ underwent clinical examination and then on the basis of these findings, arrangements were made for further diagnosis, including imaging, for a large proportion of patients. So, selection bias cannot reliably be ruled out in the comparison of clinical staging and cross-sectional imaging.

LoE 3

Five original studies^{149,167-170} comparing notably the diagnostic performance of US and MRI for detection of parametrial invasion were also identified and found that US was at least as sensitive as MRI. Four^{149,167,169,170} of them showed that US was better than MRI in terms of specificity. The first of those studies¹⁴⁹ employed a transrectal examination, while three reports¹⁶⁷⁻¹⁶⁹ used a transvaginal approach. Patients were examined either transvaginally or transrectally in the fifth study¹⁷⁰.

LoE 2-

Prasad *et al.*¹⁷¹ found poor agreement between CT and clinical examination in the evaluation of parametrial invasion (41.5%).

LoE 3

Preliminary results concerning the value of integrated PET/MRI in the detection of the invasion of parametrium have been published by Grueneisen *et al.*¹⁷² and present a high diagnostic performance in terms of sensitivity and specificity (90% (95% CI = 55-100) and 94% (95% CI = 71-100), respectively).

PET-CT, MRI, and non-fused and fusion of PET and MRI for detecting parametrial invasion were investigated by Kitajima *et al.*¹⁷³. The sensitivity for MRI, fused PET/MRI and non-fused PET/MRI was higher than that of PET-CT. However, none of the differences reached statistical significance. High diagnostic performance in terms of specificity was similar between them.

8.1.4 Identification of tumour

As part of a European multicenter trial¹⁷⁰, the agreement between US and pathology was excellent for detecting tumours, correctly classifying bulky tumours (> 4 cm) and good for classifying small tumours (< 2 cm) (kappa values 0.84, 0.82, and 0.78, respectively). The agreement between MRI and histology was good for classifying tumour as < 2 cm or > 4 cm (kappa values 0.71 and 0.76, respectively). It was moderately accurate in tumour detection (kappa value 0.52). Authors found that cone biopsy prior to imaging did not affect the accuracy

LoE 2-

of US or MRI in detecting residual tumours.

Using transrectal approach, Fischerova *et al.*¹⁴⁹ also observed that US was more accurate to MRI in detection of residual tumours following conisation and evaluation of small tumour volume ($\leq 1 \text{ cm}^3$) in early-stage cervical cancers.

A third study¹⁶⁷ was identified and reported similar sensitivity and specificity with regard to the detection of the presence of the tumour mass.

8.1.5 Detection of stromal invasion

Three original studies^{167,168,170} showed comparable performances between US and MRI for detecting stromal invasion. Stromal infiltration, as document by MRI, agreed with the histopathological findings in 75% of cases, whereas it was underestimated in 21% of cases and overestimated in 4% of patients in the study published by Manfredi *et al.*¹⁶⁵.

LoE 2-

Yang *et al.*¹⁷⁴ reported a high performance of PET-CT in terms of sensitivity for detecting stromal invasion before operation in cervical cancer (98.4%) but a low specificity (59.2%).

8.1.6 Determination of the proximal extension of early stage to the internal os

A systematic review¹⁷⁵ of the literature assessing the value of MRI for detecting involvement of the uterine internal os was identified. In the four included studies^{165,176-178} involvement of the internal os was present in 17% (13-24%) of the cases. For three studies^{165,176,178} summary estimates for specificity and sensitivity could be calculated and were 97% and 91%, respectively.

LoE 2-

Sensitivity and specificity of MRI could not be studied in a small identified study¹⁷⁹ not included in the systematic review published by de Boer *et al.*¹⁷⁹, due to the extreme low prevalence of involvement in the study population (3.7%). This study showed moderate to almost perfect interobserver values for MRI in visualization of the internal os (an agreement of 96% was achieved) and the distance between tumour and the internal os (intraclass correlation coefficient was 0.752 (95% CI = 0.406-0.909)), in patients with early stage cervical carcinoma. The distance between tumour and the internal os measured on MRI was compared with pathological findings. For the two thresholds taken into account (5 mm or 1 cm), no false-negative findings were observed. It should be noted that authors evaluated interobserver variability of two radiologists with similar experiences.

LoE 3

8.1.7 Lymph node status assessment

Choi *et al.*¹⁸⁰ performed a meta-analysis including forty-one studies^{122,128,136,138,140-142,145,146,151,158,159,178,181-210} to compare diagnostic performances of computed tomography (CT), MRI and PET or PET-CT, for detection of metastatic LNs. PET or PET-CT had an overall higher diagnostic performance (patient-based data analysis and region- or node-based data analysis) than did CT or MRI in detecting metastatic LNs (Table 2). It should be noted that (1) this may be because the criteria of the LN size were used differently in each study, and also CT and MRI cannot readily differentiate metastatic nodes from hyperplastic nodes of the similar size, (2) in some studies, the mean size of a metastatic LN was smaller than 1 cm (largest short axis diameter), that may also explain the low performance of CT and MRI when the largest short axis diameter is the diagnostic size criterion, and (3) authors did not evaluate a region-based or node-based data analysis separately because only three studies^{178,197,204} had reported the findings from a node-based data analysis.

LoE 1-

As part of a subgroup analysis based on the type of CT scanner (per-patient based comparison), sensitivity was 39% (95% CI = 30-49) for helical CT and 61% (95% CI = 52-71)

for non-helical CT, while specificity was similar between them (92% (92% CI = 89-95) and 92% (95% CI = 88-95), respectively). Authors did not evaluate diagnostic performances by type of MRI scanner because only four of thirty-two MRI studies^{142,146,181,182} did not use 1.5-tesla MR scanners.

Nine original studies^{162,165,166,174,211-215} not included in the meta-analysis¹⁸⁰ mentioned above were identified. In the study published by Manfredi *et al.*¹⁶⁵, MRI accuracy in evaluating nodal metastasis was 89%, considering a cutoff of 1 cm, and 83% with a cutoff value of 0.5 cm. Lowering the cutoff value from 1 cm to 0.5 cm led to a higher false positive rate, with consequent reduction in specificity (100% to 92%) and a slight increase in sensitivity (28% to 33%). In the second identified study¹⁶², accuracy of MRI in detecting LN involvement was 86%. Concordant findings with the meta-analysis¹⁸⁰ mentioned above were described in five identified reports^{166,211-213,215} concerning the diagnostic performances of PET, PET-CT, CT and MRI for detecting LN involvement in terms of sensitivity and specificity.

Yang *et al.*¹⁷⁴ and Signorelli *et al.*²¹⁴ reported consistent data with the meta-analysis¹⁸⁰ mentioned above concerning the high diagnostic performance of PET-CT in terms of specificity (95.0% and 97%, respectively). However, the authors reported a low sensitivity (53.8% and 32%, respectively) to diagnose LN metastasis.

Ospina *et al.*²¹⁶ described that when PET-CT (seven studies^{196,207-209,217-219}) and PET (thirteen studies^{195,205-207,210,220-227}) are evaluated for staging purposes, positive results seem to be useful to detect the stage of the disease for both techniques, but negative results are not. Authors also described that there was no statistically significant difference of performance between PET-CT and PET in the overall staging of cervical cancer.

PET-CT has limited sensitivity, but high specificity for predicting PLN metastasis in preoperative staging in two studies^{228,229} not included in the pooled analyses^{180,216} mentioned above.

Preliminary results concerning the value of integrated PET/MRI in the detection of nodal positive patients have been published by Grueneisen *et al.*¹⁷² and present a high diagnostic performance in terms of sensitivity and specificity (91% (95% CI = 59-100) and 94% (95% CI = 70-100), respectively). PET/MRI correctly identified regional metastatic disease (N1-stage) in 80% of patients and non-regional LN metastases in all patients.

PET-CT, MRI, and non-fused and fusion of PET and MRI for detecting nodal metastasis were investigated by Kitajima *et al.*¹⁷³. On a per-patient basis, similar sensitivities and specificities were found for both the fused PET/MRI and PET-CT protocols. Lower sensitivities and higher specificities were reported for non-fused PET/MRI and MRI.

A meta-analysis²³⁰ evaluating the accuracy of tests for LN status in cervical cancer and including seventy-two studies^{122,128,135,138,140-143,146,158,159,182-188,190-192,194,198,200,201,203,204,206,210,231-273} was identified. SN biopsy was the most accurate test in determining LN status as compared to PET, MRI and CT (Table 3). The failure rate for the detection of the SN was 10.9% (95% CI = 1.5-27.4). The failure rates were 8.4% (95% CI = 3.3-15.5) for using blue dye alone and 4.4% (95% CI = 2.0-7.7) for use of a combined technique (blue dye/technetium-99m colloid (^{99m}Tc)). No difference was found in accuracy between these different techniques or between open and laparoscopic surgery. Authors also showed that PET was more accurate than MRI or CT. It should be noted that multivariable analysis exploring reasons for heterogeneity showed that the differences in accuracy among included studies could not be explained by the site of LN (pelvic or para-aortic).

LoE 2-

LoE 3

LoE 1-

Four other meta-analyses, published by Kadkhodayan *et al.*²⁷⁴, van de Lande *et al.*²⁷⁵, Wang *et al.*²⁷⁶, and Tax *et al.*²⁷⁷ (including sixty-seven studies^{231,232,234,235,238,245,246,249,251,254,257-259,278-331}, twenty-four studies^{231,234-236,238,239,242,244-246,249-252,254,255,257-259,287,323,332-334}, forty-nine studies^{235,236,238,239,243-246,249-252,254,255,257-259,280,284,287,288,291,292,297,298,302,307,310,311,316,318,322,323,326-331,333,335-343}, and forty-seven studies^{236,243,257-259,278,280,284,286,288,291,297,298,300-302,306,307,309-311,316,317,320,322,328,333,335,337-340,342,344-358} respectively), and reviewing the diagnostic performance of SN detection for assessing the nodal status were identified and confirmed the high success rate in terms of detection rate and sensibility. SN detection and sensitivity were related to the mapping material, being lower with blue dye alone and highest in the combined tracer/blue dye method. A subgroup analysis on technique within a bilateral sentinel LN approach performed by Tax *et al.*²⁷⁷ showed that bilateral detection rate was highest when a combined tracer was used (Table 4). No statistical significant difference in terms of detection rate or sensitivity between laparotomy, laparoscopy, and robot-assisted method was reported.

According to subgroup analyses regarding other potential factors associated with diagnostic performance provided by Kadkhodayan *et al.*²⁷⁴, previous conisations did not impact on the detection rate of SN mapping for prediction of LN status (Table 5). SN mapping had excellent detection rate and sensitivity in the setting of fertility-sparing surgery. Immunohistochemistry (IHC) in addition to the traditional H&E pathological examination of the SN improved the sensitivity. Pooled SN detection rate in patients with a history of pre-operative treatments such as neoadjuvant chemotherapy or radiotherapy was low, however, pooled sensitivity remained high. Finally, larger tumour size (>2 cm) and a more advanced stage (> FIGO stage Ib2) were associated with low detection rate and sensitivity.

As part of subgroup analyses performed by Tax *et al.*²⁷⁷, ultrastaging resulted in higher sensitivity compared to frozen section and/or H&E analysis (94% (95% CI = 80-99) versus 68% (9% CI = 38-88)). This was due to correctly detecting metastases with ultrastaging in 80% of false negative patients on frozen section and/or H&E analysis. The risk of under treatment on ultrastaging, i.e. not detecting PLN metastases due to false negative sentinel LN results and leaving out a full PLN dissection, was 1.5%. Prerequisites such as early FIGO stage (IA2, IB1, IIA primary tumour size < 40 mm), no suspicious pre-, and per-operative LNs, and bilateral negative sentinel LNs after ultra staging resulted in remaining false negative result in 0.08 of patients. The presence or absence of anaphylactic reactions due to a dye tracer was explicitly reported in ten studies^{NA}, with anaphylactic reaction in 0.6%. At least half of these reactions were serious leading to resuscitations and/or ICU admittance.

One original study³¹³ not included in the subgroup analyses mentioned above was identified and reported that patients with optimal bilateral SN detection were significantly more likely to have any metastasis detected (33.3% versus 19.2%, $p < 0.001$) as well as micrometastasis detected in their SN (39.6% versus 11.4%). In this study published by Cibula *et al.*³¹³, SN ultrastaging resulted in a low overall false-negative rate of 2.8% and an even lower false-negative rate of 1.3% for patients with optimal bilateral mapping. Sensitivity of SN ultrastaging was 91% (95% CI = 86-95) for the whole group and 97% (95% CI = 91-99) in the subgroup with bilateral SN detection. As part of another original study³⁵⁹ not included in the subgroup analyses mentioned above, intraoperative SN assessment established the SN status correctly in as few as 56% of cases (or in 63% of cases if isolated tumour cells had been excluded). Ninety-five per cent of metastases detected intraoperatively were macrometastases. Final ultrastaging of intraoperatively negative SN confirmed macrometastases, micrometastases and isolated tumour cells in additional 3.5%, 8%, and 3.5% of patients, respectively. The intraoperative examination of the SN (as compared with final SN ultrastaging) reached the sensitivity of 56% and specificity of 100%. In a larger study³⁶⁰, there were 60% of cases with micrometastases or isolated tumour cells in the SN, and none of them were detected intraoperatively. This study³⁶⁰

LoE 2-

presented consistent results with those published by Slama *et al.*³⁵⁹ concerning inadequate intraoperative detection of micrometastases.

One original study³⁵⁶ not included in the meta-analyses^{230,274-277} mentioned above was identified and presents consistent findings with those previously reported concerning the achievability and diagnostic performance of SLN biopsy.

A small original study³⁶¹ not included in the meta-analyses^{230,274-277} mentioned above was also identified and describes consistent findings with those previously reported.

LoE 3

A systematic review³⁶² evaluating the evidence regarding the technique and the effectiveness of indocyanine green (ICG) during sentinel LN biopsy was identified. Sentinel LN was evaluated for cervical cancer in four articles^{308,325,326,363}; in two studies^{364,365}, endometrial cancer and cervical cancer were studied. These two studies^{364,365} did not report results separately from the endometrial cancer patients included in the study. Thus, data on the efficacy of ICG in cervical sentinel LN detection specifically cannot be drawn from these studies^{364,365}. Data in terms of sensitivity and specificity were available in three studies^{308,325,326}. Sensitivity varied from 83% to 100%. All the three studies reported a specificity of 100%. No complications related to ICG administration were described.

LoE 2++

Four reports³⁶⁶⁻³⁶⁹ not included in the systematic review³⁶² mentioned above and assessing the feasibility and mapping using ICG for sentinel LN mapping were identified. However, one³⁶⁶ of them did not report results separately from the endometrial cancer patients included in the study. Thus, here again data on the efficacy of ICG in cervical sentinel LN detection specifically cannot be drawn from this study³⁶⁶. Imboden *et al.*³⁶⁷ evaluated patients undergoing sentinel LN mapping for cervical cancer using ICG versus ^{99m}Tc with blue dye. The authors reported significantly better bilateral detection rates with ICG (95.5 versus 61%, $p < 0.05$) as well as a non-significant trend towards better bilateral detection rates in tumours larger than 2 cm. Consistent findings were described by Buda *et al.*³⁶⁹ with a bilateral mapping achieved in 98.5% for ICG and 76.3% for ^{99m}Tc with blue dye ($p < 0.0001$). In this study³⁶⁹, the detection rate of sentinel LN mapping was 96% and 100% for ^{99m}Tc with blue dye and ICG. Data from the study published by Beavis *et al.*³⁶⁸ confirmed a high side-specific (93.3%) and bilateral mapping rate (87%) with the use of ICG, and further demonstrated no difference in detection between small (< 2 cm) and large (≥ 2 cm) cervical tumours (88.2% versus 84.6%, $p = 1.0$).

LoE 2-

A multicenter trial³⁷⁰ assessed if PET combined with diagnostic CT improves diagnostic CT accuracy to detect LN metastases in advanced cervical cancer (FIGO stages IB2, II > 4 cm, and IIB-IVA) and concluded that addition of PET to diagnostic CT resulted in statistically borderline increase in sensitivity to detect LN metastasis in abdomen. This trial did not include any endpoints for recurrence or survival in these patients.

As part of a systematic review³⁷¹ including 22 articles^{20,21,141,145,182,192,196,199,203,218,372-395} and evaluating the preoperative imaging and surgical staging of PALNs in locally advanced cervical cancer (FIGO stages IB2-IVA), the proportions of PALNs that were positive on histological analysis when findings on imaging were abnormal were 20% to 66% for CT scan, 0% to 27% for MRI, 86% to 100% for PET, and 50% to 75% for PET-CT. Positive PALNs with normal findings on imaging was seen in 9% to 35% for CT scan and/or MRI, 4% to 11% for PET, and 6% to 15% for PET-CT. It should be noted that PALN metastases were present in 18% (range, 8%-42%) of all patients.

LoE 2++

Surgical staging led to a treatment modification in 7% to 58% of cases with a mean of 20%. The most common operation technique used for PALN dissection was laparoscopy (75%) with a

conversion rate of less than 2%. Laparotomy and robot-assisted surgery were used as operating technique in 23% and 2% of the patients, respectively. The mean complication rate of PALNs was 4% to 18% in the laparoscopic approach. Laparotomy resulted in a complication rate of 6% to 24%. Lymphocysts were the most common complication in all approaches. The complication rate in studies with routinely performed PLNs was 4% to 24%. This rate was 4% to 13% when only PALN dissection was performed.

A systematic review³⁸⁶ was performed to evaluate the effectiveness and safety of pretreatment surgical PALN assessment for women with locally advanced cervical cancer (FIGO stages IB2-IVA) and concluded that there was insufficient evidence of its potential beneficial effect. It should be noted that this conclusion was based on analysis of a small single trial³⁹³ comparing clinical staging (CT or MRI) with surgical staging (laparoscopic or extraperitoneal surgical approach).

LoE 1-

Kang *et al.*³⁹⁶ revealed that PET or PET-CT is a highly specific diagnostic tool in detecting PALN metastasis in cervical cancer whatever the probability of PALN metastasis (pooled data from ten studies^{28,32,33,44,45,48,93,96-98}). However, authors mentioned that the diagnostic performance of PET or PET-CT in terms of sensitivity is low when it is performed in the population with a low prevalence of PALN metastasis ($\leq 15\%$) (Table 6). Authors provided also the pooled comparison of diagnostic performance between PET-CT (five studies^{196,207,218,397,398}) and PET (five studies^{198,199,206,210,272}) and observed no statistical difference of specificity between the two techniques. (98% (95% CI = 87-100) and 97% (95% CI = 90-99), respectively). It should be noted that as part of this subgroup analysis PET was significantly better than PET-CT in terms of sensitivity (66% (95% CI = 33-89) and 13% (95% CI = 2-56), respectively). It should be also noted that (1) although there was no detectable contributor to the between-study heterogeneity in the regression meta-analysis, the small number of included studies might have provided insufficient power to accurately judge the cause of the heterogeneity, (2) none node-by-node or region-by-region comparison analyses are available, and (3) the frequencies of FIGO stages III-IV disease in most of the studies were less than 20% or more than 50%, that also might have played a role as a bias.

As part of a RCT³⁹⁹ not included in the systematic reviews^{371,396} mentioned above and addressing the question of the possible impact of PET on extrapelvic metastasis detection for patients with MRI-detected positive pelvic but negative para-aortic lymphadenectomy (pretreatment PET (study group) or not (control group)), PET detected PALN metastasis in 9% of patients. All PALNs detected by PET could be identified on the CT images taken for virtual simulation and their transverse diameters were reordered.

Another original study⁴⁰⁰ not included in the systematic reviews^{371,396} mentioned above was identified and confirmed the pooled results presented above concerning the diagnostic performance in terms of sensitivity and specificity of PET-CT and MRI.

LoE 3

A meta-analysis⁴⁰¹ assessing the diagnostic value of diffusion-weighted MRI for benign/malignant discrimination of PLNs was identified. Taking into account 15 articles⁴⁰²⁻⁴¹⁶, authors concluded in a usefulness of diffusion-weighted imaging for differentiation between metastatic and benign LNs (pooled sensitivity and specificity were 86% (95% CI = 84-89) and 84% (95% CI = 83-86), respectively). It should be noted that the results have to be interpreted with caution due to high heterogeneity between included studies.

LoE 1-

8.1.8 TNM classification and FIGO

The TNM classification and the FIGO staging system classify cervical cancer on the basis of the size of the tumour (T), whether the cancer has spread to LNs (N), and whether it has spread to distant sites (M).

An eighth edition of the TNM classification⁴ of malignant tumours has been published in December 2016. The FIGO staging system was last reviewed in 2009 by the FIGO Committee on gynecologic oncology⁵⁻⁷ in close collaboration with the American Joint Commission on Cancer and the Union of International Cancer Control (Table 7). The FIGO has invited the Gynecologic Cancer Intergroup (GCIIG) to make contributions for possible changes of the current FIGO staging system⁴¹⁷. The current FIGO staging, proposed changes and classification by the GCIIG are listed in Table 7 and Table 8. The GCIIG recommended to continue to use a clinical staging in cervical cancer as many cervical cancers are not surgically staged or treated.

A prospective study⁴¹⁸ comparing the revised FIGO and TNM staging systems with regard to accuracy in pretreatment staging and their reliability in the prediction of prognosis has been identified. Among the 54 included patients, 17 of 19 patients with early-stage disease underwent upfront radical surgery; and in 59% of these, FIGO did not match with final histopathologic TNM (pTNM). Among these, 7 patients had nodal metastasis, 1 patient had microinvasion of the vaginal cuff, and 2 patients had microscopic invasion of parametria on histopathologic findings. When clinical TNM (cTNM) stage was considered, in 4 patients, pTNM was different and in 13 patients, the cTNM matched with pathological TNM compared with 7 patients (41%) in FIGO. The difference between FIGO and pTNM was significant ($p = 0.02$), but that between cTNM and pTNM was not ($p = 0.62$). Among the 35 patients with advanced FIGO stage, 13 patients had different cTNM stage (37%). It was due to PLN involvement in FIGO stage IIB, where cTNM was upstaged to IIIB, and subjectively overestimated FIGO stage IIIB disease, which was actually T2 disease on imaging, thus downstaging to cTNM stage IIB.

LoE 2-

Comparison of the overall recurrence rates between patients in whom FIGO and cTNM had matched with those in whom FIGO and cTNM did not match was statistically insignificant ($p > 0.05$). Stagewise comparison of recurrence also was mostly insignificant except for recurrence rates in the patients with FIGO IIB disease ($p = 0.023$). Similarly, comparison of mortality rates between the 2 groups was statistically insignificant ($p = 0.84$). Comparison of overall recurrence rates and mortality was done between patients in whom FIGO and cTNM had matched with those in whom cTNM was upstaged. Again, although the percentage of recurrence was more in the upstaged group, it failed to achieve statistical significance ($p = 0.19$). Comparison of mortality rates between patients in whom FIGO and cTNM had matched with those in whom cTNM was upstaged did not reveal a significant result ($p = 0.8$).

8.2 Previous initiatives

Seven previous initiatives⁴¹⁹⁻⁴²⁶ presenting guidelines for staging were identified.

8.3 Development group comments

The main purpose of cancer staging is to help clinicians to predict the prognosis for a cancer patient, to guide treatment planning, to evaluate and compare treatment results, to facilitate exchange of information between health professionals and to help in identifying clinical trials that may be appropriate for the patient.

FIGO staging system is the first staging system developed to compare treatment results, however, it is subjective and mainly based on clinical findings by gynaecological examination. LN status is not taken into account. On the other hand, TNM classification is capable to include information to compare to historical results. TNM classification has not been extensively used, hence it is difficult to compare to historical results. It should be noted that TNM classification more accurately reflects the status of the primary tumour and LNs than the FIGO staging system. FIGO staging should also be documented, since both provide complementary information.

As previously mentioned, the LN involvement appears the most powerful prognostic factor influencing survival rate. The presence of a large tumour (especially tumour size > 4 cm), LVSI, deep stromal invasion

and parametrial invasion are other independent factors decreasing survival rates. On the contrary, an early stage is associated with a improvement of survival rates.

The nodal metastasis rate, paracervical invasion and 5-year cancer death rate are increased with a decrease in the thickness of the remaining intact cervical fibromuscular stroma. The minimum thickness of uninvolved stroma seems to be more useful and objective parameter than the depth of the cancer invasion, however, the threshold value of the thickness of cervical fibromuscular stroma sufficient as a barrier against extrauterine spread is not know. The prognosis of some rare tumours such as neuroendocrine carcinoma of the cervix is worse compared with cervical squamous cell carcinomas or adenocarcinomas. Non HPV-related adenocarcinomas or adenosquamous carcinomas have worse survival than squamous cell carcinomas. Grade has little direct influence on survival within any stage.

The role of pelvic examination is to assess the presence of tumour and provide a tumour biopsy. Clinical examination is insufficient to assess tumour size and rule out parametrial invasion and locally advanced disease. For local staging purposes, MRI or US performed by trained sonographer provide the highest diagnostic performance, therefore extensive clinical examination using general anesthesia should be omitted. CT is inferior to MRI to document local tumour extension, similarly the PET-CT has scan value in terms of detection of local spread because of limited spatial resolution. The implementation of MRI or US in preoperative workup make the use of cystoscopy, proctoscopy or intravenous urography redundant. Both imaging modalities can detect the depth of tumour invasion into bladder or rectosigmoid. Biopsy guided by endoscopy might be only required to exclude secondary cancer.

The detection rate of imaging regarding LN and other distant spread depends on their prevalence regarding tumour stage and on size of metastasis. Imaging (US, MRI, CT or PET-CT) shows high specificity in detection of nodal metastases (> 90%) but very low sensitivity in detection of micrometastases (≤ 2 mm) and small volume metastases (< 5 mm). In early stage, the micrometastases are often undetected on imaging and surgical LN assessment is the gold standard for the diagnosis of LN node metastasis(es) in this patient population. Stage T1a1 with no LVSI is associated with extremely low incidence of lymphatic metastases and LN staging is abundant in this category. In LACC, the incidence of extrapelvic disease at the time of initial management is ranging from 10% to 30%, particularly in PALNs and/or chest. The heterogenous data concerning the diagnostic performance of conventional and functional techniques in nodal staging makes any conclusion regarding the routine diagnostic method unreliable. PET-CT can detect PALN metastases only in patient populations with high probability for metastases. The novel imaging, whole-body diffusion weighted MRI or hybrid MRI-PET seem to be useful for differentiation between metastatic and benign LNs and may reduce false readings but their diagnostic performances will require to be evaluated in large, multicentre, prospective studies.

8.4 Guidelines

8.4.1 General recommendations

- ✓ Treatment planning should be made on a multidisciplinary basis (generally at a tumor board meeting) and based on 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 gynecologic cancers.

8.4.2 TNM classification and FIGO



Patients with cervical cancer should be staged according to the TNM classification. Clinical staging (FIGO) should also be documented (Figure 2).



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 tumor status (T), lymph node status (N), and systemic status (M), that is, clinical (c), imaging (i), and/or pathological (p) should be recorded.



LN metastases should be classified according to the TNM classification (see Principles of pathological evaluation).

8.4.3 Prognostic factors



Proper documentation of the following major tumorrelated prognostic factors is recommended:

- TNM and FIGO stage, including a maximum tumor size and detailed description of extracervical tumor extension and nodal involvement (number, size, location).
- Pathological tumor type.
- Depth of cervical stromal invasion and a minimum thickness of uninvolved cervical stroma
- Presence or absence of LVSI.
- Presence or absence of distant metastases.

8.4.4 Local clinical and radiological diagnostic workup



Pelvic examination and biopsy +/- colposcopy are mandatory components to diagnose cervical cancer.



Mandatory initial workup for assessment of pelvic tumor extent and to guide treatment options is pelvic MRI.



Endovaginal/transrectal US 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 US.

8.4.5 Nodal/distant diagnostic workup



In early stage (T1a, T1b1, T2a1), surgical/pathological staging of PLNs is the criterion standard to assess the prognosis and guide treatment (except of T1a1 and no LVSI).



In LACC (T1b2 and higher (except T2a1)) or in early-stage disease with suspicious LNs on imaging, PET-CT, or chest/abdomen CT is recommended for assessment of nodal and distant disease.



PET-CT is the preferred option for treatment planning before chemoradiotherapy with curative intent.



PALN dissection, at least up to inferior mesenteric artery, may be considered in LACC with negative PALNs 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 because it allows histological assessment of the tissue.

Figure 5. FIGO staging and TNM classification

T category ⁴	FIGO stage ⁵⁻⁷	Definition
TX		Primary tumour cannot be assessed
T0		No evidence of primary tumour
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	Tumour 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	Tumour with parametrial invasion
T3	III	Tumour extending to the pelvic sidewall* and/or involving the lower third of the vagina and/or causing hydronephrosis or nonfunctioning kidney
T3a	IIIA	Tumour involving the lower third of the vagina but not extending to the pelvic wall
T3b	IIIB	Tumour extending to the pelvic wall and/or causing hydronephrosis or nonfunctioning kidney
T4	IVA	Tumour invading the mucosa of the bladder or rectum and/or extending beyond the true pelvis (bullous edema is not sufficient to classify a tumour as T4)
	IVB	Tumour invading distant organs

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

Table 1. Pooled data published by Thomeer *et al.*¹¹⁹ on the performance of clinical examination and MRI for detection of parametrial invasion and advanced disease (FIGO stage \geq IIB)

Diagnostic test	Sensitivity	Specificity
Parametrial invasion		
Clinical examination	40% (95% CI = 25-58)	93% (95% CI = 83-89)
MRI	84% (95% CI = 76-90)	92% (95% CI = 90-95)
Advanced disease		
Clinical examination	53% (95% CI = 41-66)	97% (95% CI = 91-99)
MRI	79% (95% CI = 64-89)	93% (95% CI = 88-96)

CI confidence interval, MRI magnetic resonance imaging

Table 2. Pooled data published by Choi *et al.*¹⁸⁰ on the performance of CT, MRI, and PET or PET-CT for detection of metastatic LNs

Diagnostic test	Sensitivity	Specificity
Patient-based comparison		
CT	50% (95% CI = 43-57)	92% (95% CI = 90-94)
MRI	56% (95% CI = 51-62)	91% (95% CI = 90-93)
PET or PET-CT	82% (95% CI = 75-87)	95% (95% CI = 93-97)
Region/node-based comparison		
CT	52% (95% CI = 42-62)	92% (95% CI = 90-94)
MRI	38% (95% CI = 32-43)	97% (95% CI = 97-98)
PET or PET-CT	54% (95% CI = 46-61)	97% (95% CI = 96-98)

CI confidence interval, CT computed tomography, MRI magnetic resonance imaging, PET or PET-CT positron emission tomography or positron emission tomography-computed tomography

Table 3. Pooled data published by Selman *et al.*²³⁰ on the performance of sentinel node biopsy, PET, MRI and CT for prediction of LN status

Diagnostic test	Sensitivity	Specificity
SN biopsy	91.4% (95% CI = 87.1-94.6)	100% (95% CI = 99.6-100)
PET or PET-CT	74.7% (95% CI = 63.3-84.0)	97.6% (95% CI = 95.4-98.9)
MRI	55.5% (95% CI = 49.2-61.7)	93.2% (95% CI = 91.4-94.0)
CT	57.5% (95% CI = 53.5-61.4)	92.3% (95% CI = 91.1-93.5)

CI confidence interval, CT computed tomography, MRI magnetic resonance imaging, PET or PET-CT positron emission tomography or positron emission tomography-computed tomography, SN sentinel node

Table 4. Pooled data regarding the potential impact of mapping method and type of surgery on diagnostic performance of SN biopsy for prediction of LN status

Author ^{reference}	Year	Detection rate	Sensitivity
Mapping method			
<i>Blue dye</i>			
Kadkhodayan <i>et al.</i> ²⁷⁴	2015	80.9% (95% CI = 75.7-85.2)	86.3% (95% CI = 79.9-91.2)
Wang <i>et al.</i> ²⁷⁶	2015	87% (95% CI = 84-90)	87% (95% CI = 79-93)
Tax <i>et al.</i> ^{277,a}	2015	85% (95% CI = 81-87)	NA
Tax <i>et al.</i> ^{277,b}	2015	56% (95% CI = 50-61)	NA
van de Lande <i>et al.</i> ²⁷⁵	2007	84% (95% CI = 79-89)	81% (95% CI = 67-95)
<i>Radiotracer</i>			
Kadkhodayan <i>et al.</i> ²⁷⁴	2015	90.9% (95% CI = 87.7-93.3)	92% (95% CI = 84.3-96.7)
van de Lande <i>et al.</i> ²⁷⁵	2007	88% (95% CI = 83-92)	92% (95% CI = 79-98)
Wang <i>et al.</i> ²⁷⁶	2015	90% (95% CI = 87-93)	87% (95% CI = 78-93)
Tax <i>et al.</i> ^{277,a}	2015	89% (95% CI = 85-92)	NA
Tax <i>et al.</i> ^{277,b}	2015	54% (95% CI = 48-60)	NA
van de Lande <i>et al.</i> ²⁷⁵	2007	88% (95% CI = 83-92)	92% (95% CI = 79-98)
<i>Combined</i>			
Kadkhodayan <i>et al.</i> ²⁷⁴	2015	92.3% (95% CI = 90.2-93.9)	91.3% (95% CI = 87.5-94.2)
Wang <i>et al.</i> ²⁷⁶	2015	97% (95% CI = 96-98)	88% (95% CI = 84-91)
Tax <i>et al.</i> ^{277,a}	2015	94% (95% CI = 93-95)	NA
Tax <i>et al.</i> ^{277,b}	2015	72% (95% CI = 69-74)	NA
van de Lande <i>et al.</i> ²⁷⁵	2007	97% (95% CI = 95-98)	92% (95% CI = 84-98)
<i>Fluorescent imaging</i>			
Kadkhodayan <i>et al.</i> ²⁷⁴	2015	76.5% (95% CI = 60.7-87.2)	90.9% (95% CI = 58.7-99.8)
Type of surgery			
<i>Open</i>			
Kadkhodayan <i>et al.</i> ²⁷⁴	2015	88.5% (95% CI = 84.6-91.4)	91.7% (95% CI = 87.7-94.7)
Wang <i>et al.</i> ²⁷⁶	2015	87% (95% CI = 83-90)	86% (95% CI = 80-90)
van de Lande <i>et al.</i> ²⁷⁵	2007	93% (95% CI = 90-96)	90% (95% CI = 82-95)
<i>Laparoscopic</i>			
Kadkhodayan <i>et al.</i> ²⁷⁴	2015	93.9% (95% CI = 88.2-96.9)	93.2% (95% CI = 87-97)
Wang <i>et al.</i> ²⁷⁶	2015	93% (95% CI = 90-96)	90% (95% CI = 86-94)
van de Lande <i>et al.</i> ²⁷⁵	2007	92% (95% CI = 87-96)	81% (95% CI = 65-92)
<i>Robotic-assisted</i>			
Kadkhodayan <i>et al.</i> ²⁷⁴	2015	90.8% (95% CI = 85.3-94.3)	NA
Wang <i>et al.</i> ²⁷⁶	2015	92% (95% CI = 88-95)	84% (95% CI = 72-92)

^a at least one sentinel lymph node, ^b bilateral detection, CI confidence interval, NA not available,

Table 5. Pooled data published by Kadkhodayan *et al.*²⁷⁴ regarding other potential factors associated with diagnostic performance of SN biopsy for prediction of LN status

Factor	Detection rate	Sensitivity
History of conisation		
Yes	90.9% (95% CI = 84.3-94.9)	NA
No	91.7% (95% CI = 85.6-95.4)	NA
History of pre-surgical therapy	73.8% (95% CI = 65.8-80.4)	94.7% (95% CI = 74-99.9)
FIGO stage		
≤ Ib2	93.6% (95% CI = 88.8-96.5)	91.4% (95% CI = 87.3-94.4)
> Ib2	65.9% (95% CI = 59-72.3)	87% (95% CI = 66.4-97.2)
Tumour size		
≤ 2 cm	93.4% (95% CI = 90.8-95.2)	94.7% (95% CI = 89.3-97.8)
> 2 cm	73.9% (95% CI = 66.4-80.2)	81.7% (95% CI = 74.6-87.5)
Timing of radiotracer injection		
The day before the surgery	90% (95% CI = 87.6-91.8)	90.2% (95% CI = 85.5-93.7)
The same day	93.4% (95% CI = 90.1-95.6)	92.5% (95% CI = 86.9-96.2)
IHC		
Yes	NA	91.5% (95% CI = 88.3-94)
No	NA	88.6% (95% CI = 85.2-91.5)
Fertility sparing surgery	95.8% (95% CI = 91-98.1)	95.5% (77.2-99.9)

CI confidence interval, IHC immunohistochemistry, NA not available

Table 6. Pooled data published by Kang *et al.*³⁹⁶ on the performance of PET or PET-CT for detection of PALN metastasis

Prevalence of PALN metastasis	Sensitivity	Specificity
≤ 15%	5% (95% CI = 0.5-5)	99% (95% CI = 90-100)
> 15%	73% (95% CI = 53-87)	93% (95% CI = 86-97)
No restriction	34% (95% CI = 10-72)	97% (95% CI = 93-99)

CI confidence interval, PALN para-aortic lymph node

Table 7. FIGO staging and TNM classification

T category ⁴	FIGO stage ⁵⁻⁷	Definition
TX		Primary tumour cannot be assessed
T0		No evidence of primary tumour
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 5.00 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 T1a/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	Tumour 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	Tumour with parametrial invasion
T3	III	Tumour extending to the pelvic sidewall* and/or involving the lower third of the vagina and/or causing hydronephrosis or nonfunctioning kidney
T3a	IIIA	Tumour involving the lower third of the vagina but not extending to the pelvic wall
T3b	IIIB	Tumour extending to te pelvic wall and/or causing hydronephrosis or nonfunctioning kidney
T4	IVA	Tumour invading the mucosa of the bladder or rectum and/or extending beyond the true pelvis (bullous edema is not sufficient to classify a tumour as T4)
	IVB	Tumour invading distant organs

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

Table 8. The proposed changes and classification(s) by the GCIG⁴¹⁷

FIGO stage	Definition	Proposed staging	Proposed classification(s)
IB1	Clinically visible lesion ≤ 4.0 cm in greatest dimension	FIGO stage IB1-A	Tumour size ≤ 2 cm
		FIGO stage IB1-B	Tumour size > 2 cm
IB2	Clinically visible lesion > 4.0 cm in greatest dimension	FIGO stage IB2-A	Tumour size > 4 cm ≤ 6 cm
		FIGO stage IB2-B	Tumour size > 6 cm
IIB	With obvious parametrial invasion	FIGO stage IIB-1	Tumour size ≤ 6 cm
		FIGO stage IIB-2	Tumour size > 6 cm
IIIB	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney	FIGO stage IIIB-1	Unilateral pelvic sidewall involvement/unilateral hydronephrosis
		FIGO stage IIIB-2	Bilateral pelvic sidewall involvement/bilateral hydronephrosis

9 Management of stage T1a

9.1 Summary of available scientific evidence

9.1.1 Lymph-vascular space involvement

As part of a pooled analysis⁴²⁷ including 40 reports^{53,428-466}, LVSI was identified in only 8 IA1 microinvasive cases (2.1%) where radical hysterectomy ± LN dissection, trachelectomy, or parametrectomy was performed. Although none of them had nodal involvement, it should be noted that two patients recurred.

LoE 1-

Bisseling *et al.*⁴⁵⁴ reviewed the literature for LVSI status in relation to LN involvement (16 reports^{432,435,443,446,448-452,454,460-465} including their own original data). LVSI was present in 25 of 458 (5.5%) IA1-IA2 cases, none having positive LNs; seven cases with an invasion depth ≤ 3.0 mm, five cases with an invasion depth ≤ 5 mm, ten cases with an invasion depth between 3.1 and 5.0 mm, and three cases with an invasion depth based on tumour volume. It should be noted that absence of LVSI does not exclude the LN involvement, as is illustrated by the 4 cases (0.9%) without LVSI but with LN involvement; two cases with an invasion depth ≤ 3 mm and two cases with an invasion depth based on tumour volume.

LoE 2++

A meta-analysis published by Reynolds *et al.*⁴⁶⁷ (13 reports^{435,443,445,446,449,450,454,460,461,464-466,468} including their own original data) was identified and presents concordant data with those previously mentioned (it should be noted that 10 reports^{435,443,446,449,450,454,460,461,464,465} were also included in the review published by Bisseling *et al.*⁴⁵⁴). Of the 279 IA cases with reported LVSI, only 12 had positive LVSI (pooled proportion 5.1% (95% CI = 2.9-7.9)). There were 368 cases with known depth of invasion less than 5 mm but uncertain width of the tumour. For these 368 cases with unknown lateral extent of tumour, the presence of LVSI was nearly double (pooled proportion 9.3% (95% CI = 5.1-14.4)).

LoE 1-

Twenty-five original studies^{82,469-492} not included in the studies^{427,454,467} mentioned above were identified and present concordant data with those previously reported.

LoE 2-

9.1.2 Lymph node involvement

Of the 383-385 IA1 cases identified by Hou *et al.*⁴²⁷ and who underwent LN dissection, 4-5 (1.2%) were identified with one or more positive regional nodes. Only three patients have been reported to have more than one LN involvement, and only one with bilateral pelvic nodal involvement. Compared with IA1 microinvasive adenocarcinoma, significantly more IA2 patients had one or more positive regional nodes (1.2% versus 3.7%, $p = 0.002$).

LoE 1-

Fifteen original studies^{82,467,469-481} not included in the study published by Hou *et al.*⁴²⁷ and presenting data on LN involvement in IA1 and/or IA2 patients were identified (Table 9, Table 10). Of the 418 IA1 patients and the 343 IA2 patients who underwent LN dissection, only 8 and 13 were identified with one or more positive LNs (1.9% versus 3.8%, respectively).

LoE 2-

PLN dissection was performed in more than half of the literature cases of microinvasive adenocarcinoma identified by Bisseling *et al.*⁴⁵⁴, with a similar low incidence of positives nodes (1.5%) in both FIGO stage IA1 and IA2 disease.

LoE 2++

Of the 210 IA patients who underwent lymphadenectomy identified by Reynolds *et al.*⁴⁶⁷, two patients demonstrated LN metastasis (pooled proportion 2.2% (95% CI = 0.8-4.3)). Authors reported that the rate of LN metastasis was not appreciably different from cases with known depth of invasion less than 5 mm but uncertain width of the tumour (pooled proportion 1.9%

LoE 1-

(95% CI = 0.6-4.0)).

9.1.3 Parametrial invasion

Hou *et al.*⁴²⁷ identified 373 cases (IA1 and IA2, < 5 mm invasion) for whom the status of the parametrium was specifically addressed. Of these, parametrial invasion has been specifically identified in only one (0.27%), a patient with FIGO stage IB1 adenocarcinoma diagnosed at one year after conisation for adenocarcinoma in situ.

LoE 1-

As part of their literature review (fifteen reports^{433,438,439,446,448,450-452,454,461-465,468} including their own original data), Bisseling *et al.*⁴⁵⁴ identified a removal of parametria in 713 cases during radical surgery with comment on involvement in only half of these cases, none of which were involved.

LoE 2++

Reynolds *et al.*⁴⁶⁷ reported that there was no appreciable difference between the pooled rates of parametrial involvement between patients with known depth of invasion less than 5 mm but uncertain width of the tumour and patients who met strict FIGO definition of IA adenocarcinoma of the cervix (1.6% (95% CI = 0.3-4.0) and 1.8% (95% CI = 0.5-4.1), respectively).

LoE 1-

Seventeen original studies^{82,469,470,474,475,479,481,482,489,493-500} not included in the studies^{427,454,467} mentioned above were also identified and all of them showed that less than 1.5% of patients had parametrial involvement.

LoE 2-

9.1.4 Cone margin status

In a pooled analysis⁵⁰¹ enrolling 962 patients with FIGO stage IA1 disease⁵⁰¹⁻⁵⁰⁴, 88.5% of patients with a clear resection margin after conisation had no dysplasia in the repeat conisation/hysterectomy specimen; 45.2% and 10.9% of patients with cervical intraepithelial neoplasia (CIN) I-III at the conisation resection margin had residual CIN I-III and invasive cancer in the repeat conisation/hysterectomy specimen, respectively.

LoE 1-

Twenty-six identified studies^{82,432,433,460,465,468,469,471,474,487,488,505-519} have reported a relationship between cone margin status and the presence of residual disease in hysterectomy specimens after a LEEP or CKC. The frequencies of residual disease have been reported to be clearly higher in patients with positive margins than those with negative margins. It should be noted that the available data does not allow to know if the relatively high percentage of residual disease in case of free margins in some studies is due to inadequate sampling rather than to "skip lesions".

LoE 2-

9.1.5 Recurrence

Despite of significantly more IA2 patients having positive regional LNs (1.2% (IA1) versus 3.7% (IA2), $p = 0.002$), the recurrence rates between IA1 and IA2 patients were not significantly different in the pooled analysis published by Hou *et al.*⁴²⁷ (1.6% versus 2.8%, $p = 0.15$, respectively). With respect to fertility-sparing surgery, of 102-138 managed by cone/LEEP/LLETZ, a recurrence has been observed in only four IA1 patients (3.4%)^{436,438,447,449}. Three patients had either residual glandular and squamous dysplasia, close margin, or persistently abnormal cervical cytology^{436,447,449}. No data was available with respect to margins for the fourth⁴³⁸. One case of recurrence has been observed in the 45 IA2 cases managed by local excision (2.2%)⁴⁶⁵.

LoE 1-

As part of their literature review, Bisseling *et al.*⁴⁵⁴ noted a recurrence in 2.4% of IA1-IA2 patients. Recurrence was reported in 6 of the 383 patients (1.6%) with a known invasion depth ≤ 3 mm, and in 5 of the 336 patients (1.5%) with a known invasion depth between 3.1 and 5.0

LoE 2++

mm. No recurrences occurred in 59 FIGO stage IA1 cases with a known initial treatment of conisation alone.

Of the 217 cases of FIGO stage IA1, 47 cases of FIGO stage IA2, and 103 cases defined as FIGO stage IA but were not further stratified, 7 cases of recurrences (2, 1, and 4, respectively) were identified by Reynolds *et al.*⁴⁶⁷. For the cases with known depth of invasion less than 5 mm but uncertain width of the tumour, the pooled recurrence rate was more than double as compared with those for the cases that met criteria for FIGO stage IA (4.9% (95% CI = 2.6-8.0) and 2.2% (95% CI = 0.8-4.2), respectively).

LoE 1-

Thirty original studies^{82,469-471,473-487,489-492,509,520-525} not included in the studies^{427,454,467} mentioned above were identified and present concordant data with those previously reported concerning the low recurrence rates of the FIGO stage IA1 (1,594 cases^{82,469-471,473-476,482-487,489,520,521,525}, mean: 2.3%) and IA2 patients (714 cases^{82,469,473,475,477-482,487,490-492,509,520,522-524}, mean: 3.1%) (Table 9, Table 10).

LoE 2-

9.1.6 Survival

Of the 814-862 IA1 cases^{53,428-466} and the 487-493 IA2 cases^{53,429,432,434,435,437-439,441-444,446,449-451,453,454,456,459,462-465,526,527} identified by Hou *et al.*⁴²⁷, the overall survival (OS) rates were 99% and 98%, respectively. Although comparable to IA1 microinvasive adenocarcinoma, the IA2 patients received more aggressive therapy. The number of IA1 and IA2 patients managed by conisation, SH, RH, or other procedures (that included trachelectomy, abdominal or vaginal, and parametrectomy, usually after hysterectomy or conisation as the initial procedure) was 102-138 (12-17.2%), 159-205 (mean: 22.6%), 343-389 (43.9%), and 14-19 (2.0%) for IA1 patients (Table 9), and 49 (10%), 142-162 (30.9%), 265-276 (55.1%), and 15 (3.1%) for IA2 patients, respectively (Table 10). More IA2 patients underwent radical surgeries (IA2, 55.1% versus IA1, 43.9%, $p = 0.03$). It should be noted that radiotherapy was employed more often for IA2 than IA1 patients (5.7% versus 1.9-2.0%, $p < 0.001$).

LoE 1-

Twenty-three original studies^{469,471-478,480-482,484-487,489-492,520-522} not included in the study published by Hou *et al.*⁴²⁷ were identified and present concordant data with those previously reported concerning the high survival rates of the FIGO stage IA1 (1,131 cases^{471,472,474-476,482,484-486,489,520,521}, mean OS rate: 99.6%) and IA2 patients (617 cases^{469,472,473,475,477,478,480-482,487,490-492,520,522}, mean OS rate: 97.6%) (Table 9, Table 10).

LoE 2+

Four identified studies^{46,82,438,528} have suggested that oncologic outcomes are equivalent for conisation and hysterectomy. As part of a large-scale study⁴⁶ (3,987 patients from the Surveillance, Epidemiology, and End Results (SEER) database), survival was similar for conisation and hysterectomy for FIGO stages IA1 and IA2 adenocarcinoma (FIGO stage IA1: HR = 1.84 (95% CI = 0.66-5.17) and FIGO stage IA2: HR = 0.87 (95% CI = 0.33-2.26)). Survival was also examined in a Cox proportional hazards model in a second large-scale study (1,409 women aged 40 years or younger with FIGO stage IA1 cervical cancer)⁵²⁸. Accounting for other prognostic variables, there was no difference in survival between conisation and hysterectomy (HR = 0.65, 95% CI = 0.23-1.47). At 5 years, 98% (95% CI = 96-99) of patients who underwent hysterectomy and 99% (95% CI = 97-99) of those who underwent conisation were alive.

In the study published by Qian *et al.*⁸², there was no statistically significant difference in progression-free survival (PFS) between the FIGO stage IA1 patients treated by conisation and hysterectomy (92.3% versus 98.8%, $p = 0.07$).

9.2 Previous initiatives

Nine previous initiatives^{419,420,422-426,529-531} presenting guidelines for management of stage T1a were identified.

9.3 Development group comments

Diagnosis and management of T1a cervical cancer should be based on an accurate pathology examination by an expert pathologist. Histologic specimen should be intact on a conisation or excisional form. Fragmentation of the specimen and thermal artefacts should be avoided as they can adversely influence the pathology interpretation of the actual extent of the tumour and the marginal status. Loop or laser conisations is preferable to CKC for young women desiring fertility preservation. Orientation of the specimen is also necessary for the pathologist to determine the exact location of the tumour. A specialist pathology review should accurately measure the depth of invasion, the horizontal dimension, the marginal status and a reliable assessment of LVSI. Cone margin status represents a strong predictive factor of residual disease since it has been shown that patients with positive resection margins have a higher frequency of residual disease in hysterectomy specimens after a LEEP or CKC.

The frequencies of residual disease have been reported to be clearly higher in patients with positive margins than those with negative margins. The reported relatively high percentage of residual disease in cases of free margins could be attributed to either inadequate sampling or to “skip lesions”. It should be noted that the available scientific data are inconclusive.

Management of patients with stage T1a1 cervical cancer should be individualised. Management should depend on the age of the patient and the desire for fertility preservation. The presence or absence of LVSI should also be considered for treatment decision. LVSI has been reported as strong predictor of LN involvement for T1a1 cervical cancer patients. LN involvement is reported of low incidence for patients with T1a disease. Based on the available scientific evidence for T1a1 LVSI- patients, LN staging is not indicated. For LVSI+ patients, LN staging can be considered. Management of T1a1 cervical cancer by conisation can be considered as definitive treatment as hysterectomy does not improve survival. Recurrence rates for patients with T1a1 cervical cancer were reported low with different treatment modalities either radical or conservative.

In patients with stage T1a2 disease without LVSI, conisation alone or simple hysterectomy is an adequate treatment with an excellent local control. There is no need for parametrial resection since involvement of the parametria is not reported. LN staging for LVSI- patients can be considered since the negative LVSI status does not necessarily exclude LN involvement. In patients with stage T1a2 LVSI+, it should be noted that even if parametrial involvement is rare, it can not be excluded. LN staging should be performed in LVSI+ patients due to the possibility of LN involvement.

SLN biopsy without additional PLND is an acceptable method of LN staging in experienced centers. There are no evidence to support routine completion surgery by hysterectomy after conservative management of stage T1a2.

9.4 Guidelines

9.4.1 Diagnosis of stage T1a disease

- ✓ Diagnosis of T1a cancer should be based on a conization (or excision) specimen examined by an expert pathologist. Management must be based on an expert pathology review, with accurate measurement of the maximum horizontal 2 dimensions, depth of invasion, margin status, coexisting pathology, and reliable assessment of LVSI.
- ✓ Loop or laser conization is preferable to CKC in women desiring fertility preservation. Maximum care should be taken to provide an intact (unfragmented) specimen with minimal thermal artifact. 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).

9.4.2 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 conization should be performed to rule out more extensive invasive disease.
- B LN staging is not indicated in T1a1 LVSI-negative patients but can be considered in T1a1 LVSI-positive patients. SLN biopsy (without additional PLN dissection) is an acceptable method of LN staging.
- C Conization 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.

9.4.3 Management of stage T1a2 disease

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

Table 9. Original studies presenting data for treatment modalities, involved parametria, lymph-vascular space and LNs, recurrences and survivals in FIGO stage IA1 patients

Author ^{reference}	Year	N	Type of surgical therapy				Number of cases per parameter					Follow-up (year)
			Cone	SH	RH	other	LVSI	LND	LN+	Recurr.	DOD	
Sachs <i>et al.</i> ^{441,a}	1975	1	0	1	0	0	nr	0	0	0	0	nr
Nakajima <i>et al.</i> ^{444,a}	1983	14	0	0	7	0	nr	7	0	0	0	5
Berek <i>et al.</i> ^{430,a}	1985	6	0	0	6	0	nr	6	0	0	0	1.5-11
Simon <i>et al.</i> ^{455,a}	1986	6	0	0	0	0	0	nr	0	0	0	1-10
Teshima <i>et al.</i> ^{434,a}	1985	11	0	0	22	0	0	11	0	1	0	1-10
Andersen <i>et al.</i> ^{456,a}	1989	8	1	7	0	0	nr	0	0	0	0	0.5-8
Fu <i>et al.</i> ^{431,a}	1987	3	3	0	0	0	0	0	0	3-6	nr	nr
Matsukuma <i>et al.</i> ^{445,a,c}	1989	8	1	4	3	0	0	3	0	0	0	2.2-6.7
Rollason <i>et al.</i> ^{457,a}	1989	2	0	1	1	0	0	1	0	0	0	0.25-2
Burghardt <i>et al.</i> ^{442,a}	1989	3	0	0	3	0	0	nr	0	0	0	5
Angel <i>et al.</i> ^{458,a}	1992	9	0	1	7	1	0	8	0	0	0	0.08-10.6
Matthews <i>et al.</i> ^{53,a}	1993	24	0	0	0	0	0	24	nr	0	0	0.6-18
Jones <i>et al.</i> ^{440,a}	1993	8	1	0	7	0	0	6	0	0	0	4.3
Kaspar <i>et al.</i> ^{459,a}	1993	22	0	2	20	0	0	22	0	0	0	1-10
Östör <i>et al.</i> ⁴⁸²	1994	109	16	81	1	11	0	nr	nr	2	0	8
van den Broek <i>et al.</i> ^{436,a}	1995	1	0	1	0	0	0	1	0	1	1	2
Kennedy <i>et al.</i> ^{447,a}	1995	1	1	0	0	0	nr	0	1	1	0	1.42
Wolf <i>et al.</i> ^{429,a}	1996	2	0	2	0	0	nr	0	nr	0	0	0.58-11
Kaku <i>et al.</i> ^{435,a}	1997	21	1	20	0	0	16	0	0	0	0	2-19.3
Östör <i>et al.</i> ^{432,a}	1997	43	12	21	10	0	4	22	0	0	0	0.25-12
Kurian <i>et al.</i> ^{437,a}	1999	8	1	7	0	0	0	nr	0	0	0	2-7
Nicklin <i>et al.</i> ^{443,a}	1999	26	1	11	15	0	0	16	0	0	0	0.25-9.7
Schorge <i>et al.</i> ^{460,a,c}	1999	21	1	4	16	0	0	16	0	0	0	2.5-14.3
Covens <i>et al.</i> ^{451,a}	1999	47	0	0	47	0	1	47	0	1	0	4.17
Elliott <i>et al.</i> ^{449,a}	2000	19	nr	nr	nr	nr	0	≥ 2	1	2	2	10
Nagarsheth <i>et al.</i> ^{448,a,b,c}	2000	1	0	1	0	0	1	1	1	0	0	0.03
Schorge <i>et al.</i> ^{461,a,b,c}	2000	6	5	1	0	0	0	0	0	0	0	0.5-1.7
Lee <i>et al.</i> ^{462,a}	2000	38	22	16	0	0	nr	0	nr	nr	0	2-16
Östör <i>et al.</i> ^{433,a}	2000	22	nr	nr	4	8	0	0	nr	nr	nr	nr
McHale <i>et al.</i> ^{468,b,c}	2001	20	4	2	14	0	nr	14	0	0	nr	nr
Webb <i>et al.</i> ^{439,b}	2001	131	20	54	50	7	nr	50	0	nr	nr	nr
Utsugi <i>et al.</i> ^{452,a,b}	2001	65	nr	nr	nr	nr	nr	nr	nr	1	0	5.3
Kasamatsu <i>et al.</i> ^{450,a,b,c}	2002	24	0	3	21	0	1	21	0	1	1	0.75-29.0
Smith <i>et al.</i> ^{438,a,b}	2002	200	31	82	76	11	nr	70	2	3	3	0.5-9.9
Erzen <i>et al.</i> ^{453,a}	2002	9	12	nr	nr	nr	nr	nr	nr	0	0	3.59 ± 16.2
Hirai <i>et al.</i> ^{464,a,b,c}	2003	22	0	0	22	0	0	22	0	1	0	0.5-10.3
Balega <i>et al.</i> ^{463,a,b,c}	2004	17	0	0	17	0	0	17	0	0	0	3.59 ± 16.2
Raspagliesi <i>et al.</i> ⁴⁸³	2005	67	67	0	0	0	50	nr	nr	6	nr	10
Poynor <i>et al.</i> ^{465,a,b,c}	2006	21	2	4	14	0	0	14	0	0	0	≥ 3
Ceballos <i>et al.</i> ^{446,a,b,c}	2006	29	1	4	22	2	0	24	0	1	1	0.25-18
Lee <i>et al.</i> ⁴⁷²	2006	174	7	106	55	6	7	116	7	nr	2	3

^a study included in the review published by Hou *et al.*⁴²⁷, ^b study included in the review published by Bisseling *et al.*⁴⁵⁴, ^c study included in the review published by Reade *et al.*⁵³², Cone (cone, loop electrosurgical excision procedure, large loop excision of the transformation zone), DOD dead of disease, LN+ positive lymph nodes, LND lymph node dissection, LVSI lymph-vascular space involvement, nr not reported, Recurr. recurrence, RH radical hysterectomy ± LND, SH simple hysterectomy (abdominal or vaginal ± LND)

Original studies presenting data for treatment modalities, involved parametria, lymph-vascular space and LNs, recurrences and survivals in FIGO stage IA1 patients (continued)

Author ^{reference}	Year	N	Type of surgical therapy				Number of cases per parameter					Follow-up (year)
			Cone	SH	RH	other	LVSI	LND	LN+	Recurr.	DOD	
Tseng <i>et al.</i> ⁵²⁰	2006	41	41	0	0	0	nr	nr	nr	0	0	3.1
Bisseling <i>et al.</i> ^{454,a,b,c}	2007	29	16	9	4	0	2	10	0	0	0	6
Yahata <i>et al.</i> ^{466,a,c}	2008	16	4	0	3	nr	0	3	0	0	0	2-13
Singh <i>et al.</i> ^{428,a}	2008	1	1	0	0	0	0	0	0	1	1	4
Lee <i>et al.</i> ⁴⁸⁵	2009	85	85	0	0	0	0	nr	nr	1	0	6.75
Lee <i>et al.</i> ⁴⁸⁴	2009	75	22	27	26	0	29	nr	nr	0	0	3
Yahata <i>et al.</i> ⁴⁷¹	2010	27	10	0	17	0	0	17	0	0	0	6.25
Reynolds <i>et al.</i> ^{467,c}	2010	52	7	16	29	0	3	34	1	0	nr	6
Baalbergen <i>et al.</i> ^{473,c}	2011	33	15	14	4	0	2	4	0	1	nr	6
Yoshinaga <i>et al.</i> ⁴⁸⁶	2011	84	19	4	61	0	5	0	0	6	0	nr
Haller <i>et al.</i> ⁴⁷⁴	2011	276	152	112	12	0	11	52	0	12	3	5
Al-Kalbani <i>et al.</i> ^{475,c}	2012	36	23	5	8	0	1	11	0	0	0	3
Sopracordevole <i>et al.</i> ⁴⁸⁷	2012	6	6	0	0	0	0	nr	nr	2	nr	nr
Chen <i>et al.</i> ⁴⁸⁹	2013	81	0	60	21	0	7	nr	nr	0	0	nr
He <i>et al.</i> ⁴⁷⁶	2014	108	25	78	5	0	5	19	0	0	0	≥ 1
Qian <i>et al.</i> ⁸²	2014	280	41	200	39	0	20	39	0	5	0	2.7
Sopracordevole <i>et al.</i> ⁴⁸⁸	2014	60	16	37	6	1	2	nr	nr	nr	nr	nr
Lee <i>et al.</i> ⁴⁷⁰	2014	169	18	55	96	0	3	116	0	2	nr	nr
Yoneda <i>et al.</i> ⁴⁶⁹	2015	10	10	0	0	0	10	10	0	0	0	4.25
Day <i>et al.</i> ⁵²¹	2016	25	25	0	0	0	nr	nr	nr	0	0	7

^a study included in the review published by Hou *et al.*⁴²⁷, ^b study included in the review published by Bisseling *et al.*⁴⁵⁴, ^c study included in the review published by Reade *et al.*⁵³², Cone (cone, loop electrosurgical excision procedure, large loop excision of the transformation zone), DOD dead of disease, LN+ positive lymph nodes, LND lymph node dissection, LVSI lymph-vascular space involvement, nr not reported, Recurr. recurrence, RH radical hysterectomy ± LND, SH simple hysterectomy (abdominal or vaginal ± LND)

Table 10. Original studies presenting data for treatment modalities, involved parametria, lymph-vascular space and LNs, recurrences and survivals in FIGO stage IA2 patients

Author ^{reference}	Year	N	Type of surgical therapy				Number of cases per parameter					Follow-up (year)
			Cone	SH	RH	other	LVSI	LND	LN+	Recurr.	DOD	
Sachs <i>et al.</i> ^{441,a}	1975	1	0	0	1	0	0	1	0	0	0	nr
Nakajima <i>et al.</i> ^{444,a}	1983	9	0	0	4	0	0	0	0	0	0	5
Teshima <i>et al.</i> ^{434,a}	1985	11	0	0	11	0	0	11	0	0	0	1/4-14
Andersen <i>et al.</i> ^{456,a}	1989	1	0	1	0	0	nr	0	0	0	0	nr
Burghardt <i>et al.</i> ^{442,a}	1989	5	1	0	4	0	0	nr	0	0	0	5
Greer <i>et al.</i> ⁵⁰⁹	1990	50	0	0	50	0	nr	nr	2	3	nr	nr
Burghardt <i>et al.</i> ⁵²²	1991	89	18	23	48	0	nr	nr	nr	5	2	≥ 5
Matthews <i>et al.</i> ^{53,a}	1991	12	0	0	12	0	nr	12	nr	3	nr	0.6-18
Sevvin <i>et al.</i> ⁴⁹⁰	1992	42	0	0	42	0	5	nr	0	0	4	≥ 5
Jones <i>et al.</i> ^{527,a}	1993	3	0	0	3	0	0	nr	0	0	0	4.3
Kaspar <i>et al.</i> ^{459,a}	1993	3	3	nr	nr	3	3	nr	1-10	nr	nr	nr
Yaegashi <i>et al.</i> ⁴⁹¹	1994	22	1	3	18	0	0	0	0	0	0	5.4
Östör <i>et al.</i> ⁴⁸²	1994	91	8	33	50	0	nr	nr	nr	5	2	8
Wolf <i>et al.</i> ^{429,a}	1996	1	0	1	0	0	0	0	nr	0	0	0.58-11
Piura <i>et al.</i> ^{526,a}	1996	3	0	2	1	0	0	2	0	0	0	10
Buckley <i>et al.</i> ⁴⁷⁸	1996	94	0	0	94	0	31	94	7	5	4	6.9
Kaku <i>et al.</i> ^{435,a}	1997	8	8	1	1	8	1	1	nr	nr	nr	2-19.3
Östör <i>et al.</i> ^{432,a}	1997	34	4	14	16	0	3	26	0	2	0	1/4-12
Kurian <i>et al.</i> ^{437,a}	1999	2	0	2	0	0	0	0	nr	0	0	2-7
Nicklin <i>et al.</i> ^{443,a}	1999	4	0	0	4	0	0	0	0	0	0	1/4-9.7
Covens <i>et al.</i> ^{451,a}	1999	21	0	0	21	0	2	21	2	2	1	4.1
Elliott <i>et al.</i> ^{449,a}	2000	29	0	nr	nr	nr	nr	nr	nr	1	1	10
Lee <i>et al.</i> ^{462,a}	2000	2	0	2	0	0	2	0	0	0	0	2.16
Webb <i>et al.</i> ^{439,b}	2001	170	18	64	83	5	nr	90	1	nr	nr	nr
Smith <i>et al.</i> ^{438,a,b}	2002	286	29	116	134	7	nr	nr	1	4	4	0.08-9.9
Kasamatsu <i>et al.</i> ^{450,a,b,c}	2002	4	0	0	4	0	0	4	0	0	0	0.75-29
Erzen <i>et al.</i> ^{453,a}	2002	8	8	nr	nr	nr	nr	nr	nr	nr	nr	3.59 ± 16.2
Hirai <i>et al.</i> ^{464,a,b,c}	2003	6	0	0	6	0	0	6	0	1	0	3
Schlaerth <i>et al.</i> ⁴⁷⁷	2003	8	0	0	0	8	1	nr	0	0	0	4
Balega <i>et al.</i> ^{463,a,b,c}	2004	31	0	0	31	0	4	31	0	0	0	0.5-10.3
Poynor <i>et al.</i> ^{465,a,b,c}	2006	12	1	0	10	1	1	12	0	0	0	3
Ceballos <i>et al.</i> ^{446,a,b,c}	2006	3	0	0	3	0	0	3	0	0	0	0.42-13
Lee <i>et al.</i> ⁴⁷²	2006	28	0	1	27	0	4	27	1	nr	0	3
Tseng <i>et al.</i> ⁵²⁰	2006	15	15	0	0	0	nr	nr	nr	1	1	3.1
Bisseling <i>et al.</i> ^{454,a,b,c}	2007	9	2	3	5	7	2	7	0	0	0	6
van Meurs <i>et al.</i> ^{479,c}	2009	14	0	10	4	0	3	4	0	0	nr	5.75
Reynolds <i>et al.</i> ^{467,c}	2010	14	1	2	9	2	0	12	0	0	nr	6
Schlaerth <i>et al.</i> ^{477,c}	2003	6	6	0	0	0	0	6	0	0	nr	4
Baalbergen <i>et al.</i> ^{473,c}	2011	26	7	6	13	0	4	13	0	0	0	6
Fagotti <i>et al.</i> ⁵²³	2011	4	4	0	0	0	nr	nr	nr	0	nr	1.3

^a study included in the review published by Hou *et al.*⁴²⁷, ^b study included in the review published by Bisseling *et al.*⁴⁵⁴, ^c study included in the review published by Reade *et al.*⁵³², Cone (cone, loop electrosurgical excision procedure, large loop excision of the transformation zone), DOD dead of disease, LN+ positive lymph nodes, LND lymph node dissection, LVSI lymph-vascular space involvement, nr not reported, Recurr. recurrence, RH radical hysterectomy ± LND, SH simple hysterectomy (abdominal or vaginal ± LND)

Original studies presenting data for treatment modalities, involved parametria, lymph-vascular space and LNs, recurrences and survivals in FIGO stage IA2 patients (*continued*)

Author ^{reference}	Year	N	Type of surgical therapy				Number of cases per parameter					Follow-up (year)
			Cone	SH	RH	other	LVSI	LND	LN+	Recurr.	DOD	
Al-Kalbani <i>et al.</i> ^{475,c}	2012	9	1	0	8	0	1	9	0	0	0	3
Palaia <i>et al.</i> ⁴⁹²	2012	5	0	5	0	0	0	5	nr	0	0	3.17
Raju <i>et al.</i> ⁵²⁴	2012	7	0	5	2	0	nr	nr	nr	0	nr	8
Smrkolj <i>et al.</i> ⁴⁸⁰	2012	89	66	15	8	0	12	46	0	1	1	18.78
Sopracordevole <i>et al.</i> ⁴⁸⁷	2012	1	1	0	0	0	0	nr	nr	0	0	7.2
Mahawerawat <i>et al.</i> ⁴⁸¹	2013	58	0	0	58	0	6	58	2	1	1	6
Qian <i>et al.</i> ⁸²	2014	44	2	9	32	1	5	34	1	0	0	2.9
Sopracordevole <i>et al.</i> ⁴⁸⁸	2014	9	0	2	7	0	3	nr	nr	nr	nr	nr
Yoneda <i>et al.</i> ⁴⁶⁹	2015	40	40	0	0	0	5	40	2	1	0	4.25

^c study included in the review published by Reade *et al.*⁵³², Cone (cone, loop electrosurgical excision procedure, large loop excision of the transformation zone), DOD dead of disease, LN+ positive lymph nodes, LND lymph node dissection, LVSI lymph-vascular space involvement, nr not reported, Recurr. recurrence, RH radical hysterectomy ± LND, SH simple hysterectomy (abdominal or vaginal ± LND)

10 Management of stages T1b1/T2a1

10.1 Summary of available scientific evidence

10.1.1 Primary radiotherapy

A RCT⁸⁴ comparing the effectiveness and safety of primary surgery for early stage cervical cancer (FIGO stages IB-IIA) with primary radiotherapy was identified. The median total dose of external pelvic irradiation was 47 (range 40-53) Gy during 3-5 weeks, depending on the tumour volume and nodal status. Radical surgery consisted of a radical hysterectomy and PLN dissection. Adjuvant radiotherapy was delivered after surgery for women with surgical stage pT2b or greater, less than 3 mm of safe cervical stroma, cut-through, or positive nodes. The paraortic region was irradiated in case of metastases in the surgical specimen in common iliac or paraortic nodes. Fifty-four percent of patients with cervical diameter \leq 4 cm who underwent radical surgery also received adjuvant external pelvic irradiation (total dose : 50.4 Gy over 5-6 weeks).

LoE 1+

Among patients with cervical diameter \leq 4 cm, pelvic or distant relapses were observed in 13% of patients who underwent radical surgery alone and in 18% of patients who received radiotherapy after a median follow-up of 87 months. Five-year actuarial survival stratified by cervical diameter for the surgery (\pm radiotherapy) and radiotherapy groups was 87% and 90%, respectively. Five-year actuarial disease-free survival (DFS) for the surgery (\pm radiotherapy) and radiotherapy groups was 80% and 82%, respectively. The between-group differences were not significant. In the surgery alone group, 31% of patients with cervical diameter \leq 4 cm showed severe (grade 2-3) short-term or long-term morbidity that required medical or surgical treatment compared with 29% of patients in the surgery + adjuvant radiotherapy, and 12% of patients in the radiotherapy group.

A systematic review⁵³³ was identified but is not described because it contains only the RCT⁸⁴ mentioned above.

As part of a large-scale study (3,551 patients with tumour size < 4 cm from the SEER database), Bansal *et al.*⁸⁵ performed a Cox proportional hazards model that was adjusted for other prognostic variables (age, race, SEER registry, marital status, histologic finding, tumour grade, adjuvant radiation, tumour size, and stage) and observed that performance of radical hysterectomy was associated with a 62% reduction in mortality compared with radiation for women with tumour size < 4 cm (HR = 0.38 (95% CI = 0.30-0.48)). It should be noted that no information concerning the radiation therapy protocols evaluated is available.

LoE 2-

Another study⁵³⁴ was identified and present concordant data with those mentioned above. In this study, PFS, OS and disease-specific survival (DSS) were all longer for patients treated primarily with radical hysterectomy compared with patients treated primarily with radiotherapy (89% versus 70%, $p < 0.001$; 95% versus 70%, $p < 0.001$; 96% versus 78%, $p < 0.001$; respectively). It should be noted that 22% of patients received postoperative radiation, (2) some patients treated primarily with radiotherapy also received chemotherapy, and (3) patients treated by primary radiotherapy were older, had larger tumours, and were more likely to have medical comorbidities than patients treated primarily with radical surgery.

Derks *et al.*⁵³⁵ compared long-term morbidity and quality of life after primary surgery or primary radiotherapy for stage IB/II cervical cancer. Although global health scores were not significantly different, multivariate analysis showed that primary (chemo)radiotherapy had a negative impact on physoccal and social functioning, financial problems and symptom experience and leads to more diarrhea, sexual/vaginal symptoms, and sexual worry.

Lymphedema was significantly associated with radical hysterectomy with pelvic lymphadenectomy.

10.1.2 Primary chemoradiotherapy

Kong *et al.*⁵³⁶ compared treatment outcomes and treatment-related morbidities of radical hysterectomy followed by adjuvant therapy (radiotherapy or chemoradiotherapy) and primary chemoradiotherapy in patients with FIGO stages IB-IIA cervical cancer. Adjuvant chemoradiotherapy using a 5-FU and cisplatin regimen was given to patients who had one or more high-risk pathological features, including microscopic parametrial invasion, LN metastasis, or involvement of the resection margin. Postoperative radiotherapy was given as whole pelvis external-beam radiation therapy with or without brachytherapy with a total median pelvic dose of 49.30 Gy over 6 weeks. Brachytherapy boosts, in combination with external-beam radiotherapy, were considered for patients with tumour extension to the vaginal cuff margin. Primary chemoradiotherapy was administered with a total median pelvic dose 81.50 Gy.

LoE 2-

Both the local recurrence (5.6% in the primary chemoradiotherapy group versus 11.1% in the primary surgery group, $p = 0.489$) and distant metastasis (7.4% in both treatment groups, $p > 0.999$) was similar for both treatment groups (13.0% versus 20.4%, respectively, $p = 0.302$). No significant difference with respect to 5-year DFS was also reported (83.1% versus 77.4%, respectively, $p = 0.228$). The incidence rates of late grade 3 genitourinary adverse reactions were significantly higher in the primary surgery group (0.0% versus 14.8%, $p = 0.006$). However, no differences were observed for grade 3 hematological complications (18.5% versus 22.2%, $p = 0.633$), gastrointestinal complications (1.9% versus 5.6%, $p = 0.618$), and late grade 3 lower limb lymphedema (3.7% versus 13.0%, $p = 0.161$) between treatment groups.

Derks *et al.*⁵³⁷ compared survival and toxicity after abandoned hysterectomy and primary treatment with chemoradiotherapy versus completed hysterectomy followed by adjuvant (chemo)radiotherapy for patients with FIGO stage IB/IIA LN-positive cervical cancer. Recurrences appeared to be more pelvic in the chemoradiotherapy group compared with the radical hysterectomy with pelvic lymphadenectomy group (16% versus 2%, $p = 0.014$). Time to recurrence was longer after radical hysterectomy with pelvic lymphadenectomy group (18 months versus 11 months, $p = 0.011$). As part of a multivariate analysis, treatment modality, adjusted for LN characteristics, was not associated with DFS. In the abandoned hysterectomy and primary treatment with chemoradiotherapy group, more grades 3 and 4 toxicity was reported (59% versus 30%, $p = 0.006$). It should be noted that (1) the groups are significantly unbalanced in terms of administration of chemotherapy and/or brachytherapy, number of removed nodes and the number of positive nodes and (2) the used techniques for applying radiotherapy might be somewhat outdated.

10.1.3 Neoadjuvant chemotherapy

Kim *et al.*⁵³⁸ performed a meta-analysis to determine the efficacy of NACT in patients with FIGO stages IB1 to IIA cervical cancer when compared with primary surgical treatment. There were no differences in OS, PFS, overall and loco-regional recurrences between the two treatments. However, NACT was associated with a lower rate of distant metastasis (OR = 0.61 (95% CI = 0.42-0.89)). The authors also mentioned that NACT decreased the need for adjuvant radiotherapy when compared with primary surgical treatment (OR = 0.57 (95% CI = 0.33-0.98)). It should be noted that these results have to be interpreted cautiously due to (1) the heterogeneity of NACT regimens used in the nine included studies^{77,539-546}, and (2) the heterogeneity in terms of indications for adjuvant radiotherapy after surgery among studies.

LoE 1-

Among the nine studies^{77,539-546} included in this meta-analysis⁵³⁸, two RCTs^{77,540} present data taking into account patients with FIGO stage IB1 cervical cancer specifically. In the first one, Sardi *et al.*⁵⁴⁰ assessed if NACT consisting of cisplatin (50 mg/m²), vincristine (1 mg/m²), and bleomycin (25 mg/m², day 1-3) for 3 courses at 10-day intervals can improve survival before surgery + adjuvant whole-pelvis external irradiation (50 Gy).

A complete or partial response was observed in 90.2% of patients with FIGO stage IB1. No cases of grade 3 or 4 hematological or gastrointestinal toxicity were observed. After 8 years of follow-up, the OS was not statistically significant between the control group and the NACT group. Pelvic recurrences were almost the same in both groups (10.6% versus 9.8%, respectively). It should be noted that DFS and OS rates between the control group and the chemotherapy responders in the NACT group were not significantly different. It should also be noted that (1) the operative rate was not increased by the use of NACT (all patients in both groups were treated surgically), and (2) LVSI and LN metastases were significantly more frequent in the control group ($p < 0.007$ and $p < 0.04$, respectively).

In the second one⁷⁷, the NACT schedule was cisplatin (75 mg/m² on day 1) and 5-FU (24 mg/kg/d from day 1 to day 5). This treatment was repeated at 3-week intervals for two courses. After NACT, all patients underwent radical hysterectomy and PLN dissection. Within the NACT group, surgery was followed by pelvic radiation in 61.5% of patients. In the primary surgery group, 53.7% of patients received adjuvant whole pelvic radiation.

LoE 1+

The overall clinical response rate to NACT was 84.6% and included complete response in 7.7% of patients, partial response in 76.9% of patients, and stable disease in the remaining patients (15.4%). None of the patients showed progressive disease. For patients whose cervical diameter was 4 cm or smaller, the 5-year actuarial survival for NACT and primary surgery groups was 85.7% and 75.0%, respectively, with no significant difference between the groups ($p = 0.17$).

Results from the sixteen other identified studies⁵⁴⁷⁻⁵⁶² are limited notably by the small number of patients evaluated and the heterogeneity of NACT regimens used.

LoE 3

10.1.4 Neoadjuvant brachytherapy

Preliminary results of a RCT⁵⁶³ comparing preoperative brachytherapy followed by surgery with surgery alone were identified. The study included patients with operable cervical carcinoma from FIGO stage IA2 to proximal IIB. The preoperative high-dose rate brachytherapy delivered two fractions of 8 Gy followed by Piver class III radical hysterectomy and pelvic lymphadenectomy. Concerning the IB1 subgroup (53.3% of the patients), pathologic complete response was 38.5% after brachytherapy versus 12.8% without brachytherapy (where the tumour was probably removed after preliminary excision or conisation) and 25.6% of the patients needed adjuvant therapy in the brachytherapy with surgery arm versus 34.6% in the surgery alone arm.

LoE 1-

A study⁵⁶⁴ comparing the oncologic outcomes in patients with early stage cervical carcinoma without PLN involvement, when treated by combined treatment associating an intracavitary brachytherapy followed by a simple hysterectomy or by a radical hysterectomy alone was identified. An extra fascial hysterectomy was performed 6-8 weeks after uterovaginal brachytherapy. In the other group, proximal radical hysterectomies have been performed. Tumour was classified as FIGO stage IB1 in 86.48% and 83.11% of patients, respectively. Tumour was classified as FIGO stages IA1-IIA in other patients.

LoE 2-

A complete response was observed in almost half of patients (47.3%). One pelvic node

recurrence and one local recurrence were reported (2.7%). Concerning brachytherapy toxicity, only 2 grade 4 complications (2.7%) were found. The actuarial OS rate was 92.3% in patients treated with preoperative brachytherapy followed by simple hysterectomy and 100% in patients treated by a radical hysterectomy ($p = 0.046$) and the DFS rate was 92.3% and 98.7%, respectively ($p = 0.18$).

Escande *et al.*⁵⁶⁵ examined the clinical results of a preoperative image-guided pulse-dose-rate brachytherapy in early stage cervical cancer. Tumour was classified as FIGO stage IB1 and IIA1 in 96.1% and 3.9% of patients, respectively. Brachytherapy procedure consisting of intracavitary uterovaginal implantation was followed, 6-8 weeks later, by a radical hysterectomy/bilateral salpingo-oophorectomy plus pelvic \pm para-aortic LN dissection. Patients with positive LNs had postoperative chemoradiation.

On hysterectomy specimen 70.1% presented a complete histological response. After median follow-up of 3.9 years, only one local recurrence (1.3%) was observed. Most radiation-related acute toxicities were mild to moderate. In a log rank analysis, time interval between brachytherapy and surgery longer than nine weeks was significantly associated with a worse OS and DFS (4.7 years versus 9.5 years, $p = 0.02$ and 4.7 years versus 9.0 years, $p = 0.05$, respectively). It should be noted that (1) 15.6% of patients received a postoperative external beam radiation therapy to the pelvis \pm concurrent chemotherapy \pm para-aortic irradiation, and (2) no multivariate analysis was performed given the low number of events.

In another non-comparative study⁵⁶⁶, the patients with FIGO stage IB1 cervical cancer received preoperative uterovaginal brachytherapy followed by a radical hysterectomy with bilateral salpingo-oophorectomy \pm lymphadenectomy about 6 weeks later. No patients received adjuvant treatment except for those with nodal involvement who were treated with chemoradiotherapy. A relapse of disease was observed in 5.5% of patients. It should be noted that no patient whose tumour size was < 2 cm experienced relapse. At 5 years, OS and DFS rates were 95.0% and 94.3%, respectively.

Results from the other identified studies^{567,568} are limited notably by the small number of patients evaluated. **LoE 3**

10.1.5 Types of hysterectomy

Many radical procedures that accord with different degrees of radicality have been described and done. To date, three classifications of radical hysterectomies which are used for the simplification of the surgical protocols were identified: Piver-Rutledge-Smith classification⁵⁶⁹ which is the oldest, the classification proposed by the European Organization for Research and Treatment of Cancer-Gynecological Cancer Group (EORTC-GCG)^{570,571}, and Querleu-Morrow classification⁸ (Table 11, Table 12, Table 13). The last one is the most evolved and recent classification. Its techniques can be adapted for conservative operations and for different types of surgical approaches: abdominal, vaginal, laparoscopic or robotic.

Two RCTs^{38,91} assessing the role of the primary surgical radicality in patients with FIGO stages IB1-IIA cervical carcinoma with respect to survival, pattern of relapse, and morbidity were identified. In the first one⁹¹, patients were randomized to receive either class II or class III radical hysterectomy. All operations were performed by the same surgical team according to the Piver-Rutledge-Smith classification⁵⁶⁹ (Table 11). Mean blood loss, number of patients requiring blood transfusions and mean postoperative length of stay were similar between patients undergoing class II hysterectomy compared to patients undergoing class III hysterectomy (530 ml versus 580 ml ($p = 0.2$), 35% versus 43% ($p = 0.3$), and 9.1 versus 9.5 ($p = 0.4$), respectively). The authors reported significantly shorter mean operative time in the group of patients undergoing class II hysterectomy (135 min versus 180 min, $p = 0.04$). **LoE 1+**

Positive surgical resection margins did not appear to be significantly related to the surgical procedure adopted.

Intraoperative and early complications were similar between the two groups of patients (5% versus 4%). The incidence of late morbidity differed between the two groups, affecting 28% of patients in the class II group compared with 38% in the class III group. However, the difference did not reach statistical significance. It should be noted that vesical complications were significantly more frequent in the class III group, as demonstrated by a longer self-catheterization time ($p = 0.02$) and a higher rate of bladder dysfunctions (atonic bladder, stress incontinence, low-compliance bladder, $p = 0.02$).

Concerning the pattern of recurrences and survival, the extension of the surgical dissection did not appear to significantly influence pelvic recurrences, as 34% of recurrences were observed inside the pelvis after a class II operation compared with 42% after a class III operation ($p = 0.7$). Similarly, sites of pelvic recurrences are equally shared between the two groups (70% versus 69%). The recurrence rate in patients with small (≤ 4 cm) cervical diameter was 21% in the class II group and 24% in the class III group ($p = 0.8$). Patients with a large cervical diameter (> 4 cm) had a higher recurrence rate 34% in the class II group and 33% in the class III arm ($p = 0.8$). In both cases, however, no significant difference between the two classes could be found and survival within each group of cervical diameter did not depend on the type of surgery performed. Five-year OS was 81 and 77%, and DFS was 75 and 73%, respectively, in the group of patients submitted to class II and class III radical hysterectomy. These differences were not statistically significant. Multivariate was carried out and confirmed the lack of benefit of more radical surgery (class III hysterectomy) across all subgroups of patients.

In the second identified RCT³⁸, patients were randomized to receive either class I or class III radical hysterectomy. Both surgical treatments included bilateral pelvic lymphadenectomy and were performed according to the Piver-Rutledge-Smith classification⁵⁶⁹ by the same surgical team by means of laparotomy through a midline incision (Table 11). Recurrences were observed in 24% and 13% of patients in the class I group and class III group, respectively ($p = 0.11$). Pelvic recurrences were equal in both groups. Seventy-three percent and 75% of the relapsed patients in class I and class III group respectively, were alive with no evidence of disease after salvage therapy after a minimum follow-up time of 280 months.

Survival curves of tumours measuring ≤ 3 cm did not show statistical differences, as the 15-year survival is 76% and 80% for the class I group and class III group, respectively ($p = 0.88$). A significant difference can be observed between the two treatment groups in patients with cervical size between 3.1 and 4 cm (15-year OS: 74% versus 97% respectively, $p = 0.03$). A multivariate analysis confirmed that OS did not depend on the degree of surgical radicality. The type of surgery influenced deeply the rate of morbidity (double as much in the class III group compared to class I).

10.1.6 Surgical approaches for hysterectomy

Perioperative outcomes: using the technique of meta-analysis, Cao *et al.*⁵⁷² (twenty-two studies^{14,320,573-592}) and Wang *et al.*⁵⁹³ (eleven studies^{573,575,576,578,580-584,590,592,594}) examined the effectiveness and safety of laparoscopic radical hysterectomy compared to abdominal radical hysterectomy. Laparoscopic radical hysterectomy was systematically associated with a significant reduction of intraoperative blood loss, a shorter length of hospital stay, and a longer operative time. It should be noted that ten^{573,575,576,578,580-584,590,592} of the eleven studies^{573,575,576,578,580-584,590,592,594} included in the pooled analyses performed by Wang *et al.*⁵⁹³ have also been taken into account by Cao *et al.*⁵⁷². No significant differences in terms of need for blood transfusion (eight studies^{573,575,576,578,580,584,592,594}) or number of total LNs (nine

LoE 1-

studies^{573,575,578,580-583,592,594}), PLNs (sixteen studies^{14,320,573,575,577-583,585,586,589,590,592}), or PALNs (two studies^{580,583}) were described between the two surgical techniques (Table 14).

Two original studies^{595,596} not included in the meta-analyses^{572,593} mentioned above and comparing laparoscopic and open hysterectomy were identified. Consistent findings were observed by the first one⁵⁹⁵ with respect to LNs. The second one⁵⁹⁶ describes consistent findings with the pooled data previously presented concerning the blood loss, and the hospital stay. However, the authors found significantly shorter operative time (270.8 min versus 310.2 min), higher mean number of dissected LNs (20.5 versus 24.3, $p = 0.008$) and lower blood transfusion rate (13.2% versus 52.3%) for patients in laparoscopy group compared with those in the laparotomy group.

LoE 2-

As part of another meta-analysis, Park *et al.*⁵⁹⁷ included ten studies^{3,4,7,15-17,20-23} reporting comparative data about perioperative outcomes between robotic-assisted laparoscopic and conventional laparoscopic hysterectomy. The pooled data showed significantly shorter length of stay (six studies^{594,598-602}), and decreased transfusion rate (five studies^{594,598,599,603,604}) with robotic-assisted laparoscopic hysterectomy than conventional laparoscopic hysterectomy. No significant differences in terms of operative time (seven studies^{594,598-602,605}), estimated blood loss (six studies^{594,598-601,605}) or number of total or PLNs (four studies^{594,598,602,605} and three studies⁵⁹⁹⁻⁶⁰¹, respectively) were described between the two surgical techniques. Fully consistent data are provided with respect to duration of operation (four studies^{598,606-608}), need for blood transfusion (two studies^{598,606}), and the number of LNs resected (three studies^{598,606,607}) by a second identified meta-analysis⁶⁰⁹. However, no significant difference in length of stay (three studies^{598,606,607}) was found by the authors⁶⁰⁹ and the use of the robot was associated with reduced blood loss during surgery (three studies^{598,606,607}) (Table 15). Shazly *et al.*⁶¹⁰ reported also no differences in terms of operative time (thirteen studies^{594,598-600,603-608,611-613}), blood loss (twelve studies^{594,598-600,603-607,611-613}), number of LNs (eleven studies^{594,598-600,603-606,611-613}), and length of stay (eleven studies^{594,598-600,604-607,611-613}) between robotic-assisted laparoscopic and conventional laparoscopic hysterectomy.

LoE 1-

Another identified meta-analysis⁶¹⁴, including sixteen studies^{594,598-601,603,605,607,612,613,615-620}, reported consistent results with respect to operative time (thirteen studies^{594,598-601,603,605,612,613,615,616,619,620}) and number of LNs harvested (fourteen studies^{594,598-601,603,605,607,612,613,615,616,618,619}) with the three meta-analyses^{597,609,610} mentioned above (Table 15). As Park *et al.*⁵⁹⁷, Zhou *et al.*⁶¹⁴ found that the use of robot was associated with a shorter length of stay (twelve studies^{594,598-601,607,612,613,615,616,618,619}). But like Reza *et al.*⁶⁰⁹, this meta-analysis⁶¹⁴ found that the use of the robot was associated with reduced blood loss during surgery (thirteen studies^{594,598-601,603,605,607,612,613,615,618}). It should be noted that Zhou *et al.*⁶¹⁴ and Shazly *et al.*⁶¹⁰ reported no significant difference in need for blood transfusion between the two surgical techniques (Table 15).

A systematic review published by Kruijdenberg *et al.*⁶²¹ (twenty-seven studies^{576,578,587,598,606,607,622-638} including their own original data) was also identified and presents fully concordant data with the pooled findings mentioned above in terms of operative time (231 min versus 202 min, $p = 0.22$), and number of LNs retrieved (24 versus 21, $p = 0.28$). The authors reported also a lower blood transfusion rate (17 versus 72, $p = 0.02$) and shorter length of hospital stay (3.3 days versus 6.2 days, $p = 0.04$) with robotic-assisted laparoscopic hysterectomy.

Fifteen studies^{594,598,600,602,603,627,633,635,639-645} reporting data about perioperative outcomes of robotic-assisted laparoscopic and open hysterectomy were examined by Park *et al.*⁵⁹⁷. The pooled data showed significantly shorter length of stay (seven studies^{594,598,600,602,635,642,644}),

LoE 1-

lower estimated blood loss (eight studies^{594,598,600,627,635,640,642,644}), decreased transfusion rate (ten studies^{594,598,603,627,633,635,641-644}), and lower number of retrieved LNs (three studies^{600,603,640}) with robotic-assisted laparoscopic hysterectomy than open hysterectomy. No significant differences in terms of operative time (twelve studies^{594,598,600,602,603,627,633,635,639,640,642,644}) or number of total LNs (nine studies^{594,598,602,627,633,635,642,644,645}) were described between the two surgical techniques. Fully consistent data are provided with respect to length of stay, operative time, blood loss, transfusion rate, and number of LNs by the meta-analysis published by Shazly *et al.*⁶¹⁰ (Table 16). It should be noted that eleven^{594,598,600,602,603,627,633,635,639,642,644} of the thirteen studies^{594,598,600,602,603,606,627,633,635,639,642,644,646} from which these analyses are based on have also been taken into account by Park *et al.*⁵⁹⁷. Fully consistent data are also provided with respect to hospital stay, blood loss during surgery, need for blood transfusion, duration of operation, and number of LNs resected by another identified meta-analysis⁶⁰⁹ (Table 16). It should be noted that (1) all the studies^{598,606,627,633,635} from which these analyses are based on have also been taken into account by Shazly *et al.*⁶¹⁰, and (2) four^{598,627,633,635} of these five studies^{598,606,627,633,635} have also been taken into account by Park *et al.*⁵⁹⁷.

One original study⁶⁴⁷ not included in the meta-analyses^{597,609,610} mentioned above and comparing robotic-assisted laparoscopic and open hysterectomy was identified and presents consistent findings concerning the length of surgery, the number of LNs retrieved, the blood loss, and the transfusion rates. However, the authors found that the use of robot was associated with a longer mean operative time (220 min versus 156 min, $p < 0.001$).

LoE 2-

As part of a systematic review including twenty-one studies^{NA} of laparoscopic radical hysterectomy, fourteen studies^{NA} of open radical hysterectomy and twelve studies^{NA} of robotic radical hysterectomy, Geetha *et al.*⁶⁴⁸ reported that mean blood loss is significantly higher in abdominal radical hysterectomy compared to both laparoscopic radical hysterectomy and robotic radical hysterectomy. This difference between laparoscopic and robotic radical hysterectomy was not statistically significant. Both laparoscopic and robotic radical hysterectomy had significantly lower proportion of patients with blood transfusion compared to open method. Although the robotic radical hysterectomy appeared to require less blood transfusion, the difference between laparoscopic and robotic radical hysterectomy was not big enough to be statistically significant. Though laparoscopic and robotic radical hysterectomy appeared to take more time compared to open radical hysterectomy, the difference was not big enough to be statistically significant. Duration of stay in hospital for robotic radical hysterectomy was significantly less than the other two methods. The mean numbers of LNs obtained across the three surgical techniques were similar.

LoE 1-

A health technology assessment report⁶⁴⁹ was identified but is not described because it presents only pooled data about endometrial and cervical cancers. No separate data, taking into account data about cervical cancers specifically, is available. Another identified systematic review⁶⁵⁰ is not described because it contains no additional studies beyond those already captured by the systematic reviews/meta-analyses mentioned above.

Kim *et al.*⁶⁵¹ performed a meta-analysis (twenty studies⁶⁵²⁻⁶⁷¹) to compare notably perioperative outcomes between conventional radical surgery and nerve-sparing radical surgery in patients with cervical cancer. Crude analyses showed that blood loss and hospital stay were significantly less in patients treated with nerve-sparing radical surgery. The length of the resected vagina was significantly shorter in nerve-sparing radical surgery than in conventional radical surgery. However, there were no significant differences in operative time and the length of the resected parametrium between the two surgical techniques (Table 17). Fully concordant data by respect to hospital stay are provided by a second identified meta-

analysis⁶⁷² (twenty-seven studies^{656-661,665,666,668,669,673-689}). However, nerve-sparing radical surgery was associated with a significantly longer operative time. Moreover, no differences of blood loss were found between the two surgical techniques (Table 17).

Results of the three identified studies⁶⁹⁰⁻⁶⁹² evaluating the feasibility of performing a nerve-sparing radical hysterectomy robotically and assessing the oncological and functional outcomes associated with this surgery are limited notably by the very small number of patients evaluated (all studies have accrued less than 15 patients).

LoE 3

One original study⁶⁹³ not included in the meta-analyses^{651,672} mentioned above and comparing conventional radical surgery and nerve-sparing radical surgery was identified and presents consistent findings with those reported by van Gent *et al.*⁶⁷² concerning the blood loss and length of surgery.

LoE 2-

A study⁶⁹⁴ comparing vaginal-assisted laparoscopic radical hysterectomy (VALRH) and laparoscopic-assisted radical vaginal hysterectomy (LARVH) was also identified. The mean duration of the surgery was significantly shorter in the VALRH group than in the LARVH group (298 min versus 333 min, $p < 0.001$). No significant difference in terms of pelvic lymphadenectomy was reported between the groups (21 versus 22, $p = 0.684$). It should be noted that the significant difference in the paraortic LNs count is due to the learning curve of the surgeons. The mean blood loss and prevalence of blood transfusion due to surgery were significantly lower in the VALRH group (1.9 versus 3.2 g/dl, $p < 0.001$ and 2 versus 39, $p < 0.001$, respectively). After VALRH, the matched patients were discharged after a median of 10 days that was significantly earlier than after the LARVH with a median hospital stay of 14 days ($p < 0.001$).

A study⁶⁹⁵ comparing LARVH and time-matched radical abdominal hysterectomy was also identified. The median operative time was significantly longer in the LARVH group (3.5h versus 2.5h, $p < 0.001$). However, the median blood loss was significantly less in the LARVH group (300 ml versus 500 ml, $p < 0.001$). It should be noted that the incidence of blood transfusion was not statistically different between the groups (7% versus 8%, $p > 0.05$). The median postoperative hospital stay was significantly shorter for the LARVH (1 day versus 5 days, $p < 0.001$).

Results from the nine other identified studies^{632,696-703} are limited notably by the number of patients evaluated.

LoE 3

Complication rate/Quality of life: Park *et al.*⁵⁹⁷ provided also pooled data about the surgical safety in terms of intra- and post-operative major complications and postoperative minor complications of the three surgical techniques mentioned above. The pooled estimate demonstrated a significantly lower overall complication rate (seven studies^{594,602,603,627,633,643,645}) with robotic-assisted laparoscopic hysterectomy compared to open hysterectomy (RR = 0.59 (95% CI = 0.35-0.99)). No significant differences were reported in terms of intraoperative (nine studies^{594,598,600,602,633,639-641,644}) or postoperative (six studies^{594,598,602,633,639,641}) complications between these two surgical techniques (RR = 1.18 (95% CI = 0.43-3.27) and RR = 0.78 (95% CI = 0.42-1.43), respectively). Among the individual complications, robotic-assisted hysterectomy showed a lower incidence of wound infection (five studies^{594,603,627,633,642}), fever (four studies^{598,603,635,642}), and urinary tract infection (three studies^{600,603,642}) but a higher risk of vaginal cuff complications (six studies^{598,603,627,635,639,643}) (Table 18). The conversion rate of robotic-assisted laparoscopic hysterectomy to open hysterectomy was reported in 9 studies^{594,602,603,627,633,635,640,642,643}. Of these, eight reported zero conversion^{594,602,627,633,635,640,642,643}. In only one study⁶⁰³, the conversion rate for this surgical

LoE 1-

technique was 2.9%. No significant differences were seen with respect to the proportion of patients with complications (five studies^{598,606,627,633,635}, OR = 0.66 (M-H: 0.36, FEM: 1.21)) or the need to resort to another type of surgery (two studies^{606,633}, RD = 0.00 (M-H: -0.05, FEM: 0.05)) in the second identified meta-analysis published by Reza *et al.*⁶⁰⁹.

Fully consistent findings with respect to intraoperative complications were reported by Shazly *et al.*⁶¹⁰ (ten studies^{594,598,600,602,603,606,617,633,635,644}, OR = 1.07 (95% CI = 0.55-2.06)). Although it was not statistically significant, the pooled prevalence of aggregate complications was lower among women treated with robotic-assisted hysterectomy and the effect estimate was close to significance (fourteen studies^{594,598,600,602,603,606,617,627,633,639,642-644,646}, OR = 0.56 (95% CI = 0.30-1.03)). Both techniques were comparable with respect to pelvic infection and abscess formation, cardiopulmonary complications, cuff-related complications, intestinal obstruction/ileus, lymphovascular complications, thrombotic events, uretero-renal complications, urinary retention, readmission and reoperation. However, robotic-assisted hysterectomy was associated with significantly lower febrile morbidity and wound-related complications compared to abdominal radical hysterectomy (Table 19).

In a original study⁶⁴⁷ not included in the meta-analyses^{597,609} mentioned above and comparing robotic-assisted laparoscopic and open hysterectomy, although overall complications were similar, the use of robot was associated with lower intra-operative complication rate (4% versus 10%, $p = 0.004$).

LoE 2-

There were no significant differences between robotic-assisted laparoscopic hysterectomy and conventional laparoscopic hysterectomy in the overall (three studies^{594,599,602}, RR = 0.62 (95% CI = 0.30-1.28)), intra-operative (nine studies^{594,598-604,607}, RR = 0.87 (95% CI = 0.43-1.77)), and postoperative complications (seven studies^{594,598-600,602,604,607}, RR = 0.78 (95% CI = 0.49-1.23)). There were also no significant differences between these two surgical techniques in the rate of individual major or minor complications. The conversion rate of robotic-assisted laparoscopic hysterectomy to laparotomy was reported in five studies^{594,601,602,607,704} and the pooled analysis showed a lower trend with robotic-assisted laparoscopic hysterectomy than conventional laparoscopic hysterectomy (RR = 0.23 (95% CI = 0.04-1.29)). No significant differences in the proportion of patients with complication (four studies^{598,606-608}, OR = 1.07 (M-H: 0.53, FEM: 2.15)) or the need for conversion to another type of surgery (three studies^{598,606,607}, RD = -0.02 (M-H: -0.09, FEM: 0.05)) were reported in the second identified meta-analysis published by Reza *et al.*⁶⁰⁹.

LoE 1-

Fully consistent findings with respect to intraoperative complications were also reported by Shazly *et al.*⁶¹⁰ (fourteen studies^{594,598-601,603,604,606-608,611-613,617}, OR = 1.05 (95% CI = 0.58-1.92)). No differences in aggregate complications were also observed (fourteen studies^{594,598-601,603,604,606-608,611-613,617}, OR = 0.96 (95% CI = 0.55-1.66)). Individual postoperative complications did not differ between both techniques (Table 19). The use of robot was associated with higher proportions of major postoperative complications (9.6% versus 5.5%, $p < 0.05$) in the systematic review published by Kruijdenberg *et al.*⁶²¹. The authors reported no significant difference in the proportion of reoperation after complications.

Concerning the comparison of complications of laparoscopic radical hysterectomy and abdominal radical hysterectomy, Cao *et al.*⁵⁷² and Wang *et al.*⁵⁹³ reported no difference with respect to intraoperative complication between the two surgical techniques (ten studies^{14,573,576,578,580,581,586,587,589,592}, OR = 1.48 (95% CI = 0.75-2.91), and nine studies^{573,576,578,580,581,583,584,592,594}, OR = 1.36 (95% CI = 0.86-2.15), respectively). However, laparoscopic radical hysterectomy was systematically associated with lower postoperative complications (eighteen studies^{14,573-582,584-587,589,591,592}, OR = 0.75 (95% CI = 0.62-0.91), and ten

studies^{573,575,576,580-584,592,594}, OR = 0.46 (95% CI = 0.34-0.63), respectively). Laparoscopic radical hysterectomy was associated with lower perioperative complication rates (four studies^{14,584-586}, OR = 0.6 (95% CI = 0.36-0.90)). No significant differences were found for the recovery of bladder function (three studies^{580,587,588}, WMD = -2.48 (95% CI = -5.16-0.19)), but a significant difference was found in the number of days for anorectal function recovery (three studies^{580,583,588}, WMD = -0.80 (95% CI = -1.16--0.44)).

One original study⁵⁹⁶ not included in the meta-analyses^{572,593} mentioned above and comparing laparoscopic and open hysterectomy was identified and presents consistent findings concerning the intraoperative and postoperative complications.

LoE 2-

Geetha *et al.*⁶⁴⁸ found that postoperative infectious morbidity was significantly higher among patients who underwent open radical hysterectomy compared to the other two surgical techniques and a higher rate of cystotomy in laparoscopic radical hysterectomy.

LoE 1-

As showed by Kim *et al.*⁶⁵¹, nerve-sparing radical surgery was associated with less common intraoperative complications compared to conventional radical surgery. However there were no significant differences in postoperative complications between the two surgical techniques. In regard to urinary dysfunctions, crude analyses demonstrated that duration of postoperative catheterization was shorter and urinary frequency and abnormal sensation were less common in nerve-sparing radical surgery. However, there were no significant differences in urinary incontinence, urinary retention, dysuria, and urinary urgency between the two surgical techniques. In terms of anorectal dysfunctions, there were also no significant differences in constipation, diarrhea, and fecal incontinence between the two treatments. Furthermore, a decrease in sexual interest, dyspareunia, a decrease in orgasm, or sexual satisfaction, and vaginal dryness were not significantly different between the two surgical techniques (Table 20). Van Gent *et al.*⁶⁷² found that the time to micturition after surgery was significantly shorter in patients treated with nerve-sparing radical hysterectomy (SDM = -0.84 (95% CI = -1.07--0.60)).

One original study⁶⁹³ not included in the meta-analyses^{651,672} mentioned above and comparing these two surgical methods was identified and presents consistent findings with those previously concerning the postoperative complications.

LoE 2-

In the identified study⁶⁹⁴ comparing VALRH and LARVH, no conversion to laparotomy due to intraoperative complication was reported. Bladder function was restored significantly earlier after VALRH with a mean of 8 postoperative days than after LARVH with a mean of 11 days ($p < 0.001$). In the VALRH group, no intraoperative injuries of bladder, ureter, blood vessel or bowel occurred. In the LARVH group, the most frequent intraoperative injuries occurred to the bladder while opening the cervico-vesical space in 7.0% of patients. Further intraoperative complications in the LARVH group were injury of the ureter (3.5%), a blood vessel (2.0%) and of the bowel (0.5%). The difference of complications during the surgery between the groups was significant ($p < 0.001$). The difference between the groups and the matched pairs among the groups concerning the rate of postoperative complications failed significance. Only a trend in favour of VALRH was reported.

In the study⁶⁹⁵ comparing LARVH and time-matched radical abdominal hysterectomy, all laparoscopic procedures were completed successfully with no conversions to laparotomy. The intraoperative complication rate was greater for the LARVH patients (13% versus 4%, $p < 0.03$). Postoperative infectious and non-infectious morbidity was not significantly different between the groups (9% versus 5%, $p > 0.05$ and 5% versus 2%, $p > 0.05$, respectively). The median number of days to a urinary residual <100 ml for the LARVH was significantly longer (10 days versus 5 days, $p < 0.001$).

Oncologic outcomes: as part of the meta-analysis published by Park *et al.*⁵⁹⁷, no significant differences were found in survival outcomes between robot-assisted laparoscopic hysterectomy compared to conventional laparoscopy or laparotomy. Concerning the comparison of robotic-assisted laparoscopic hysterectomy versus open hysterectomy, the OS and DFS rates were examined in three studies^{598,602,639}, though they provide no significant clinical meaning because the follow-up periods differed between the two treatment groups in the studies. Four studies^{598,600,603,633} reported a positive resection margin rate, and the pooled analysis showed no significant difference (RR = 0.66 (95% CI = 0.22-1.96)). Once again, fully consistent data are provided with respect to rate of positive margins by Reza *et al.*⁶⁰⁹ (two studies^{598,633}, OR = 0.58 (M-H: 0.14, FEM: 2.33)). It should be noted that the two studies^{598,633} from which this analysis is based on have also been taken into account by Park *et al.*⁵⁹⁷.

LoE 1-

One original study⁶⁴⁷ not included in the meta-analyses^{597,609} mentioned above and comparing robotic-assisted laparoscopic and open hysterectomy was identified and presents consistent findings.

LoE 2-

Concerning the comparison of robotic-assisted laparoscopic hysterectomy versus conventional laparoscopic hysterectomy, the OS and DFS rates were examined in two studies^{598,602} and four studies^{598,601,602,604} respectively, and no significant differences were observed between these two surgical approaches. Five studies^{598-600,607,704} reported a positive resection margin rate. The positive margin rate was also not significantly different between these surgical techniques (RR = 0.87 (95% CI = 0.29-2.62)). Fully consistent data are provided with respect to rate of positive margins by Reza *et al.*⁶⁰⁹ (two studies^{598,607}, OR = 0.84 (M-H: 0.20, FEM: 3.42)). It should be noted that the two studies^{27,36} from which this analysis is based on have also been taken into account by Park *et al.*⁵⁹⁷. Both methods were similar in respect to recurrence rate (5.2% versus 5.6%, $p = 0.88$) in the systematic review published by Kruijdenberg *et al.*⁶²¹.

LoE 1-

Concerning the comparison of laparoscopic radical hysterectomy versus abdominal radical hysterectomy, ten studies^{14,573,575,579,580,583-587}, six studies^{14,573,575,584-586}, and thirteen studies^{14,575,577,579-587,590} included in the meta-analysis published by Cao *et al.*⁵⁷², assessed 5-year DFS, 5-year OS and recurrence rate, respectively. No significant differences were found between the two surgical techniques (HR = 0.01 (95% CI = -0.10-0.11), HR = -0.02 (95% CI = -0.14-0.10), and OR = 0.82 (95% CI = 0.61-1.11), respectively). Fully consistent data are provided in terms of DFS and OS by Wang *et al.*⁵⁹³ (five studies^{573,575,580,583,584}, HR = 0.97 (95% CI = 0.56-1.68), and three studies^{573,575,584}, HR = 0.91 (95% CI = 0.48-1.71), respectively). It should be noted that all the studies^{573,575,580,583,584} from which these analyses are based on have also been taken into account by Cao *et al.*⁵⁷². Wang *et al.*⁵⁹³ also pooled data relative to the positive resection margins (four studies^{576,578,584,590}). Here again, no significant differences were reported (OR = 1.24 (95% CI = 0.46-3.35)).

Two original studies^{596,705} not included in the meta-analyses^{572,593} mentioned above and comparing laparoscopic and open hysterectomy were identified. In the first one⁵⁹⁶, consistent findings concerning the DFS, OS, and recurrence rates were reported. In the second one⁷⁰⁵, the authors found that the experienced surgeon was more likely to select patients with earlier-stage disease and resect tumours with shorter vaginal tumour-free margin using laparoscopic radical hysterectomy than the inexperienced surgeons. After matching, which equalized stage and risk factors between the two surgeon groups, vaginal tumour-free margin of the laparoscopic radical hysterectomy approach was shorter than that of abdominal radical hysterectomy in the experienced surgeon group, while even longer than that of abdominal radical hysterectomy in the inexperienced surgeon group. Although PFS of laparoscopic radical hysterectomy in the experienced surgeon group was significantly better than that in the

LoE 2-

inexperienced surgeon group's laparoscopic radical hysterectomy patients, statistical significance of the difference disappeared after matching.

Mean positive margin and recurrence rate across the three types of radical hysterectomy studies were similar in the systematic review published by Geetha *et al.*⁶⁴⁸. The authors mentioned that positive margin was zero in all except one study^{NA} pertaining to robotic radical hysterectomy.

LoE 1-

According to the two identified meta-analyses^{651,672} comparing nerve-sparing radical surgery and conventional radical surgery, no significant differences in DFS or OS were found between the two surgical techniques (Table 21).

One original study⁶⁹³ not included in these two meta-analyses^{651,672} was identified and presents fully consistent findings.

LoE 2-

In the study⁶⁹⁵ comparing LARVH and time-matched radical abdominal hysterectomy, there was no statistically significant difference in actuarial 2-year recurrence-free survival (94% for both groups, $p > 0.05$). There were no port-site recurrence, nor was there a difference in the pattern of recurrences between the two procedures.

In the identified study⁶⁹⁴ comparing VALRH and LARVH, no difference with respect to the 5-year recurrence-free survival rate and OS for FIGO stage IB1 cervical cancer were reported (92.8% versus 88.2%, $p = 0.589$ and 95.2% versus 90.5%, $p = 0.740$, respectively).

10.1.7 Adjuvant radiotherapy

Meta-analysis⁷⁰⁶ of two RCTs⁷⁰⁷⁻⁷⁰⁹ indicated no significant differences in survival at 5 years between women with FIGO stage IB cervical cancer who received radiation and those who received no further treatment after radical hysterectomy and PLN dissection (RR = 0.8 (95% CI = 0.3-2.4)). Patients in the radiation therapy group received EBRT in doses between 46 Gy in 23 fractions to 50.4 Gy in 28 fractions, and no brachytherapy in the first included RCT^{707,708}. Women received 52 Gy of whole pelvic EBRT, at a rate of 2 Gy per day in the second trial⁷⁰⁹. Women who received radiation had a significantly lower risk of disease progression at 5 years (RR = 0.6 (95% CI = 0.4-0.9)). In the first included RCT^{707,708}, only 9% of the patients with adenocarcinoma or adenosquamous tumours who received radiotherapy had disease recurrence, compared with 44% in those who did not, suggesting that radiotherapy may be beneficial for patients with non-squamous histology.

LoE 1-

Although the risk of serious adverse events was consistently higher if women received radiotherapy rather than no further treatment, these increased risks were not statistically significant, probably because the rate of adverse events was low. It should be noted that although the authors found no statistically significant difference in risk of grade 3 and 4 adverse events in women who did and did not receive radiotherapy, this might be because the trials reported very few side effects and so lacked the statistical power to detect any difference in risk that might be present.

Fully consistent results are provided by Sandadi *et al.*⁷¹⁰ with respect to the absence of impact of an adjuvant radiotherapy on OS (91% versus 96%, $p = 0.332$) and rate of grade 3 or higher complication rates (4% versus 5%, $p = 0.999$). However, no significant difference in 5-year PFS was observed (90% versus 93%, $p = 0.172$).

LoE 2-

As part of the large-scale study⁸⁵ mentioned above, multivariate analysis showed that adjuvant radiation was associated with a reduction in mortality rate for women with tumour size < 4 cm (HR = 0.45 (95% CI = 0.38-0.54) after controlling for age, race, SEER registry,

marital status, histologic finding, tumour grade, adjuvant radiation, and stage. Adjuvant radiation therapy was also associated with improved OS (HR = 0.17 (95% CI = 0.04-0.69, p = 0.01) on multivariate analysis after adjustment for age, stage, histology, type of surgery, grade, tumour size, and LVSI in the study published by Fleming *et al.*⁷¹¹. However, it was not significantly associated with PFS. Discordant data were provided as part of a study published by Ayhan *et al.*⁶⁴, mentioning that adjuvant radiotherapy was not found as independent prognostic factor in OS and DFS for women with FIGO stage IB cervical cancer.

In a study⁷¹² evaluating extended-field irradiation in patients with stages FIGO IB-IIB after radical surgery, the 5-year DFS rates were significantly different between squamous cell carcinomas and nonsquamous cell carcinomas (72% versus 27%, p = 0.0051). In the subset of pT1b cases with one or two risk factors on the surgical specimen (LVSI and/or stromal invasion > 1/3 of total cervical stroma) in the study published by Sartori *et al.*⁴⁴, there was no difference in DFS between the patients treated or not with adjuvant pelvic radiotherapy (50.4 Gy).

Richard *et al.*⁷¹³ compared the 5-year survival rates for women with FIGO stage IB cervical cancer who had a completed versus abandoned RH with postoperative radiotherapy in the presence of positive LNs. No statistically significant differences were noted in terms of median survival, DFS, OS, mean number of LNs dissected, and mean number of positive LNs.

Results from the six other identified studies⁷¹⁴⁻⁷¹⁹ are limited notably by the small number of patients evaluated.

LoE 3

10.1.8 Adjuvant chemo(radio)therapy

A systematic review⁷²⁰ of RCTs was performed to evaluate the effectiveness and safety of adjuvant platinum-based chemotherapy after radical hysterectomy, radiotherapy, or both in the treatment of early stage (FIGO stages IA2-IIA) cervical cancer. In this review, four small trials⁷²¹⁻⁷²⁴ were analysed. All of them used chemotherapy regimens consisting of cisplatin alone or in combination with other agents and all included women underwent surgery first. Three⁷²¹⁻⁷²³ of them compared chemotherapy combined with radiotherapy versus radiotherapy alone, and one trial⁷²⁴ compared chemotherapy (given sequentially) followed by radiotherapy versus radiotherapy alone. It should be noted that (1) no trials compared adjuvant platinum-based chemotherapy with no adjuvant chemotherapy after surgery for early cervical cancer with risk factors for recurrence, (2) the available results were based on an interim analysis of the data for one trial⁷²¹, (3) another trial was closed early due to lack of accrual⁷²², and (4) none of the included studies reported data on long-term toxicities or quality of life.

LoE 1-

Compared with adjuvant radiotherapy, chemotherapy combined with radiotherapy significantly reduced the risk of death (pooled HR = 0.56 (95% CI = 0.36-0.87)) and disease progression (pooled HR = 0.47 (95% CI = 0.30-0.74)). The combined therapy was associated with more severe side effects (grade 4) than radiotherapy alone (pooled RR = 6.26 (95% CI = 2.50-15.67)). In the trial⁷²⁴ that compared adjuvant chemotherapy followed by radiotherapy with adjuvant radiotherapy alone there was no difference in disease recurrence between the groups (HR = 1.34 (95% CI = 0.24-7.66)).

It should be noted that these results have to be interpreted cautiously because since subgroup analyses according to stage and size were not possible, it is not clear that the survival benefits apply equally to all early stage lesions.

Six RCTs^{83,725-729} not included in the systematic review⁷²⁰ mentioned above were also identified. In the first one⁷²⁵, women randomly received adjuvant chemotherapy (400 mg/m²

carboplatin, and 30 mg bleomycin), external pelvic radiation therapy (mean dose : 50 Gy), or no further treatment. After a median follow-up of 4.1 years there were no significant differences in rates of recurrence or death between in the three study arms. It should be noted that these results have to be interpreted cautiously notably due to the small number of patients in the three treatment arms and the ensuing statistical power.

Patients with FIGO stages IB-IIA cervical cancer initially treated with radical hysterectomy and pelvic lymphadenectomy were randomized to receive single agent cisplatin and radiotherapy or docetaxel/cisplatin and radiotherapy in the second identified RCT⁷²⁶. Radiotherapy in both groups was external radiation (46-54 Gy) followed by high-dose rate brachytherapy (12-24 Gy). Patients were given cisplatin (40 mg/m²) every week for 5 cycles of docetaxel (30 mg/m²) and cisplatin (30 mg/m²) every week for 5 cycles. The addition of docetaxel did not increase OS (HR = 0.65 (95% CI = 0.39-1.09), p = 0.098) but had the trend of increasing relapse-free survival (RFS) (HR = 0.64 (95% CI = 0.40-1.03), p = 0.061). There were no significant differences in the seriousness of late grade 3-4 side effects between the treatment groups.

A RCT⁸³ was conducted to compare paclitaxel (175 mg/m²) plus carboplatin (area under the curve 5) followed by radiation (50.4 Gy) versus simultaneous radiochemotherapy with cisplatin (40 mg/m²) in patients with FIGO stages IB-IIB after surgery. Sequential chemotherapy and radiation could not show any significant survival benefit in terms of 2-year PFS and 5-year survival rates. The sequential arm appeared to have a significantly more favorable toxicity profile when compared with the simultaneous arm regarding the rate of overall hematological grade 3-4 toxicity (34% versus 48%, p = 0.028). In terms of quality of life, no significant changes were recorded regarding the functional assessment of cancer therapy-anemia (FACT-An) scores.

As part of a large RCT⁷²⁷, patients with FIGO stage IB or FIGO stage II cervical cancer having surgery alone or surgery and radiotherapy (SR) were randomly assigned to receive or not oral 5-FU for one year. Patients who received surgery obtained no benefit from 5-FU (RR = 0.826 (95% CI = 0.421-1.596), p = 0.575), whereas 5-FU-treated SR patients had significantly better 5-year survival than those not receiving chemotherapy (RR = 0.744 (95% CI = 0.558-0.991), p = 0.043). The SR patients without nodal metastases had a better survival rate if they received 5-FU (RR = 0.423 (95% CI = 0.273-0.656), p < 0.001), whereas those with nodal metastases did not (RR = 1.247 (95% CI = 0.831-1.871), p = 0.286).

It should be noted that the results reported by these three identified RCTs^{83,726,727} have also to be interpreted cautiously because since subgroup analyses according to stage and/or size were not possible, it is not clear if the data apply equally to all stage lesions.

The fifth identified RCT⁷²⁸, comparing concurrent chemoradiotherapy (CCRT) versus chemotherapy or radiotherapy alone after radical hysterectomy in FIGO stages IB-IIA cervical carcinoma patients, was prematurely closed due to suboptimal accrual and protocol violation. The sixth and last identified RCT⁷²⁹ comparing adjuvant chemotherapy alone versus chemotherapy plus whole pelvic radiation therapy in patients with FIGO stages IB-IIA who underwent radical hysterectomy and pelvic lymphadenectomy was also prematurely closed due to less than optimal accrual.

Six non-randomized studies⁷³⁰⁻⁷³⁵ were also identified. Iwasaka *et al.*⁷³⁰ compared the efficacy of adjuvant chemotherapy (combination of 50 mg of cisplatin, 1 mg of vincristine, 8 mg/m² of mitomycin c, and 5 mg of peplomycin) after radical hysterectomy with that of adjuvant radiotherapy (41-50 Gy). The overall cumulative survival rate in the chemotherapy group was significantly higher than that in the radiotherapy group, which reflects different survival rates over the 5-year period. In the chemotherapy group, intra- and extrapelvic recurrences

LoE 2-

accounted for 85% and 23% of all recurrences, respectively, whereas recurrences were noted for 38% and 71% in the radiotherapy group, respectively ($p < 0.01$).

As part of a comparison⁷³¹ of adjuvant chemotherapy with two other therapeutic approaches (radiation and chemoirradiation), no significant differences among these three groups in the 5-year RFS rate and recurrence rates were reported. The authors observed that most of the recurrence in patients who had received pelvic radiation was at a distant site as compared to the patients who had received chemotherapy only.

The adoption of adjuvant chemotherapy which included cisplatin, bleomycin and vinblastine did not produce statistically significant results in terms of OS and DFS in the study published by Mossa *et al.*⁷³².

Park *et al.*⁷³³ mentioned that postoperative adjuvant CCRT (cisplatin (100 mg/m²), or paraplatin (350 mg/m²), 5-FU (1,000 mg/m²), radiation therapy (45 Gy)) appears to be superior to postoperative radiotherapy or postoperative adjuvant chemotherapy alone in terms of survival rates in patients with histopathologic high-risk factors. However, due to the small numbers of patients included in the subgroups of each treatment modality according to histopathologic high-risk factors, they were unable to prove statistical significance.

It should be noted that the results reported by these two non-randomized studies^{732,733} have to be interpreted cautiously due to the small number of patients included.

In a study evaluating CCRT according to the SWOG #87-97 (GOG #109) protocol⁷²¹ in patients with high-risk factors who had underwent radical abdominal hysterectomy with pelvic lymphadenectomy and PALN dissection, Ryu *et al.*⁷³⁴ did not observe any statistically significant difference in the OS rate or PFS rate between these patients and patients who did not receive adjuvant therapy after surgery. It should be noted that significantly increased number of patients with lesion size, parametrial invasion, deep stromal invasion, PLN involvement, and LVSI was observed in the patients treated with adjuvant therapy.

In the sixth non-randomized study⁷³⁵, chemotherapy was compared with CCRT after radical hysterectomy and lymphadenectomy in patients with FIGO stages IB1-IIB cervical cancer. CCRT consisted of radiotherapy, which was given as whole-pelvis external irradiation (50.4 Gy in 28 fractions), combined with 5-FU (700 mg/m²) and cisplatin (70 mg/m²). No significant differences between the two arms in terms of recurrence and death rates were reported. The chemotherapy group contained significantly more patients with severe neutropenia than the CCRT group (66.7% versus 23.0%, respectively $p < 0.001$) while this group contained significantly more patients with diarrhea than the chemotherapy group (10.8% versus 0%, respectively, $p = 0.04$).

Results from the fifteen other identified studies^{80,736-749} are limited notably by (1) the heterogeneity in the chemo(radio)therapy regimens, and (2) the small number of patients evaluated (only five studies^{741,742,744,748,749} have accrued in excess of 60 patients).

LoE 3

10.2 Previous initiatives

Eight previous initiatives^{419,420,422-426,529,531} presenting guidelines for management of stages T1b1/T2a1 were identified.

10.3 Development group comments

There was unanimous agreement with the overall statement that the treatment strategy should aim to avoid combining radical surgery and radiotherapy because of the highest morbidity.

The majority of patients that present with T1b1/T2a1, determined by combined gynaecological examination and optimal imaging, will have no suspicious LNs on imaging (cN0) and will not have an indication for postoperative radiotherapy and can be managed effectively with lymphadenectomy (pN0) and radical hysterectomy alone, which is the preferred treatment approach. Small tumours without deep stromal invasion have a low incidence of LN metastasis and surgery alone provides excellent outcomes. In contrast, larger tumours with deep stromal invasion, and especially in the presence of LVSI, are associated with a higher incidence of nodal involvement and a higher risk of recurrence.

In patients that are node negative on imaging, the first priority is to rule out nodal involvement and the standard surgical procedure is systematic lymphadenectomy. SN technique has the highest sensitivity and specificity in detecting nodal involvement compared to optimal imaging and has less morbidity compared to systematic lymphadenectomy. Therefore, SN technique is strongly recommended as a first step to rule out nodal involvement in patients that are node negative on imaging. SN technique has the advantage that in case of detection of an involved node, further more radical surgical procedures can be avoided since there is already an indication for radiotherapy.

With regard to optimal type of radical hysterectomy for T1b1/T2a1 tumours there was more debate among the gynaecological oncologists. This resulted in the proposed tailored approach that takes tumour size, depth of stromal invasion and presence of LVSI into account, with less radical hysterectomy for favourable tumours. The excellent outcomes with surgery alone in small tumours and the risk of surgical morbidity after the standard radical hysterectomy, have inspired the development of less radical hysterectomy approaches. Several series find that less radical, nerve sparing, hysterectomy seem not to compromise oncological outcomes while associated with less post-surgical morbidity. This concept is currently a subject of research. On the other hand, despite the great improvement in modern imaging techniques for assessment of local tumour status (MRI, US) over the last decades, these techniques are not 100% accurate in ruling out adverse prognostic factors.

Especially in larger T1b1/T2a1 tumours with deep stromal invasion, radical hysterectomy may unintentionally result, through histopathological examination, in the detection of involved parametria or surgical margins, or a combination of unfavourable risk factors (tumour size, deep stromal invasion, LVSI). Therefore, in these patients, less radical hysterectomy approaches should be avoided. A surgical approach can be recommended only in those centers that are experienced with surgery alone in the presence of a combination of risk factors (tumour size, deep stromal invasion, LVSI). Given the excellent oncological outcomes after definite chemoradiotherapy and brachytherapy for T1b1/T2a1 tumours this represents an alternative approach, especially if a combination of risk factors is known at diagnosis, which would require an adjuvant treatment. Another alternative option, which is used in a limited number of centers, is preoperative brachytherapy followed by surgery. This is an acceptable alternative option only in team experienced with this approach.

Although there was unanimous agreement in favour of adjuvant (chemo)radiotherapy in case of involved LN(s), parametria or surgical margin, there was debate regarding the role of adjuvant radiotherapy in case of combinations of risk factors (tumour size, deep stromal invasion, LVSI). Despite evidence from a randomized trial in favour of adjuvant radiotherapy in these patients, good results with surgery alone were reported in selected centers, experienced with this strategy. This is, however, applicable using appropriately tailored surgery.

10.4 Guidelines

10.4.1 General recommendation

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

10.4.2 Negative lymph nodes on radiological staging

10.4.2.1 *Surgical treatment*

- B** Radical surgery by a gynecologic oncologist is the preferred treatment modality. Minimally invasive approach is favored.
- B** The standard LN staging procedure is systematic pelvic lymphadenectomy. SN biopsy before pelvic lymphadenectomy is strongly recommended. Combination of blue dye with radiocolloid or use of indocyanine green alone is the recommended technique.
- ✓ LN assessment should be performed as the first step of surgical management. Intraoperative assessment of LN status (frozen section) is recommended. All SNs from both sides of the pelvis and/or any suspicious LNs should be sent for frozen section. If SN is not detected, intraoperative assessment of the PLNs should be considered.
- ✓ If intraoperative LN assessment is negative or not done, systematic PLN dissection should be performed. At present, SN biopsy alone cannot be recommended outside prospective clinical trials. Systematic LN dissection should include the removal of lymphatic tissue from regions with the most frequent occurrence of positive LNs (SNs) including obturator fossa, external iliac regions, common iliac regions bilaterally, and presacral region. Distal external iliac LNs (so-called circumflex iliac LNs) should be spared if they are not macroscopically suspicious.
- ✓ The type of radical hysterectomy (extent of parametrial resection, type A-C2) should be based on the presence of prognostic risk factors identified preoperatively (Figure 3). Major prognostic factors for oncological outcome as tumor size, maximum stromal invasion, and LVSI are used to categorize patients at high, intermediate, and low risk of 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 (Figure 4).
- ✓ Ovarian preservation should be offered to premenopausal patients with squamous cell carcinoma and usual-type (HPV-related) adenocarcinoma. Bilateral salpingectomy should be considered.
- C** If LN involvement is detected intraoperatively including macrometastases or micrometastases, further PLN dissection and radical hysterectomy should be avoided. Patients should be referred for definitive chemoradiotherapy. PALN 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. PLN dissection should be avoided. PALN dissection, at least up to inferiormesenteric artery, may be considered in patients with negative PALN on imaging.

Figure 6. 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 Figure 4)

Figure 7. Querleu-Morrow classification⁸

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

10.4.2.2 *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 centers. It is an acceptable alternative option only in teams experienced in this approach.

C NACT followed by surgery is not recommended.

10.4.3 **Positive pelvic lymph nodes on radiological staging**

C In patients with unequivocally involved PLNs on imaging, definitive chemoradiotherapy is recommended (see Principles of radiotherapy). PALN dissection, at least up to inferior mesenteric artery, may be considered in patients with negative PALNs on imaging.

✓ Debulking of suspicious PLNs may be considered.

10.4.4 **Adjuvant treatment**

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

✓ When in these situations an adequate type of radical hysterectomy has been performed (Figure 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 PLNs, including the presence of macrometastases pN1 or micrometastases pN1(mi) in either SN or any other PLNs detected by intraoperative or final pathologic assessment ⇒ chemoradiotherapy
- positive surgical margins (vagina/parametria) ⇒ chemoradiotherapy, brachytherapy boost may be considered
- parametrial involvement ⇒ chemoradiotherapy

10.4.5 **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.

Table 11. Piver-Rutledge-Smith classification⁵⁶⁹

Class I	<p>Extrafascial hysterectomy:</p> <ul style="list-style-type: none"> • The identification of ureters through transparency and avoiding the ureters' injury by running them outside the operator field, without a dissection; • The uterine artery is laterouterine sectioned and ligated; • Uterosacral and cardinal ligaments are not removed; • No vaginal portion is excised.
Class II	<p>Modified radical hysterectomy (Wertheim):</p> <ul style="list-style-type: none"> • Ureters are dissected in the paracervical region but are not resected from the pubovesical ligament; • The uterine arteries are sectioned beside and medial the ureter; • Uterosacral ligament are excised midway from their sacral insertion; • Resection of the cardinal ligaments up to their medial half; • Removal of the upper third of the vagina; • Pelvic lymphadenectomy
Class III	<p>Classical radical hysterectomy (Meigs):</p> <ul style="list-style-type: none"> • Complete dissection of ureters pubovesical ligaments except for a small part where the umbilical bladder artery is situated to the level of their penetration into the bladder; • Uterine arteries are cut off at the origin of a hypogastric region (a. umbilical bladder); • Uterosacral ligaments are excised at their sacred insertion; • Cardinal ligaments are resected as close to the pelvic wall; • Removing the upper half of the vagina; • Routine pelvic lymphadenectomy.
Class IV	<p>It differs from the previous class according to the following aspects which give a higher radicality:</p> <ul style="list-style-type: none"> • Complete dissection of the ureter from the pubovesical ligament; • Umbilical-vesical artery is sacrificed; • Removal of the 3/4 of the upper vagina.
Class V	<p>It is more radical than the previous class with the addition of excision of a portion of the ureter or bladder which is invaded and then the reimplantation of the ureter into the bladder.</p>

Table 12. EORTC-GCG classification^{570,571}

Type I	Simple hysterectomy
Type II	<p>Modified radical hysterectomy:</p> <ul style="list-style-type: none"> • Ureters are dissected up to the point they enter the bladder; • Uterine arteries are sectioned and ligated at the medial half of parameters; • Proximal uterosacral ligament resection; • The medial half of the cardinal ligament is excised; • 1-2 cm from the upper portion of the vagina is removed.
Type III	<p>Radical hysterectomy:</p> <ul style="list-style-type: none"> • Removal as far as possible from the uterosacral ligaments; • Parameter is resected as near as possible to the pelvic wall; • Uterine vessels are ligated at the origin; • 1/3 of the upper vagina is removed.
Type IV	<p>Extended radical hysterectomy:</p> <ul style="list-style-type: none"> • Similar to type III with the removal of 3/4 of the vagina and paravaginal tissue counterpart.
Type V	<p>Partial pelvectomy:</p> <ul style="list-style-type: none"> • Terminal ureter or a portion of the bladder or rectum is resected together with the uterus and parameters (suprlevatorial).

Table 13. Querleu-Morrow classification⁸

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 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

Table 14. Pooled data on the perioperative outcomes of laparoscopic radical hysterectomy compared to abdominal radical hysterectomy

Author ^{reference}	Year	LRH versus ARH
Length of stay		
Cao <i>et al.</i> ⁵⁷²	2015	WMD = -4.36 (95% CI = -5.38--3.34)
Wang <i>et al.</i> ⁵⁹³	2015	MD = -3.22 (95% CI = -4.21--2.23)
Operative time		
Cao <i>et al.</i> ⁵⁷²	2015	WMD = 18.76 (95% CI = 2.13-35.39)
Wang <i>et al.</i> ⁵⁹³	2015	MD = 26.95 (95% CI = 8.08-45.82)
Blood loss		
Cao <i>et al.</i> ⁵⁷²	2015	WMD = -193.61 (95% CI = -236.80--150.43)
Wang <i>et al.</i> ⁵⁹³	2015	MD = -268.36 (95% CI = -361.60--175.11)
Transfusion		
Wang <i>et al.</i> ⁵⁹³	2015	OR = 0.11 (95% CI = 0.01-1.01)
Total LNs		
Wang <i>et al.</i> ⁵⁹³	2015	MD = -1.06 (95% CI = -4.03-1.91)
PALNs		
Cao <i>et al.</i> ⁵⁷²	2015	WMD = -1.79 (95% CI = -6.39-2.82)
PLNs		
Cao <i>et al.</i> ⁵⁷²	2015	WMD = -1.44 (95% CI = -4.14-1.27)

ARH abdominal radical hysterectomy, CI confidence interval, LN lymph node, LRH laparoscopic radical hysterectomy, MD mean difference, OR odds ratio, PALNs para-aortic lymph nodes, PLNs pelvic lymph nodes, WMD weighted mean difference

Table 15. Pooled data on the perioperative outcomes of robotic-assisted laparoscopic hysterectomy compared to conventional laparoscopy

Author ^{reference}	Year	RH versus LH
Length of stay		
Park <i>et al.</i> ⁵⁹⁷	2016	WMD = -1.39 (95% CI = -2.44--0.35)
Zhou <i>et al.</i> ⁶¹⁴	2016	MD = -1.10 (95% CI = -1.71--0.48)
Shazly <i>et al.</i> ⁶¹⁰	2015	MD = -0.51 (95% CI = -1.57-0.55)
Reza <i>et al.</i> ⁶⁰⁹	2010	MD = -0.52 (IV: -1.24, REM: 0.21)
Operative time		
Park <i>et al.</i> ⁵⁹⁷	2016	WMD = -24.90 (95% CI = -78.96-29.16)
Zhou <i>et al.</i> ⁶¹⁴	2016	MD = -13.30 (95% CI = -40.39-13.79)
Shazly <i>et al.</i> ⁶¹⁰	2015	WMD = -14.59 (95% CI = -41.30-12.13)
Reza <i>et al.</i> ⁶⁰⁹	2010	MD = -14.01 (IV: -42.85, REM: 14.82)
Blood loss		
Park <i>et al.</i> ⁵⁹⁷	2016	WMD = -78.08 (95% CI = -192.08-35.92)
Zhou <i>et al.</i> ⁶¹⁴	2016	MD = -66.37 (95% CI = -115.45--17.30)
Shazly <i>et al.</i> ⁶¹⁰	2015	WMD = -44.31 (95% CI = -89.19-0.56)
Reza <i>et al.</i> ⁶⁰⁹	2010	MD = -63.52 (IV: -100.49, FEM: -26.54)
Transfusion		
Park <i>et al.</i> ⁵⁹⁷	2016	RR = 0.32 (95% CI = 0.13-0.77)
Zhou <i>et al.</i> ⁶¹⁴	2016	OR = 0.57 (95% CI = 0.28-1.15)
Shazly <i>et al.</i> ⁶¹⁰	2015	OR = 0.61 (95% CI = 0.30-1.26)
Reza <i>et al.</i> ⁶⁰⁹	2010	OR = 2.46 (M-H: 0.25, FEM: 24.36)
Total LNs		
Park <i>et al.</i> ⁵⁹⁷	2016	WMD = 2.81 (95% CI = -3.68-9.30)
Zhou <i>et al.</i> ⁶¹⁴	2016	MD = 1.33 (95% CI = -0.72-3.38)
Shazly <i>et al.</i> ⁶¹⁰	2015	MD = 2.62 (95% CI = -0.42-5.65)
Reza <i>et al.</i> ⁶⁰⁹	2010	MD = 2.73 (IV: -8.39, REM: 13.85)
PLNs		
Park <i>et al.</i> ⁵⁹⁷	2016	WMD = 0.44 (95% CI = 3.46-4.35)

CI confidence interval, FEM fixed-effects method, IV inverse variance, LH conventional laparoscopic hysterectomy, LNs lymph nodes, MD mean difference, M-H Mantel- Haenszel, nr not reported, OR odds ratio, PLNs pelvic lymph nodes, REM random-effects method, RH robot-assisted laparoscopic hysterectomy, RR relative risk, WMD weighted mean difference

Table 16. Pooled data on the perioperative outcomes of robotic-assisted laparoscopic hysterectomy compared to open hysterectomy

Author ^{reference}	Year	RH versus OH
Length of stay		
Park <i>et al.</i> ⁵⁹⁷	2016	WMD = -4.33 (95% CI = -5.96--2.70)
Shazly <i>et al.</i> ⁶¹⁰	2015	MD = -3.55 (95% CI = -5.00--2.10)
Reza <i>et al.</i> ⁶⁰⁹	2010	MD = -2.05 (IV: -2.80, REM: -1.29)
Operative time		
Park <i>et al.</i> ⁵⁹⁷	2016	WMD = 16.76 (95% CI = -11.87-45.38)
Shazly <i>et al.</i> ⁶¹⁰	2015	MD = 28.79 (95% CI = -2.15-59.74)
Reza <i>et al.</i> ⁶⁰⁹	2010	MD = 31.39 (IV: -10.33, REM: 73.11)
Blood loss		
Park <i>et al.</i> ⁵⁹⁷	2016	WMD = -409.04 (95% CI = -551.97--266.11)
Shazly <i>et al.</i> ⁶¹⁰	2015	WMD = -384.29 (95% CI = -534.84--233.73)
Reza <i>et al.</i> ⁶⁰⁹	2010	MD = -334.17 (IV: -459.44, REM: -208.91)
Transfusion		
Park <i>et al.</i> ⁵⁹⁷	2016	RR = 0.12 (95% CI = 0.07-0.2)
Shazly <i>et al.</i> ⁶¹⁰	2015	OR = 0.12 (95% CI = 0.06-0.25)
Reza <i>et al.</i> ⁶⁰⁹	2010	OR = 0.18 (M-H: 0.07, FEM: 0.44)
Total LNs		
Park <i>et al.</i> ⁵⁹⁷	2016	WMD = 0.56 (95% CI = -2.76-3.88)
Shazly <i>et al.</i> ⁶¹⁰	2015	MD = -0.69 (95% CI = -3.37-1.99)
Reza <i>et al.</i> ⁶⁰⁹	2010	MD = 1.29 (IV: -4.16, REM: 6.73)
PLNs		
Park <i>et al.</i> ⁵⁹⁷	2016	WMD = -3.71 (95% CI = -5.88--1.53)

CI confidence interval, FEM fixed-effects method, IV inverse variance, LNs lymph nodes, MD mean difference, M-H Mantel- Haenszel, nr not reported, OH open hysterectomy, OR odds ratio, PLNs pelvic lymph nodes, REM random-effects method, RH robot-assisted laparoscopic hysterectomy, RR relative risk, WMD weighted mean difference

Table 17. Pooled data on the perioperative outcomes of nerve-sparing radical surgery compared to conventional radical surgery

Perioperative outcomes	Year	NSRS versus CRS
Length of stay		
Van Gent <i>et al.</i> ⁶⁷²	2016	SDM = -0.82 (95% CI = -1.50--0.15)
Kim <i>et al.</i> ⁶⁵¹	2015	SDM = -0.224 (95% CI = -0.400--0.047)
Operative time		
Van Gent <i>et al.</i> ⁶⁷²	2016	SDM = 0.48 (95% CI = 0.16-0.79)
Kim <i>et al.</i> ⁶⁵¹	2015	SDM = -0.047 (95% CI = -0.635-0.542)
Blood loss		
Van Gent <i>et al.</i> ⁶⁷²	2016	SDM = -0.30 (95% CI = -0.64-0.04)
Kim <i>et al.</i> ⁶⁵¹	2015	SDM = -0.251 (95% CI = -0.391--0.110)
Length of the resected vagina		
Kim <i>et al.</i> ⁶⁵¹	2015	SDM = -0.498 (95% CI = -0.795--0.201)
Length of the parametrium		
Kim <i>et al.</i> ⁶⁵¹	2015	SDM = -0.320 (95% CI = -0.707-0.064)

CI confidence interval, CRS conventional radical surgery, NSRS nerve-sparing radical surgery, SDM standard differences in means

Table 18. Pooled data published by Park *et al.*⁵⁹⁷ about the complications relative to the robotic-assisted laparoscopic hysterectomy compared to conventional laparoscopy and laparotomy

Complications	RH versus OH	RH versus LH
Intra-operative major complications		
Bladder injury	RR = 0.14 (95% CI = 0.01-2.68)	RR = 0.14 (95% CI = 0.01-2.70)
Ureteral injury	RR = 1.03 (95% CI = 0.26-4.06)	RR = 0.91 (95% CI = 0.14-6.09)
Cystotomy	RR = 1.65 (95% CI = 0.36-7.61)	RR = 1.18 (95% CI = 0.48-2.89)
Post-operative major complications		
Vaginal complications	RR = 3.16 (95% CI = 1.00-9.99)	RR = 1.48 (95% CI = 0.31-7.02)
Thromboembolism	RR = 0.74 (95% CI = 0.17-3.24)	RR = 0.43 (95% CI = 0.07-2.56)
Ileus/bowel obstruction	RR = 0.57 (95% CI = 0.25-1.31)	RR = 1.40 (95% CI = 0.34-5.81)
Wound infection	RR = 0.27 (95% CI = 0.08-0.90)	nr
Post-operative minor complications		
Fever	RR = 0.28 (95% CI = 0.12-0.69)	RR = 0.45 (95% CI = 0.09-2.10)
Urinary tract infection	RR = 0.27 (95% CI = 0.09-0.82)	RR = 0.37 (95% CI = 0.09-1.48)

CI confidence interval, LH conventional laparoscopic hysterectomy, nr not reported, OH open hysterectomy, RH robot-assisted laparoscopic hysterectomy, RR relative risk

Table 19. Pooled data published by Shazly *et al.*⁶¹⁰ about the complications relative to the robotic-assisted laparoscopic hysterectomy compared to conventional laparoscopy and laparotomy

Complications	RH versus OH	RH versus LH
Pelvic infection and abscess formation	OR = 1.58 (95% CI = 0.58-4.35)	OR = 1.09 (95% CI = 0.23-5.03)
Cardiopulmonary complications	OR = 0.84 (95% CI = 0.34-2.07)	OR = 1.83 (95% CI = 0.45-7.47)
Cuff related complications	OR = 1.79 (95% CI = 0.54-5.93)	OR = 0.79 (95% CI = 0.19-3.21)
Febrile morbidity	OR = 0.43 (95% CI = 0.20-0.89)	OR = 0.47 (95% CI = 0.20-1.09)
Intestinal obstruction	OR = 0.71 (95% CI = 0.29-1.71)	OR = 1.14 (95% CI = 0.28-4.61)
Lymphovascular complications	OR = 1.00 (95% CI = 0.41-2.46)	OR = 0.80 (95% CI = 0.36-1.74)
Thrombotic events	OR = 2.27 (95% CI = 0.76-6.82)	OR = 1.10 (95% CI = 0.30-1.26)
Readmission	OR = 1.11 (95% CI = 0.36-3.36)	OR = 1.26 (95% CI = 0.31-5.16)
Reoperation	OR = 0.62 (95% CI = 0.21-1.82)	nr
Uretero-renal complications	OR = 0.80 (95% CI = 0.24-2.68)	OR = 0.94 (95% CI = 0.42-2.12)
Urinary retention	OR = 1.35 (95% CI = 0.20-8.85)	OR = 0.62 (95% CI = 0.21-1.86)
Wound related complications	OR = 0.31 (95% CI = 0.13-0.73)	OR = 0.49 (95% CI = 0.13-1.80)

CI confidence interval, LH conventional laparoscopic hysterectomy, nr not reported, OH open hysterectomy, RH robot-assisted laparoscopic hysterectomy

Table 20. Pooled data published by Kim *et al.*⁶⁵¹ on the complication of nerve-sparing radical surgery compared to conventional radical surgery

Complications	CRS versus NSRS
Postoperative complications	OR = 0.750 (95% CI = 0.527-1.068)
Duration of postoperative catheterization	SDM = -1.369 (95% CI = -1.865--0.873)
Urinary frequency	OR = 0.347 (95% CI = 0.183-0.658)
Urinary incontinence	SDM = 0.595 (95% CI = 0.294-1.207)
Urinary retention	OR = 0.130 (95% CI = 0.015-1.116)
Dyuria	SDM = 0.220 (95% CI = 0.012-4.145)
Urinary urgency	OR = 0.711 (95% CI = 0.377-1.341)
Abnormal sensation	OR = 0.067 (95% CI = 0.013-0.340)
Constipation	OR = 0.409 (95% CI = 0.150-1.113)
Diarrhea	OR = 0.407 (95% CI = 0.094-1.758)
Fecal incontinence	OR = 0.258 (95% CI = 0.030-2.199)
Decrease in sexual interest	OR = 0.525 (95% CI = 0.237-1.160)
Dyspareunia	OR = 0.683 (95% CI = 0.378-1.233)
Decrease in orgasm	OR = 0.846 (95% CI = 0.430-1.663)
Decrease in sexual satisfaction	OR = 0.666 (95% CI = 0.330-1.341)
Vaginal dryness	OR = 0.843 (95% CI = 0.264-2.689)

CI confidence interval, CRS conventional radical surgery, NSRS nerve-sparing radical surgery, OR odds ratio, SDM standard differences in means

Table 21. Pooled data on the oncologic outcomes of nerve-sparing radical surgery compared to conventional radical surgery

Oncologic outcomes	Year	NSRS versus CRS
OS		
Kim <i>et al.</i> ⁶⁵¹	2015	HR = 1.030 (95% CI = 0.646-1.641)
2-year OS		
Van Gent <i>et al.</i> ⁶⁷²	2016	RR = 1.02 (95% CI = 0.99-1.05)
3-year OS		
Van Gent <i>et al.</i> ⁶⁷²	2016	RR = 1.01 (95% CI = 0.95-1.08)
5-year OS		
Van Gent <i>et al.</i> ⁶⁷²	2016	RR = 1.03 (95% CI = 0.99-1.08)
DFS		
Kim <i>et al.</i> ⁶⁵¹	2015	HR = 1.056 (95% CI = 0.700-1.593)
2-year DFS		
Kim <i>et al.</i> ⁶⁵¹	2015	RR = 1.01 (95% CI = 0.95-1.05)
3-year DFS		
Kim <i>et al.</i> ⁶⁵¹	2015	RR = 0.99 (95% CI = 0.94-1.03)
5-year DFS		
Kim <i>et al.</i> ⁶⁵¹	2015	RR = 1.00 (95% CI = 0.95-1.06)

CI confidence interval, CRS conventional radical surgery, DFS disease-free survival, HR hazard ratio, NSRS nerve-sparing radical surgery, OS overall survival, RR relative risk

11 Fertility sparing treatment

11.1 Summary of available scientific evidence

11.1.1 Simple trachelectomy or conisation

Fertility outcomes: Bentivegna *et al.*⁷⁵⁰ performed a systematic review of the literature to evaluate the fertility results, obstetric outcomes, and the management of infertility in patients with FIGO stage IB submitted to FSS. Five different FSS procedures were studied (simple trachelectomy or conisation, vaginal radical trachelectomy, laparotomic radical trachelectomy, pure or robot-assisted laparoscopic radical trachelectomy, and NACT followed by conservative surgery).

LoE 1-

The authors reported fertility results and obstetric outcomes from ten included series^{285,350,492,510,523,524,751-757} evaluating simple trachelectomy^{285,350,524,751,752}, cone resection (conisation, CKC, LEEP, LLETZ, or laser conisation)^{510,523,753-757}, or extrafascial trachelectomy⁴⁹² (Table 22). Exclusion for oncologic reasons (nodal involvement, involvement of the upper part of the trachelectomy specimen, inadequate margins, other histologic poor prognostic factors) depriving of FSS management was observed in 5.7% of patients. The rate of postoperative morbidity exerting an impact on subsequent fertility was low (3%, only cervical stenoses). Only four^{492,523,524,754,757} of ten series^{285,350,492,510,523,524,751-757} mentioned the number of patients who attempted to become pregnant. This may explain why the overall pregnancy rate seems to be artificially low (56%), even if the crude number of pregnancies per total number of procedures is high (Table 22). No discriminative fertility rates were described according to the type of cervical procedure used (cone resection versus simple trachelectomy). The prematurity rate was low compared with that observed after vaginal radical trachelectomy (15% versus 39%, $p < 0.001$).

Using the technique of meta-analysis, Kyrgiou *et al.*⁷⁵⁸ investigated the effect of excisional techniques (CKC (ten studies⁷⁵⁹⁻⁷⁶⁸), LLETZ (ten studies^{508,769-777}), laser conisation (seven studies^{773,778-783})) and destructive techniques (laser ablation (four studies^{773,782-784})) on subsequent maternal and fetal outcomes. It should be noted that the authors included studies considering conservative methods of FIGO stage IA1 cervical cancer and/or cervical intraepithelial neoplasia and that no separate analyses taking into account only patients with FIGO stage IA1 cervical cancer is available.

LoE 1-

LLETZ and CKC were associated with a significant increase in the risk of preterm delivery. The association between laser conisation and preterm delivery was marginally non-significant (Table 23). Significant interstudy heterogeneity was observed for the laser conisation studies, which was due to one conflicting study⁷⁸³. The exclusion of this outlying study reduced the heterogeneity and resulted in a significant effect (RR = 1.91 (95% CI = 1.03-3.55)). It should be noted that authors did not provide a clear reason for these outlying results. They mentioned that it could be possibly caused by the study design (the study selected controls matched for age and parity from the pre-laser interval of the same women). Laser ablation was not significantly associated with this outcome.

In three included studies^{773,774,778}, the risk of preterm delivery associated with LLETZ or laser conisation was specified according to the depth of the excised cone (less versus more than 10 mm). In all three studies, authors recorded a significantly increased risk if the depth was more than 10 mm (pooled RR = 2.6 (95% CI = 1.3-5.3)). If the cone depth was less than 10 mm, results were heterogeneous; two studies^{773,778} did not identify a raised risk, whereas one⁷⁷⁴ did not show a significant association, resulting in a non significant association (pooled RR =

1.5 (95% CI = 0.6-3.9)).

LLETZ and CKC were associated with a significant increase in the risk of low birthweight (< 2,500 g). For laser conisation and laser ablation, the pooled estimates of relative risk did not reach statistical significance (Table 23). Among the four procedures (CKC, LLETZ, laser conisation, laser ablation), CKC was the only one for which an association with a significant increase in the risk of caesarean section was reported. Among the three procedures (LLETZ, laser conisation, laser ablation) investigated in the meta-analysis⁷⁵⁸ mentioned above, LLETZ was the only one for which an association with a significant increase in the risk of pPROM was reported. None association with a significant increase in the risk of perinatal mortality was reported for the four procedures. It should be noted that the association between laser conisation and perinatal mortality was marginally non-significant.

Another meta-analysis⁷⁸⁵ examining the association of LEEP and subsequent pregnancy outcomes was identified but is not described because it contains no additional studies beyond those already captured by the meta-analysis⁷⁵⁸ mentioned above.

Four original studies^{454,468,471,473} not included in the systematic reviews/meta-analyses^{750,758} mentioned above and reporting data about childbearing after conservative treatment by conisation only were identified. Of the 30 patients with FIGO stage IA1 disease evaluated in three of them^{454,468,471}, fifteen patients had twenty-one pregnancies resulting in sixteen live births, and the two patients with FIGO stage IA2 disease had together three successful pregnancies. Of the 22 patients treated by conisation in the fourth identified study⁴⁷³, fifteen had a FIGO stage IA1 and seven had FIGO stage IA2 disease. Eleven of these women had eighteen pregnancies with thirteen live births and four spontaneous abortions.

LoE 3

As part of a large-scale study⁷⁸⁶, deliveries subsequent to LEEP had a significantly increased risk of subsequent spontaneous preterm delivery (OR = 2.07 (95% CI = 1.88-2.27)). Comparing deliveries subsequent to LEEP with deliveries subsequent to biopsy only, the risk was still significantly increased (OR = 1.66 (95% CI = 1.49-1.84)). Both ablation and biopsy before delivery were associated with significantly higher risks for spontaneous preterm delivery, compared with deliveries with no previous procedure (OR = 1.40 (95% CI = 1.13-1.73) and OR = 1.28 (95% CI = 1.20-1.35), respectively). The risk for spontaneous preterm delivery subsequent to a LEEP, compared with no LEEP, was significantly increased in all 3 categories of gestational age (moderately preterm (32-36 weeks): OR = 1.89 (95% CI = 1.71-2.09), very preterm (28-31 weeks): OR = 3.28 (95% CI = 2.56-4.19), and extremely preterm (21-27 weeks): OR = 3.16 (95% CI = 2.27-4.40)).

LoE 2-

When the deliveries of primiparous women were included, the increased risk for preterm delivery was attenuated only marginally for the LEEP group (OR = 1.98 (95% CI = 1.75-2.23)). When only the deliveries of women who had at least one delivery both before LEEP and after LEEP were included, the increase risk was still significant (OR = 2.55 (95% CI = 1.42-4.57)). However, no significant association was observed when only the deliveries of women who had at least one delivery both before biopsy and after biopsy were included (OR = 0.71 (95% CI = 0.45-1.11)).

Quality of life: only one small study⁷⁸⁷ analyzing the quality of life in terms of sexual and reproductive outcome in patients suffering from early stage cervical cancer, submitted to an excisional cone as fertility-sparing treatment, was identified. After surgery, all women had regular menstruation after a median time of 30 days. One patient (4.4%) had trouble in lubricating, 3 (13%) had anxiety about performance, 6 (26.1%) complained of dyspareunia which was resolved within 3 subsequent months. Overall, 11 (48%) showed concerns about a

LoE 3

future pregnancy, of whom 7 (30%) had a fear of possible inability to conceive, 1 (4.4%) to maintain the pregnancy, 2 (8.7%) to have a recurrence during the pregnancy and 1 (4.4%) had the fear of possible negative impact of their cancer history on the baby. Sixteen women (70%) had an immediate psychological and physical recovery, 4 (17%) after 3 months and 2 (9%) after 12 months. No patient wrote to have concerns about choosing this fertility-sparing treatment.

Oncologic outcomes: as part of another systematic review (13 series or case reports^{285,475,492,510,523,524,751,753,755-757,788,789}), Bentivegna *et al.*⁷⁹⁰ covered the oncologic outcomes after such management in patients with FIGO stage IB1 tumours of 2 cm or smaller (Table 24). All patients except four (98%) underwent PLN dissection (total pelvic lymphadenectomy or SN dissection). Five per cent of patients were excluded because of nodal involvement. Four patients (three local and one nodal) had recurrent disease (1.7%). No invasive recurrence was seen in patients without LVSI. It should be noted that initial data are missing for one patient.

LoE 1-

11.1.2 Vaginal radical trachelectomy (Dargent's operation)

Fertility outcomes: nearly half of the FSS modalities identified by Bentivegna *et al.*⁷⁵⁰ were performed using vaginal radical trachelectomy. The authors reported fertility result cases and obstetric outcomes from 19 series^{70,477,524,791-826} (Table 22). Oncologic reasons led to abandon the FSS procedure in 11% of patients. Seventeen^{70,477,524,791-823} of the nineteen teams^{70,477,524,791-826} used a prophylactic cerclage at the end of the procedure. It should be noted that this information was not mentioned by three teams^{524,811,823}. Cervical stenoses were the most common complication likely to impact fertility (8%). The infertility after the surgical procedure was related to cervical factors in at least 49% of cases (it should be noted that the cause of infertility was not reported in about one fifth of cases). Fifty-three per cent of these patients had achieved at least one pregnancy after management of infertility.

LoE 1-

Two other systematic reviews^{827,828} found are not described because they contain no additional studies beyond those already captured by the systematic review⁷⁵⁰ mentioned above.

An original study⁸²⁹ not included in the systematic reviews^{750,827,828} mentioned above was identified and presents consistent findings with those previously reported.

LoE 2-

Two other original studies^{830,831} not included in the systematic reviews^{750,827,828} mentioned above were also identified but its results are limited notably by the very small number of patients evaluated.

LoE 3

Perioperative outcomes: as part of a systematic review comparing the effects of vaginal radical trachelectomy and radical hysterectomy (five studies^{799,801,803,808,832}), Han *et al.*⁸³³ revealed that radical vaginal trachelectomy was associated with fewer blood transfusions, less blood loss, and a shortened hospital stay. It should be noted that need for blood transfusion is the only criterion for which pooled data are reported (RR = 0.33 (95% CI = 0.12-0.90)). Blood loss was recorded in four studies^{799,801,803,832}. The data from three studies^{799,801,803} showed a lower volume of blood loss in radical vaginal trachelectomy compared with radical hysterectomy. Statistical analysis was not performed in the remaining study⁸³². Four of the included studies^{799,801,803,832} presented data on the duration of hospital stays. The overall collected data on hospital stay strongly favored radical vaginal trachelectomy. Lastly, data on the duration of the operation were available in the 5 included studies^{799,801,803,808,832}. Two of these studies^{803,808} revealed that there was no significant difference in the duration of the operation, whereas two studies^{799,801} indicated that the duration of the operation for radical vaginal trachelectomy was longer than that for radical hysterectomy. The other study⁸³² did not provide statistical results.

LoE 1-

Complication rate/Quality of life: pooled analyses, performed by Han *et al.*⁸³³, of radical vaginal trachelectomy in comparison with radical hysterectomy failed to detect significant differences in intraoperative (five studies^{799,801,803,808,832}, RR = 1.99 (95% CI = 0.61-6.25)) and postoperative complications (four studies^{801,803,808,832}, RR = 0.36 (95% CI = 0.10-1.27)). Intraoperative complications included vascular injury resulting from LN dissection and injury to the bladder or ureter resulting from surgical manipulation of the vagina or abdominal cavity.

LoE 1-

In a study describing the quality of life after radical vaginal trachelectomy, Alenxander-Sefre *et al.*⁷⁹⁹ showed that there was a higher incidence of psychological problems (17% versus 10%) and dyspareunia in patients after radical vaginal trachelectomy (20% versus 2%).

LoE 2-

Oncologic outcomes: based on 21 series^{70,477,524,791-793,795-820,822-826,834-837}, Bentivegna *et al.*⁷⁹⁰ reported positive or close margins (< 5 mm) in 3% of patients. Among patients with FIGO stage IB1 tumours larger than 2 cm, 17% of patients had recurrent disease, compared with 4% of patients with FIGO stage IB1 tumours 2 cm or smaller (p = 0.001). None of the included studies provided the number, locations (inside the tumour or around it), and type (vascular or lymphatic) of LVSI foci. Five per cent of LVSI negative cases with tumours of 2 cm or smaller had recurrent disease as compared to 7% of LVSI positive cases (p = 0.15).

LoE 1-

Data from four trials^{801,803,808,832} included in the systematic review performed by Han *et al.*⁸³³ were available to calculate the relative risk for 5-year PFS rate. There was no significant difference in 5-year PFS rate between radical vaginal trachelectomy and radical hysterectomy (RR = 0.99 (95% CI = 0.95-1.02)). The 5-year OS rate, based on three studies^{803,808,832}, did not differ between radical vaginal trachelectomy and radical hysterectomy (RR = 0.97 (95% CI = 0.93-1.02)).

Six original studies^{477,798,809,810,814,838} not included in the systematic review published by Han *et al.*⁸³³ have also been identified and revealed that vaginal radical trachelectomy does not increase recurrence rate compared with radical hysterectomy.

LoE 2-

11.1.3 Abdominal radical trachelectomy

Fertility outcomes: Bentivegna *et al.*⁷⁵⁰ provided also fertility results, obstetric outcomes, and the management of infertility in patients with FIGO stage IB submitted to laparotomic radical trachelectomy from twenty-one series^{291,693,815,824,839-869} (Table 22). Exclusion for oncologic reasons depriving of FSS management was observed in 12.5% of patients. Cervical stenoses were the most common complication likely to impact fertility (8%). Several cases of severe intra-abdominal sepsis were reported (tubo-ovarian abscess or intra-abdominal abscess/local peritonitis (1.7%)), likely to impact on subsequent fertility, were reported with this surgical approach. The fertility rate in patients submitted to a laparotomic radical trachelectomy was 44% versus 57% and 65% (p < 0.001) in patients treated with a vaginal or a minimally invasive radical trachelectomy (minimally invasive laparoscopy), respectively. Similar pregnancy rates in cases of preservation or ligation of uterine arteries were reported (45% versus 44%, p > 0.05). Regarding the impact of uterine cerclage on the live birth rate, these rates were, respectively 61% and 70% in series mentioning the use or not of a prophylactic cerclage (p > 0.05). The prematurity rate was higher in patients undergoing radical trachelectomy by laparotomy as compared to those undergoing vaginal or minimally invasive radical trachelectomy but without any difference on live birth rate (Table 22).

LoE 1-

Cervical stenoses (9.5%) were also the most common complication likely to impact fertility in the systematic review published by Pareja *et al.*⁸⁷⁰ (twelve reports of case series^{291,842,843,846,847,852,853,855,857,858,862,871} and seventeen case reports^{NA}). Eighty-five per cent of patients were able to maintain their fertility. Thirty-eight per cent attempted to get pregnant,

and 59.3% of them were able to conceive.

Concerning the minimally invasive radical trachelectomy, Bentivegna *et al.*⁷⁵⁰ included 10 series^{76,819,826,856,867,872-880} evaluating pure laparoscopic surgery and/or robot-assisted laparoscopic surgery. Exclusion for oncologic reasons depriving of FSS management was observed in 7% of patients. All the teams used a prophylactic cerclage at the end of the procedure. Eight teams preserved the uterine arteries. It should be noted that this information was not mentioned by one team. All but two teams^{856,873} preserved the uterine arteries (one team⁸⁵⁶ did not mention these data). Here again, cervical stenoses were the most common complication likely to impact fertility (5%). Cervical erosion was the second most common complication likely to impact fertility (3.8%).

Another systematic review⁸⁸¹ was identified but is not described because (1) it contains no additional studies beyond those already described above and (2) no separate data taking into account the type of radical trachelectomy are described.

An original study⁸⁸² not included in the systematic reviews^{750,881} mentioned above was identified. Among the 34 patients who attempted to conceive after abdominal radical trachelectomy, eight patients achieved pregnancy (24%). All infants were delivered by cesarean section.

LoE 2-

An original study⁸⁸³ not included in the systematic reviews^{750,881} mentioned above and evaluating the surgical and obstetrical outcomes of patients who underwent laparoscopic radical trachelectomy was also identified but its results are limited notably by the very small number of patients evaluated.

LoE 3

Perioperative outcomes: a meta-analysis⁸⁸⁴ of three controlled clinical trials^{70,803,808} assessed the efficacy and safety of radical trachelectomy and radical hysterectomy for patients with early cervical cancer. No difference in blood transfusion (OR = 0.29 (95% CI = 0.06-1.36)) was reported. The authors could not performed meta-analysis concerning the operative time, blood loss, LNs count, and hospital stay. In the first trial⁷⁰, the operative time of radical trachelectomy was significantly longer, but this was not the case in the two other trials^{803,808}. One trial⁸⁰³ provided data concerning the postoperative hospital stay and duration to normal urine residual volumes, both of which were significantly shorter for radical trachelectomy (1 day versus 6 days, $p < 0.001$ for both). Discordant findings^{70,808} were observed with respect to the count of LNs removed.

LoE 1-

Consistent findings were reported in terms of blood transfusion by an original study published by Li *et al.*⁸⁸⁵ which is not included in the meta-analysis⁸⁸⁴ mentioned above. No differences with respect to the operative time, the estimated blood loss, and hospital stay were noted.

LoE 2-

Complication rate: the meta-analysis⁸⁸⁴ of three controlled clinical trials^{70,803,808} mentioned above showed also no significant between radical trachelectomy and radical hysterectomy in terms of intra- and post-operative overall complications (OR = 1.66 (95% CI = 0.11-25.28) and OR = 0.52 (95% CI = 0.11-2.48), respectively). Compared with radical hysterectomy, radical trachelectomy neither increased nor decreased the risk of postoperative infectious and non-infectious complications (OR = 0.46 (95% CI = 0.16-1.33) and OR = 0.53 (95% CI = 0.09-3.03), respectively).

LoE 1-

Fully consistent findings were described by Li *et al.*⁸⁸⁵ in terms of intra- and post-operative complications.

LoE 2-

Quality of life: the quality of life after radical trachelectomy was described in four identified studies^{813,886-889}. In the first one^{813,886}, the authors reported that there was a reduction in the proportion of patients who were afraid to have sex, from 83% to 23% after surgery at the 12-month assessment. Dyspareunia decreased over time and lessened along with the fear of intercourse. The mean sexual activity of patients was found to rise from 37% to 70% by the 6-month follow-up assessment.

LoE 3

The second one⁸⁸⁷ documented preoperative struggles faced by all young patients in the midst of considering treatment options (radical trachelectomy or radical hysterectomy), and their vulnerability during the immediate postoperative period. Women choosing radical hysterectomy and those choosing radical trachelectomy demonstrated scores suggestive of depression and distress preoperatively (based on the Center for epidemiologic studies depression scale (CES-D) and the Impact of events scale (IES), respectively). Measurements of mood, distress, sexual function and quality of life did not differ significantly by surgical type. Both groups had a decline in quality of life and sexual dysfunction postoperatively compared to preoperative baseline measures (as measured by the Functional assessment of cancer therapy-cervix (FACT-Cx), CES-D, IES, and Female sexual functioning index (FSFI)). However, both groups demonstrated adaptive processes over the next 2 years with improvement in scores from the initial postoperative decline.

The third identified study⁸⁸⁸ used several validated questionnaires including the FSFI, the Sexual function-vaginal changes questionnaire, and the EORTC cervical cancer module. This study demonstrated that patients undergoing radical vaginal trachelectomy had a significant decline in sexual dysfunction and global health status during the 12 months post-treatment. However, despite sexual activity increasing over the follow-up period, the scores never reached those of healthy controls. Using the FACT-Cx, FSFI, General health-related quality of life (SF-12), MD Anderson symptom inventory, and Satisfaction with decision scale the fourth identified study⁸⁸⁹ showed that several quality of life, sexual, and functional assessments decline immediately postoperatively after radical trachelectomy, however, most return to baseline measures by 6 months postoperatively. A persistent decline in emotional well-being was seen up to 4 years after the radical trachelectomy procedure.

Oncologic outcomes: after a median follow-time of 31.6 months, the systematic review published by Pareja *et al.*⁸⁷⁰ (twelve reports of case series^{291,842,843,846,847,852,853,855,857,858,862,871} and seventeen case reports^{NA}) identified a recurrence in 3.8% of patients. Death from cervical cancer after abdominal radical trachelectomy was reported in 0.4% of patients.

LoE 1-

Bentivegna *et al.*⁷⁹⁰ (twenty-eight series^{291,693,700,824,839,843-847,849-852,855-858,860,862-869,871,890-895}) observed a recurrent disease in 5% of cases, of which 29% died. Among at least 167 patients with FIGO stage IB1 tumours specified as measuring 2-4 cm, eight (5%) had recurrent disease. The authors provided also data on pure laparoscopic radical trachelectomy (eighteen series^{76,826,856,867,872-874,877,878,896-902}). All except four teams^{856,873,899,900} preserved the uterine artery, and four^{874,898,901,902} also used nerve-sparing surgery. Six per cent of patients had recurrent disease, of whom 17% had FIGO stage IB1 tumours larger than 2 cm (Table 24). Only one^{819,879,880} from the nine series^{555,819,855,856,879,880,898,903-908} providing data on robot-assisted laparoscopic radical trachelectomy reported a follow-up longer than 24 months. Four⁹⁰⁵⁻⁹⁰⁸ of them did not report any follow-up. It should be noted that available data suggest that robot-assisted laparoscopic radical trachelectomy is still in the feasibility stage with no clear data on specific outcomes or the usefulness of this procedure compared with pure laparoscopic radical trachelectomy.

As part of the meta-analysis⁸⁸⁴ of three controlled clinical trials^{70,803,808} mentioned above,

radical trachelectomy neither increased nor decreased the risk of recurrence (OR = 1.38 (95% CI = 0.58-3.28)), the risk of postoperative mortality (OR = 1.14 (95% CI = 0.42-3.11)), the 5-year RFS (OR = 1.17 (95% CI = 0.54-2.53)), and the 5-year OS (OR = 0.86 (95% CI = 0.30-2.43)) compared with radical hysterectomy.

Here again, Li *et al.*⁸⁸⁵ described fully consistent findings with those reported by the meta-analysis⁸⁸⁴ mentioned above. In the series published by Okugawa *et al.*⁸⁸², the relapse rate after abdominal radical trachelectomy was 1.1% with no mortality.

LoE 2-

11.1.4 Neoadjuvant chemotherapy followed by conservative surgery

Fertility outcomes: Bentivegna *et al.*⁷⁵⁰ reported fertility results and obstetric outcomes from 9 included series^{547,548,550-552,557-560,693,795,909-911} evaluating NACT followed by conservative surgery (Table 22). Two surgical procedures were used: a simple trachelectomy/cone resection (31%) and a radical trachelectomy (69%). When a radical trachelectomy was performed after NACT, all the teams used a prophylactic cerclage at the end of the procedure. FSS procedure was abandoned or not retained for oncologic reasons in 8% of patients. Cervical stenoses were observed in 8% of patients.

LoE 1-

Among patients who had at least one pregnancy, 48% and 38% of patients had respectively undergone a simple cervical resection and a radical trachelectomy. The prematurity rate was lower compared with that observed after a vaginal or an abdominal radical trachelectomy (15% versus 39% and 57%, $p < 0.001$). Eighty-two per cent of preterm deliveries were related to pPROM. The reported fertility rate was high in patients who had received NACT before FSS, but it may be due to a very recent series⁹¹¹ that comprised nearly half of the NACT cases reported in the literature identified by Bentivegna *et al.*⁷⁵⁰ and included 86% of patients wishing to become pregnant who had achieved at least one pregnancy. The rate after excluding this recent series was similar to that obtained with the other radical trachelectomy techniques.

As part of another systematic review, Pareja *et al.*⁹¹² identified 14 reports^{548-560,913} addressing the use of NACT in patients with early-stage (FIGO stages IB1-IIA) cervical cancer interested in future fertility. A total of 8 patients did not preserve fertility and among the remaining 65 patients (89%) who preserved fertility after NACT, 20 pregnancies were reported (30.7%), with 16 deliveries (6 preterm and 10 at term), 2 ongoing pregnancies, 1 ectopic pregnancy, and 3 miscarriages (some women delivered more than one baby).

It should be noted that the results described in the systematic reviews^{750,912} mentioned above have to be interpreted cautiously due to (1) the heterogeneity of NACT regimens used in the included studies, (2) the heterogeneity concerning the type of surgical procedures used after NACT, and (3) the number of patients evaluated (only one study⁹¹¹ has accrued at least 60 patients).

Results from two identified studies^{914,915} not included in the systematic reviews^{750,912} mentioned above and evaluating outcomes of fertility and pregnancy in patients with cervical cancer after undergoing NACT are limited notably by the very small number of patients evaluated. In eight (67%) patients seeking pregnancy after the treatments, four pregnancies occurred in three women.

LoE 3

Oncologic outcomes: Bentivegna *et al.*⁷⁹⁰ included seventeen series or case reports^{547-549,551-556,558-560,693,795,822,896,909,910,913,916,917} assessing NACT to promote fertility preservation in patients with invasive cervical cancer of whom 87% underwent uterine conservation. Among the patients with FIGO stage IB1 disease (75%), 61% had tumours of 2-4 cm. The most frequently used neoadjuvant regimen was three courses of platinum-based chemotherapy. Nineteen per

LoE 1-

cent of patients required adjuvant therapy, with 79% of them requiring hysterectomy. A recurrent disease was observed in 6% of patients who underwent uterine conservation, of whom one third died (Table 24). Two recurrences (33%) were seen in patients with initial FIGO stage IB2 disease (with residual disease measuring 3 mm and 15 mm), three (50%) in patients with initial FIGO stage IB1 tumours of 2 cm or larger, and one (17%) in a patient with an initial FIGO stage IB1 tumour smaller than 2 cm.

The case of a patient with FIGO stage IB2 who exhibited pathological complete regression to NACT, published by Feng *et al.*⁹¹⁵, did not show any recurrent disease 72 months after surgery. **LoE 3**

11.1.5 Other fertility sparing techniques

Ovarian preservation: including 5 studies⁹¹⁸⁻⁹²², Jiao *et al.*⁹²³ evaluate the safety of ovarian preservation according to the histological type. The incidence of ovarian metastasis of patients with early-stage adenocarcinoma and squamous cell carcinoma were 2% and 0.4%, respectively (OR = 5.27 (95% CI = 2.14-13.45). In 1,427 patients with adenocarcinoma or squamous cell carcinoma of the cervix (FIGO stage IIA disease) who underwent hysterectomy, no ovarian recurrences were observed after unilateral or bilateral ovarian preservation in adenocarcinoma patients in the follow-up (30-68 months). However, it should be noted that 15 patients with squamous cell carcinoma developed pelvic recurrence. **LoE 1-**

Based of data from six studies^{919,920,922,924-926}, Touhami *et al.*⁹²⁷ observed that at least one of the following risk factors was present in 97% of patients with ovarian metastasis from adenocarcinoma of the cervix: age > 45 years, FIGO stage > IB, positive LNs, deep stromal invasion, LVSI, corpus invasion, parametrial invasion or tumour size > 4 cm. All included FIGO stage IB adenocarcinoma series^{919-922,925,928} report an incidence of ovarian metastasis under 4%, with an overall global incidence of 2%. In 119 patients with adenocarcinoma of the cervix (FIGO stage IIA) included by Touhami *et al.*⁹²⁷ (five studies^{919,929-932}), none developed an ovarian relapse after ovarian preservation with a mean follow-up time of 56 months.

An original study⁹³³ not included in the systematic review/meta-analysis^{923,927} mentioned above was also identified. As part of this study evaluating the impact of ovarian preservation on prognosis in women with cervical adenocarcinoma, no significant difference in DFS or OS between women with bilateral salpingo-oophorectomy and ovarian preservation was found. **LoE 2-**

Ovarian transposition: the available data⁹³⁴⁻⁹⁵⁴ evaluating the OT for preserving ovarian function in cervical cancer patients are limited notably due to (1) the very small number of patients included in the majority of identified studies, (2) the wide variation in the type of ovarian transposition surgery performed (bilateral robotic OT, unilateral laparoscopic OT, unilateral laparoscopic OT with contralateral oophorectomy, bilateral laparoscopic OT, unilateral OT via laparotomy, bilateral OT via laparotomy), and (3) the absence of analysis taking into account the type of postoperative treatments performed (vaginal brachytherapy, external radiation therapy, external radiation therapy and vaginal brachytherapy). The available data investigating the potential risk factors related to the recurrence of cervical cancer following ovarian transposition are also too limited to define a pattern of particular risk factors. **LoE 3**

Uterine transplantation: to date, 11 uterine transplantations⁹⁵⁵⁻⁹⁵⁷ were performed worldwide in patients (only one patient had previously undergone radical hysterectomy for cervical cancer of an unspecified stage). Of these, seven maintained their reproductive potential, with viable transplanted uteri and regular menstrual cycles. All the women received immunosuppression to prevent rejection of the transplant. Their uterine artery blood flow was unchanged. In september 2014, Brännström *et al.*⁹⁵⁸ reported the first live birth (with normal **LoE 3**

weight for gestational age (31 weeks and 5 days)) after uterus transplantation, in a patient suffering from Rokytanski syndrome, after in vitro fertilization treatment of both the patient and her partner. Pregnancy had no complications, with a benign fetal evaluation and uneventful throughout pregnancy.

11.1.6 Vaginal progesterone prophylaxis

Past history of spontaneous preterm birth: as part of a systematic review⁹⁵⁹ assessing the benefits and harms of progesterone for the prevention of preterm birth for women considered to be at increased risk of preterm birth and including eleven RCTs⁹⁶⁰⁻⁹⁹⁴, there was a statistically significant reduction in perinatal mortality overall for women administered progesterone during pregnancy (Table 25). There were also significant differences in preterm birth less than 34 weeks' gestation, infant birthweight less than 2,500 g, use of assisted ventilation, necrotizing enterocolitis, neonatal death, NICU admission, and pregnancy prolongation in weeks between progesterone and placebo.

LoE 1-

However, for infant outcomes Apgar score < 7 at 5 minutes, respiratory distress syndrome, intrauterine fetal death, intraventricular haemorrhage (all grades, grade III or IV), periventricular leucomalacia, retinopathy of prematurity, neonatal sepsis, patent ductus arteriosus, intrauterine fetal death, neonatal length of hospital stay, threatened preterm labour, spontaneous vaginal birth, adverse drug reaction, caesarean birth, use of antenatal corticosteroids, the use of antenatal tocolysis, developmental delay, intellectual impairment, motor impairment, visual impairment, hearing impairment, cerebral palsy, learning difficulties, height less than 5th centile, weight less than the 5th centile, infant weight at 6, 12 and 24 months' follow-up, infant length at 6, 12, and 24 months' follow-up, or infant head circumference at 6, 12 and 24 months' follow-up, there were no statistically significant differences identified. It should be noted also that the authors found no differential effect on the majority of outcomes examined when considering route of administration of progesterone (intramuscular, vaginal or oral).

Women with a short cervix identified on ultrasound: the systematic review⁹⁵⁹ mentioned above provided also data on the benefits and harms of progesterone for women with a short cervix identified on ultrasound (four RCTs⁹⁹⁵⁻¹⁰⁰⁰). Women administered progesterone were significantly less likely to have a preterm birth at less than 34 weeks' gestation, less than 28 weeks' gestation, and more likely to experience the adverse drug reaction urticaria (Table 26).

LoE 1-

For perinatal death, preterm less than 37 weeks' gestation, infant birthweight less than 2,500 g, respiratory distress syndrome, Apgar score less than 7 at 5 minutes, need for assisted ventilation, intraventricular haemorrhage (all grades, and grades III or IV), periventricular leucomalacia, retinopathy of prematurity, necrotizing enterocolitis, neonatal sepsis, intrauterine fetal death, neonatal death, NICU admission, threatened preterm labour, pPROM, adverse drug reactions (any, injection site, nausea), pregnancy prolongation, caesarean section, or antenatal tocolysis, there were no statistically significant differences identified.

The authors found no differential effect on the outcomes examined (periventricular leucomalacia, retinopathy of prematurity, and necrotizing enterocolitis) when considering route of administration of progesterone (intramuscular versus vaginal) (Table 26). Subgroup analyses by total cumulative dose of progesterone (< 500 mg versus > 500 mg) were also performed. No differential effect for the two outcomes examined was reported (periventricular leucomalacia: RR = 1.49 (95% CI = 0.13-16.87) and NICU admission: RR = 1.09 (95% CI = 0.72-1.65)). It should be noted that the authors could not assess the effect of gestational age at commencing therapy.

Women with multiple pregnancy: ten RCTs^{972,1001-1022} were included in the meta-analysis performed by Dodd *et al.*⁹⁵⁹. For women administered progesterone during pregnancy, perinatal death, preterm birth less than 34 weeks' gestation, preterm birth less than 37 weeks' or 28 weeks' gestation, infant birthweight less than 2,500 g, Apgar score less than 7 at 5 minutes, respiratory distress syndrome, need for ventilation, intraventricular haemorrhage, periventricular leucomalacia, retinopathy of prematurity, chronic lung disease, necrotizing enterocolitis, neonatal death, NICU admission, pPROM, adverse drug reaction, caesarean section, spontaneous birth, assisted birth, satisfaction with the therapy, antenatal tocolysis or antenatal corticosteroids, there were no statistically significant differences identified when compared with placebo (Table 27, Table 28).

LoE 1-

No differential effect was found on the majority of outcomes examined when considering route of administration of progesterone (intramuscular versus vaginal). However, for spontaneous birth, infant birthweight less than 2,500 g and NICU admission, the subgroup analyses indicated a differential effect between the two routes of administration (Table 27). It should be noted that for two outcomes, some of the subgroups contained only one trial. No effect of time of commencement of supplementation (prior to 20 weeks' gestation versus after 20 weeks' gestation) on preterm birth less than 37 weeks' gestation (RR = 0.99 (95% CI = 0.82-1.20)), neonatal death (RR = 0.95 (95% CI = 0.47-1.93)), and NICU admission (RR = 1.16 (95% CI = 0.95-1.43)) was reported.

Subgroup analyses by total weekly cumulative dose of progesterone (< 500 mg versus > 500 mg) were also performed. No differential effect was observed for the 8 outcomes examined (perinatal death, preterm birth less than 34 weeks' gestation, antenatal tocolysis, preterm birth less than 37 weeks' gestation, respiratory distress syndrome, fetal death, infant birthweight less than 2,500 g, and NICU admission).

Women following presentation with threatened preterm labour: the systematic review⁹⁵⁹ mentioned above provided also data on the benefits and harms of progesterone for women following presentation with threatened preterm labour (five RCTs¹⁰²³⁻¹⁰³²). For women administered progesterone during pregnancy, when compared with placebo, there was a significant reduction in the risk of infant birthweight less than 2,500 g.

LoE 1-

However, there were no statistically significant differences for any of the other outcomes analysed (perinatal death, preterm birth less than 34 weeks' gestation, preterm birth less than 37 weeks' gestation, respiratory distress syndrome, intraventricular haemorrhage (grades III or IV), periventricular leucomalacia, need for mechanical ventilation, necrotizing enterocolitis, neonatal sepsis, fetal death, neonatal death, neonatal length of hospital stay, pregnancy prolongation, spontaneous vaginal birth, caesarean section, and use of tocolysis) (Table 29). No differential effect on some of the outcomes examined was found when considering route of administration of progesterone (intramuscular versus vaginal). However, for pregnancy prolongation and preterm birth less than 37 weeks' gestation, the subgroup analyses indicated a differential effect between the different routes of administration. It should be noted that in both analyses the subgroups contained only one trial.

Subgroup analyses by total weekly cumulative dose of progesterone (< 500 mg versus > 500 mg) were also performed. No differential effect was observed for the 5 outcomes examined (pregnancy prolongation, preterm birth less than 37 weeks' gestation, respiratory distress syndrome, neonatal sepsis, and neonatal death). It should be noted that the authors could not assess the effect of gestational age at commencing therapy.

Women at risk of preterm birth: including women at risk of preterm birth (because of previous spontaneous birth (\leq 34 weeks and \geq days of gestation, or a cervical length \leq 25 mm, or

LoE 1-

because of a positive fetal fibronectin test combined with other clinical risk factors for preterm birth (any one of a history in a previous pregnancy of preterm delivery birth, second trimester loss, preterm premature fetal membrane rupture, or a history of a cervical procedure to treat abnormal smears)), a RCT¹⁰³³ not included in the systematic review⁹⁵⁹ mentioned above revealed that vaginal progesterone was not associated with reduced risk of fetal death or birth before 34 weeks and 0 days gestation, or composite neonatal adverse outcomes (a composite of death, brain injury, or bronchopulmonary dysplasia) and had no long-term benefit or harm on outcomes in children at 2 years of age (Bayley-III cognitive composite score at 22-26 months of chronological age). It should be noted that no subgroup analyses taking into account the type of risk of preterm birth specifically are available.

11.1.7 Cervical stitch (cerclage)

Singleton pregnancy: Alfirevic *et al.*¹⁰³⁴ assessed whether the use of cervical stitch in singleton pregnancy at high risk of pregnancy loss based on a woman's history and/or ultrasound finding of "short cervix" improves subsequent obstetric care and fetal outcome.

LoE 1-

Compared with expectant management (no treatment, nine studies¹⁰³⁵⁻¹⁰⁷⁵), the cerclage was associated with a significant reduction in preterm births consistent across all gestation time points and all clinical subgroups. The cerclage was also associated with higher caesarean section rates (elective and emergency), and higher rates of pyrexia. Although there is no conclusive evidence of a difference between cerclage and expectant management (no treatment), it should be noted that there were fewer perinatal deaths in the cerclage group (RR = 0.78 (95% CI = 0.61-1.00)). No conclusive evidence of a difference between the two groups was also reported with respect to serious neonatal morbidity, stillbirths, neonatal deaths before discharge, miscarriages, serious intracranial pathology (intraventricular hemorrhage or periventricular leucomalacia), serious respiratory morbidity (respiratory distress syndrome or oxygen dependency after 28 days of life), necrotising enterocolitis, retinopathy of prematurity, maternal side effects (vaginal discharge, bleeding, pyrexia not requiring antibiotics), pPROM, and chorioamnionitis (Table 30). There was no evidence of any important differences across all prespecified clinical subgroups (history-indicated, ultrasound-indicated).

The sole included study¹⁰⁷⁶ comparing cerclage with weekly intramuscular injection of 17 α -hydroxyprogesterone caproate in women with a short cervix detected by transvaginal ultrasound scan was interrupted after 3 years of recruitment because interim analysis did not reveal any obvious differences in obstetric and neonatal outcomes.

Multiple pregnancy: Rafael *et al.*¹⁰⁷⁷ assessed whether the use of cervical stitch in multiple pregnancy at high risk of pregnancy loss based on just the multiple gestation (history-indicated cerclage), or the ultrasound findings of "short cervix" improves subsequent obstetric and perinatal outcomes.

LoE 1-

Compared with expectant management (no treatment, five studies^{1035-1041,1043,1044,1047-1050,1068-1070,1072-1074,1078-1080}), there is no evidence that cerclage is an effective intervention for preventing preterm birth and reducing perinatal deaths or neonatal morbidity. No conclusive evidence of a difference between the two groups was also reported with respect to serious neonatal morbidity, stillbirths, neonatal deaths, mean gestational age at delivery, low birthweight (< 2,500 g), very low birthweight (< 1,500 g), respiratory distress syndrome, intraventricular hemorrhage, sepsis, NICU admission, caesarean section (elective and emergency), or maternal side-effects (vaginal discharge, bleeding, pyrexia not requiring antibiotics) (Table 31). Data relative to the differences between prespecified subgroups have to be interpreted cautiously due to the low number of trials and/or substantial heterogeneity and subgroup differences. It should also be noted that no study comparing cervical stitch

versus any other preventative therapy (e.g. progesterone) in multiple gestations was included by the authors.

11.2 Previous initiatives

Nine previous initiatives^{419,420,422-424,529,531,1081-1083} presenting guidelines for fertility sparing treatment were identified.

11.3 Development group comments

In highly industrialized countries, FST is gaining more and more importance, since more than 40% of early stage invasive cervical carcinomas occur in patients under the age of 44 and women's age at first pregnancy/delivery increases. Given the possible spectrum of FST patient's counselling and treatment should only be done in centers, which can offer all kinds of FST (sentinel and full pelvic lymphadenectomy, conisation, simple trachelectomy, radical trachelectomy, FST following NACT, comprehensive staging in patients with necessity to abandon FST).

Recurrence rate after conisation as FST ranges from 0% to 13%. However, in a considerable percentage of patients repeated conisation is necessary to reach aim of FST, sometimes 3 times. Of note conisation itself is associated with higher likelihood of PROM and/or preterm delivery. To date, four different approaches are established for radical trachelectomy. Most data with longest follow-up exist for radical vaginal trachelectomy, less for abdominal radical trachelectomy, few for total laparoscopic radical trachelectomy and only small series for robotic-assisted radical trachelectomy. Techniques for different approaches are standardized and permanent cerclage should be placed in all patients. However, best material for permanent cerclage is undecided. Coverage of residual tumour with adequate vaginal cuff and avoidance of uterine manipulator use seems to be advantageous.

It is undecided which of primary radical trachelectomy or NACT followed by FST is superior to the other in women with proven cervical cancer > 2 cm. Rate of possible fertility preserving surgery and obstetrical outcomes seems superior after NACT compared to upfront radical trachelectomy. However, there is a couple of unclear issues in the concept of NACT:

- Should lymphadenectomy be performed as staging procedure before NACT?
- Is radical trachelectomy superior to simple trachelectomy after good response to NACT?
- Is radical trachelectomy superior to simple trachelectomy after good response to NACT?
- What is the best management in suboptimal responders?
- Which is the best NACT regimen?

No recommendation can be provided for earliest possible realization of childbearing following FST. After finishing of wound healing pregnancy seems possible, also use of in vitro fertilisation techniques. Radical trachelectomy inherently has increased risk of premature delivery and second trimester miscarriage due to PROM and/or ascending infection. These problems are probably associated with shortened remaining cervix and/or permanent cerclage and represent major challenges in obstetrical management of women following trachelectomy. Various preventive methods can be discussed with the patient (e.g. regular measurement of vaginal pH- value, laparoscopic placement of cerclage, bed-rest and abstain from sexual intercourse, sick note, progesteron application, etc.).

Routine hysterectomy following FST and finished family planning is not generally recommended because it does not seem to increase oncologic safety despite limited available data. Secondary hysterectomy should only applied in patients with recurrent clinical symptoms such as dysmenorrhoea, dyspareunia, vaginal discharge, irregular bleeding or repeated cervical stenosis. Repeated abnormal Pap test after FST is

frequently observed with lower clinical relevance. Patient's strong wish can be another reason for secondary hysterectomy.

11.4 Guidelines

- ✓ Before starting FST, consultation at a fertility center is recommended.
- ✓ FST should exclusively be undertaken in gynecologic-oncological centers with comprehensive expertise in this kind of oncologic therapy.
- ✓ For patients who consider FST, prognostic factors, clinical staging, and preoperative workup 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 equal to or less than 2 cm of the largest diameter should be counseled about the possibility of FST. This consultation should encompass the risk of FST abandonment if there are positive margins or LN involvement and 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 behavior.
- ✓ Expert sonography and/or pelvic MRI are recommended imaging tests to measure remaining (after cone biopsy) cervical length and noninvolved 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 PLN status is the precondition for any FST. Therefore, PLN (SLN) staging should always be the first step in each FST procedure. Identification of SLN and its ultrastaging is highly recommended because it increases staging accuracy, namely, the identification of micrometastases and small macrometastases. The involvement of suspicious LNs should be confirmed by histology. Intraoperative assessment of LN status is highly recommended. All SLNs from both sides of the pelvis or any suspicious LNs should be sent for frozen section. If bilateral SLN is not detectable, intraoperative assessment of PLNs should be considered (see Management of stages T1b1/T2a1). LN 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 tumor with adequate free margins and preservation of the 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** Conization and simple trachelectomy are adequate fertility sparing procedures for stages T1a1 and T1a2, LN-negative, LVSI-negative patients.
- B** Radical trachelectomy (type A) can be considered for stages T1a1 and T1a2, LN-negative, LVSI-positive patients. Conization or simple trachelectomy is an option.
- B** Radical trachelectomy (type B) should be performed for patients with cervical cancer stage T1b1 equal to or less than 2 cm of the largest diameter, LN-negative, LVSI ±.

- ✓ Intraoperative placement of permanent cerclage should be performed during simple or radical trachelectomy.
- ✓ FST in patients with tumors greater than 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 center. Following simple or radical trachelectomy with its inherent placement of a permanent cerclage delivery can be performed only by cesarean section.
- ✓ Routine hysterectomy after finishing fertility plans is not necessary.

Table 22. Fertility outcomes published by Bentivegna *et al.*⁷⁵⁰ according to fertility-sparing surgery procedures

Parameter	Simple trachelectomy	Dargent	Radical trachelectomy		NACT
	/cone resection	procedure	Laparotomy	Mini invasive	
N	200	1,205	643	292	148
Pregnancies	103	499	175	74	93
Fetal loss (1st trimester)	9	67	18	15	12
Fetal loss (2 nd trimester)	5	34	8	2	5
Fetal loss (1st or 2 nd trimester)	0	0	11	0	0
Interruption-abortion	2	21	1	0	0
Ectopic pregnancy	1	6	0	0	1
Ongoing pregnancy	14	18	17	7	4
Preterm delivery (< 36 WG)	8	120	59	25	11
between 22 and 28 WG	1	11	8	6	2
between 29 and 33 WG	3	25	15	5	5
between 34 and 36 WG	0	24	26	12	2
undetermined or other cutoff	4	60	10	2	2
Pregnancy rate	22/39 (56%)	241/424 (57%)	135/310 (44%)	57/87 (65%)	60/78 (77%)
Live birth rate	51/69 (74%)	308/460 (67%)	120/175 (68%)	50/64 (78%)	71/93 (76%)
Prematurity rate	8/51 (15%)	113/285 (39%)	59/104 (57%)	25/50 (50%)	11/71 (15%)

NACT neoadjuvant chemotherapy, WG weeks gestation

Table 23. Pooled data published by Kyrgiou *et al.*⁷⁵⁸ on the obstetric outcomes after LLETZ, laser conisation, laser ablation and CKC

Obstetric outcomes	LLETZ		Laser conisation		Laser ablation		CKC	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Preterm delivery (< 37 weeks)	1.70	1.24-2.35	1.71	0.93-3.14	0.87	0.63-1.20	2.59	1.80-3.72
Low birthweight (< 2,500 g)	1.82	1.09-3.06	1.23	0.39-3.94	0.84	0.45-1.58	2.53	1.19-5.36
Caesarean delivery	0.88	0.71-1.09	1.16	0.64-2.09	0.79	0.49-1.25	3.17	1.07-9.40
Precipitous delivery (< 2 h)	1.26	0.75-2.11	-	-	-	-	-	-
pPROM	2.69	1.62-4.46	2.18	0.77-6.16	1.23	0.56-2.70	-	-
NICU admission	1.25	0.93-1.67	-	-	-	-	-	-
Perinatal mortality	3.40	0.62-18.63	8.00	0.91-70.14	0.67	0.11-3.96	1.89	0.77-4.65

CI confidence interval, CKC cold knife conisation, LLETZ large loop excision of the transformation zone, NICU neonatal intensive care unit, pPROM preterm spontaneous rupture of membranes, RR relative risk

Table 24. Oncologic outcomes published by Bentivegna *et al.*⁷⁹⁰ according to fertility-sparing surgery procedures

Parameter	Simple trachelectomy	Dargent	Radical radical trachelectomy			NACT
	/cone resection	procedure	Laparotomic	laparoscopic	Robot-assisted	
N	230	1,364	660	238	89	99
FIGO stage						
IA	not included	316	153	55	25	0
IB1 (all)	228	1,065	559	215	54	85
IB1 (> 2 cm)	0	≥ 84	≥ 167	≥ 42	unknown	≥ 52
IB2	0	3	19	2	1	25
IIA	0	9	4	1	0	3
Tumour type						
Squamous-cell carcinoma	60	892	549	167	37	70
Adenocarcinoma	25	432	168	50	29	41
Other, mixed, or unknown	157	199	44	35	35	3
LVSI positive	≥ 71	401	≥ 198	≥ 52	≥ 5	nr
Recurrent disease	4	58	31	15	2	6-7
Died from disease	0	24	9	3	0	2

LVSI lymph-vascular space involvement, NACT neoadjuvant chemotherapy, nr not reported

Table 25. Pooled data published by Dodd *et al.*⁹⁵⁹ on the effectiveness and safety of progesterone for preventing preterm birth in women with a past history of spontaneous preterm birth compared to placebo/no treatment

Parameter	Progesterone versus placebo	Parameter	Progesterone versus placebo
Perinatal mortality		Preterm birth (< 34 weeks)	
Intramuscular	RR = 0.41 (95% CI = 0.23-0.73)	Intramuscular	not estimable
Vaginal	RR = 0.67 (95% CI = 0.34-1.29)	Vaginal	RR = 0.21 (95% CI = 0.10-0.44)
Oral	RR = 0.43 (95% CI = 0.12-1.59)	Oral	RR = 0.59 (95% CI = 0.39-0.90)
Total	RR = 0.50 (95% CI = 0.33-0.75)	Total	RR = 0.31 (95% CI = 0.14-0.69)
Preterm birth (< 37 weeks)		Threatened preterm labour	
Intramuscular	RR = 0.62 (95% CI = 0.52-0.75)	Intramuscular	RR = 1.17 (95% CI = 0.73-1.87)
Vaginal	RR = 0.52 (95% CI = 0.29-0.92)	Vaginal	RR = 0.62 (95% CI = 0.35-1.11)
Oral	RR = 0.46 (95% CI = 0.19-1.11)	Oral	not estimable
Total	RR = 0.55 (95% CI = 0.42-0.74)	Total	RR = 0.87 (95% CI = 0.47-1.62)
Spontaneous vaginal delivery		Caesarean section	
Intramuscular	Not estimable	Intramuscular	RR = 0.94 (95% CI = 0.68-1.30)
Vaginal	RR = 1.07 (95% CI = 0.97-1.18)	Vaginal	RR = 1.01 (95% CI = 0.79-1.30)
Oral	Not estimable	Oral	not estimable
Total	RR = 1.07 (95% CI = 0.97-1.18)	Total	RR = 0.98 (95% CI = 0.81-1.20)
Antenatal corticosteroids		Antenatal tocolysis	
Intramuscular	RR = 0.87 (95% CI = 0.58-1.30)	Intramuscular	RR = 1.12 (95% CI = 0.73-1.72)
Vaginal	RR = 0.95 (95% CI = 0.72-1.26)	Vaginal	RR = 1.10 (95% CI = 0.70-1.74)
Oral	not estimable	Oral	RR = 0.75 (95% CI = 0.42-1.35)
Total	RR = 0.92 (95% CI = 0.73-1.16)	Total	RR = 1.03 (95% CI = 0.78-1.35)
Infant birthweight (< 2,500 g)		Respiratory distress syndrome	
Intramuscular	RR = 0.63 (95% CI = 0.49-0.81)	Intramuscular	RR = 0.63 (95% CI = 0.38-1.04)
Vaginal	RR = 0.22 (95% CI = 0.07-0.74)	Vaginal	RR = 0.92 (95% CI = 0.59-1.43)
Oral	not estimable	Oral	RR = 0.10 (95% CI = 0.03-0.30)
Total	RR = 0.58 (95% CI = 0.42-0.79)	Total	RR = 0.45 (95% CI = 0.17-1.16)
Use of assisted ventilation		Preventricular leucomalacia	
Intramuscular	RR = 0.59 (95% CI = 0.35-1.01)	Intramuscular	not estimable
Vaginal	RR = 0.24 (95% CI = 0.07-0.81)	Vaginal	RR = 3.13 (95% CI = 0.13-75.52)
Oral	RR = 0.11 (95% CI = 0.01-1.92)	Oral	not estimable
Total	RR = 0.40 (95% CI = 0.18-0.90)	Total	RR = 3.13 (95% CI = 0.13-75.52)
Intraventricular haemorrhage (all grades)		Intraventricular haemorrhage (grades III or IV)	
Intramuscular	RR = 0.25 (95% CI = 0.08-0.82)	Intramuscular	RR = 2.52 (95% CI = 0.12-52.09)
Vaginal	RR = 1.31 (95% CI = 0.46-3.77)	Vaginal	RR = 0.98 (95% CI = 0.06-15.55)
Oral	not estimable	Oral	not estimable
Total	RR = 0.70 (95% CI = 0.20-2.46)	Total	RR = 1.59 (95% CI = 0.21-11.75)
Retinopathy of prematurity		Necrotising enterocolitis	
Intramuscular	RR = 0.50 (95% CI = 0.15-1.69)	Intramuscular	RR = 0.06 (95% CI = 0.00-1.03)
Vaginal	not estimable	Vaginal	RR = 0.53 (95% CI = 0.15-1.92)
Oral	not estimable	Oral	not estimable
Total	RR = 0.50 (95% CI = 0.15-1.69)	Total	RR = 0.30 (95% CI = 0.10-0.89)
Neonatal sepsis		Patent ductus arteriosus	
Intramuscular	RR = 1.13 (95% CI = 0.35-3.59)	Intramuscular	RR = 0.44 (95% CI = 0.16-1.18)
Vaginal	RR = 0.13 (95% CI = 0.02-1.01)	Vaginal	not estimable
Oral	not estimable	Oral	not estimable
Total	RR = 0.42 (95% CI = 0.08-2.23)	Total	RR = 0.44 (95% CI = 0.16-1.18)
Intrauterine fetal death		Neonatal death	
Intramuscular	RR = 0.49 (95% CI = 0.14-1.69)	Intramuscular	RR = 0.38 (95% CI = 0.17-0.87)
Vaginal	RR = 1.22 (95% CI = 0.33-4.51)	Vaginal	RR = 0.53 (95% CI = 0.24-1.18)
Oral	not estimable	Oral	RR = 0.43 (95% CI = 0.12-1.59)
Total	RR = 0.66 (95% CI = 0.26-1.69)	Total	RR = 0.45 (95% CI = 0.27-0.76)

CI confidence interval, RR risk ratio

Pooled data published by Dodd *et al.*⁹⁵⁹ on the effectiveness and safety of progesterone for preventing preterm birth in women with a past history of spontaneous preterm birth compared to placebo/no treatment (continued)

Parameter	Progesterone versus placebo	Parameter	Progesterone versus placebo
Development delay		Intellectual impairment	
Intramuscular	RR = 0.85 (95% CI = 0.36-2.04)	Intramuscular	RR = 1.29 (95% CI = 0.05-31.34)
Vaginal	not estimable	Vaginal	not estimable
Oral	not estimable	Oral	not estimable
Total	RR = 0.85 (95% CI = 0.36-2.04)	Total	RR = 1.29 (95% CI = 0.05-31.34)
Motor impairment		Visual impairment	
Intramuscular	RR = 0.64 (95% CI = 0.11-3.76)	Intramuscular	RR = 0.85 (95% CI = 0.16-4.57)
Vaginal	not estimable	Vaginal	not estimable
Oral	not estimable	Oral	not estimable
Total	RR = 0.64 (95% CI = 0.11-3.76)	Total	RR = 0.85 (95% CI = 0.16-4.57)
Hearing impairment		Cerebral palsy	
Intramuscular	RR = 0.34 (95% CI = 0.09-1.24)	Intramuscular	RR = 0.14 (95% CI = 0.01-3.48)
Vaginal	not estimable	Vaginal	not estimable
Oral	not estimable	Oral	not estimable
Total	RR = 0.34 (95% CI = 0.09-1.24)	Total	RR = 0.14 (95% CI = 0.01-3.48)
Learning difficulties		Height (< 5 th centile)	
Intramuscular	RR = 0.85 (95% CI = 0.38-1.92)	Intramuscular	RR = 0.75 (95% CI = 0.23-2.49)
Vaginal	not estimable	Vaginal	not estimable
Oral	not estimable	Oral	not estimable
Total	RR = 0.85 (95% CI = 0.38-1.92)	Total	RR = 0.75 (95% CI = 0.23-2.49)
Weight (< 5 th centile)		Adverse drug reactions	
Intramuscular	RR = 0.79 (95% CI = 0.30-2.05)	Intramuscular	not estimable
Vaginal	not estimable	Vaginal	not estimable
Oral	not estimable	Oral	RR = 0.71 (95% CI = 0.24-2.15)
Total	RR = 0.79 (95% CI = 0.30-2.05)	Total	RR = 0.71 (95% CI = 0.24-2.15)
Pregnancy prolongation		Apgar score < 7	
Intramuscular	not estimable	Intramuscular	RR = 0.55 (95% CI = 0.24-1.25)
Vaginal	not estimable	Vaginal	not estimable
Oral	RR = 4.47 (95% CI = 2.15-6.79)	Oral	not estimable
Total	RR = 4.47 (95% CI = 2.15-6.79)	Total	RR = 0.55 (95% CI = 0.24-1.25)
NICU admission		Neonatal length of hospital stay	
Intramuscular	not estimable	Intramuscular	not estimable
Vaginal	RR = 0.21 (95% CI = 0.09-0.49)	Vaginal	not estimable
Oral	RR = 0.26 (95% CI = 0.14-0.49)	Oral	RR = -1.00 (95% CI = -7.67-5.67)
Total	RR = 0.24 (95% CI = 0.14-0.40)	Total	RR = -1.00 (95% CI = -7.67-5.67)
Infant weight (6 months follow-up)		Infant length (6 months follow-up)	
Intramuscular	not estimable	Intramuscular	not estimable
Vaginal	RR = 29.00 (95% CI = -209.62-267.62)	Vaginal	RR = 0.10 (95% CI = -0.59-0.79)
Oral	not estimable	Oral	not estimable
Total	RR = 29.00 (95% CI = -209.62-267.62)	Total	RR = 0.10 (95% CI = -0.59-0.79)
Infant weight (12 months follow-up)		Infant length (12 months follow-up)	
Intramuscular	not estimable	Intramuscular	not estimable
Vaginal	RR = -88.00 (95% CI = -381.48-205.48)	Vaginal	RR = -0.10 (95% CI = -0.80-0.60)
Oral	not estimable	Oral	not estimable
Total	RR = -88.00 (95% CI = -381.48-205.48)	Total	RR = -0.10 (95% CI = -0.80-0.60)
Infant weight (24 months follow-up)		Infant length (24 months follow-up)	
Intramuscular	not estimable	Intramuscular	not estimable
Vaginal	not estimable	Vaginal	RR = -0.20 (95% CI = -1.23-0.83)
Oral	RR = -40.00 (95% CI = -482.41-402.41)	Oral	not estimable
Total	RR = -40.00 (95% CI = -482.41-402.41)	Total	RR = -0.20 (95% CI = -1.23-0.83)

CI confidence interval, NICU neonatal intensive care unit, RR risk ratio

Pooled data published by Dodd *et al.*⁹⁵⁹ on the effectiveness and safety of progesterone for preventing preterm birth in women with a past history of spontaneous preterm birth compared to placebo/no treatment (continued)

Parameter	Progesterone versus placebo	Parameter	Progesterone versus placebo
Infant length (24 months follow-up)		Infant head circumference (6 months follow-up)	
Intramuscular	not estimable	Intramuscular	not estimable
Vaginal	RR = -0.20 (95% CI = -1.23-0.83)	Vaginal	RR = 0.10 (95% CI = -0.23-0.43)
Oral	not estimable	Oral	not estimable
Total	RR = -0.20 (95% CI = -1.23-0.83)	Total	RR = 0.10 (95% CI = -0.23-0.43)
Infant head circumference (at 12 months follow-up)		Infant head circumference (24 months follow-up)	
Intramuscular	not estimable	Intramuscular	not estimable
Vaginal	RR = 0.10 (95% CI = -0.26-0.46)	Vaginal	RR = 0.20 (95% CI = -0.21-0.61)
Oral	not estimable	Oral	not estimable
Total	RR = 0.10 (95% CI = -0.26-0.46)	Total	RR = 0.20 (95% CI = -0.21-0.61)
CI confidence interval, RR risk ratio			

Table 26. Pooled data published by Dodd *et al.*⁹⁵⁹ on the effectiveness and safety of progesterone for preventing preterm birth in women with a short cervix identified on ultrasound compared to placebo/no treatment

Parameter	Progesterone versus placebo	Parameter	Progesterone versus placebo
Perinatal death		Preterm birth (< 34 weeks)	
Intramuscular	RR = 1.12 (95% CI = 0.46-2.72)	Intramuscular	RR = 0.79 (95% CI = 0.43-1.46)
Vaginal	RR = 0.56 (95% CI = 0.27-1.17)	Vaginal	RR = 0.58 (95% CI = 0.38-0.87)
Total	RR = 0.74 (95% CI = 0.42-1.29)	Total	RR = 0.64 (95% CI = 0.45-0.90)
Preterm labour		pPROM	
Intramuscular	RR = 1.05 (95% CI = 0.63-1.74)	Intramuscular	RR = 1.33 (95% CI = 0.68-2.62)
Vaginal	not estimable	Vaginal	not estimable
Total	RR = 1.05 (95% CI = 0.63-1.74)	Total	RR = 1.33 (95% CI = 0.68-2.62)
Side effects (any)		Side effects (injection site)	
Intramuscular	RR = 1.02 (95% CI = 0.92-1.13)	Intramuscular	RR = 1.04 (95% CI = 0.93-1.17)
Vaginal	not estimable	Vaginal	not estimable
Total	RR = 1.02 (95% CI = 0.92-1.13)	Total	RR = 1.04 (95% CI = 0.93-1.17)
Side effects (urticaria)		Side effects (nausea)	
Intramuscular	RR = 5.03 (95% CI = 1.11-22.78)	Intramuscular	RR = 0.70 (95% CI = 0.27-1.83)
Vaginal	not estimable	Vaginal	not estimable
Total	RR = 5.03 (95% CI = 1.11-22.78)	Total	RR = 0.70 (95% CI = 0.27-1.83)
Pregnancy prolongation		Caesarean section	
Intramuscular	RR = -2.00 (95% CI = -10.29-6.29)	Intramuscular	RR = 1.05 (95% CI = 0.79-1.40)
Vaginal	not estimable	Vaginal	not estimable
Total	RR = -2.00 (95% CI = -10.29-6.29)	Total	RR = 1.05 (95% CI = 0.79-1.40)
Antenatal tocolysis		Preterm birth (< 37 weeks)	
Intramuscular	RR = 0.81 (95% CI = 0.60-1.11)	Intramuscular	RR = 1.03 (95% CI = 0.83-1.28)
Vaginal	not estimable	Vaginal	RR = 0.89 (95% CI = 0.68-1.16)
Total	RR = 0.81 (95% CI = 0.60-1.11)	Total	RR = 0.97 (95% CI = 0.82-1.15)
Preterm birth (< 28 weeks)		Infant birweight (< 2,500 g)	
Intramuscular	RR = 0.69 (95% CI = 0.36-1.30)	Intramuscular	RR = 0.97 (95% CI = 0.73-1.30)
Vaginal	RR = 0.50 (95% CI = 0.25-0.97)	Vaginal	RR = 0.89 (95% CI = 0.73-1.09)
Total	RR = 0.59 (95% CI = 0.37-0.93)	Total	RR = 0.92 (95% CI = 0.78-1.09)
Respiratory distress syndrome		Apgar score < 7	
Intramuscular	RR = 0.95 (95% CI = 0.58-1.58)	Intramuscular	RR = 0.80 (95% CI = 0.41-1.55)
Vaginal	RR = 0.49 (95% CI = 0.290.85)	Vaginal	not estimable
Total	RR = 0.69 (95% CI = 0.48-1.00)	Total	RR = 0.80 (95% CI = 0.41-1.55)
Need for assisted ventilation		Periventricular leucomalacia	
Intramuscular	not estimable	Intramuscular	RR = 1.78 (95% CI = 0.38-8.24)
Vaginal	RR = 0.65 (95% CI = 0.36-1.16)	Vaginal	not estimable
Total	RR = 0.65 (95% CI = 0.36-1.16)	Total	RR = 1.78 (95% CI = 0.38-8.24)
Intraventricular haemorrhage (grades III or IV)		Intraventricular haemorrhage (all grades)	
Intramuscular	RR = 2.01 (95% CI = 0.18-22.08)	Intramuscular	not estimable
Vaginal	RR = 0.32 (95% CI = 0.01-7.73)	Vaginal	RR = 0.51 (95% CI = 0.05-5.53)
Total	RR = 0.98 (95% CI = 0.17-5.60)	Total	RR = 0.51 (95% CI = 0.05-5.53)
Retinopathy of prematurity		Necrotising enterocolitis	
Intramuscular	RR = 0.34 (95% CI = 0.04-3.21)	Intramuscular	RR = 0.40 (95% CI = 0.08-2.06)
Vaginal	RR = 5.07 (95% CI = 0.25-104.70)	Vaginal	RR = 0.96 (95% CI = 0.30-3.11)
Total	RR = 1.01 (95% CI = 0.23-4.42)	Total	RR = 0.70 (95% CI = 0.27-1.78)
Neonatal sepsis		Intrauterine fetal death	
Intramuscular	RR = 0.27 (95% CI = 0.08-0.97)	Intramuscular	RR = 4.04 (95% CI = 0.45-35.92)
Vaginal	RR = 0.58 (95% CI = 0.15-2.25)	Vaginal	RR = 0.82 (95% CI = 0.28-2.42)
Total	RR = 0.46 (95% CI = 0.18-1.20)	Total	RR = 1.21 (95% CI = 0.48-3.04)
Neonatal death		NICU admission	
Intramuscular	RR = 0.76 (95% CI = 0.27-2.16)	Intramuscular	RR = 0.76 (95% CI = 0.27-2.16)
Vaginal	RR = 0.41 (95% CI = 0.15-1.15)	Vaginal	RR = 0.41 (95% CI = 0.15-1.15)
Total	RR = 0.55 (95% CI = 0.26-1.13)	Total	RR = 0.55 (95% CI = 0.26-1.13)

CI confidence interval, NICU neonatal intensive care unit, pPROM preterm spontaneous rupture of membranes, RR risk ratio

Table 27. Pooled data published by Dodd *et al.*⁹⁵⁹ on the effectiveness and safety of progesterone (200 mg) for preventing preterm birth in women with multiple pregnancy compared to placebo/no treatment

Parameter	Progesterone versus placebo	Parameter	Progesterone versus placebo
Perinatal death		Preterm birth (< 34 weeks)	
Intramuscular	RR = 1.06 (95% CI = 0.30-3.71)	Intramuscular	RR = 1.37 (95% CI = 0.74-1.27)
Vaginal	RR = 0.75 (95% CI = 0.24-2.41)	Vaginal	RR = 0.92 (95% CI = 0.69-1.23)
Total	RR = 0.93 (95% CI = 0.45-1.94)	Total	RR = 0.97 (95% CI = 0.74-1.27)
pPROM		Adverse drug reaction	
Intramuscular	RR = 1.11 (95% CI = 0.72-1.71)	Intramuscular	RR = 0.74 (95% CI = 0.54-1.01)
Vaginal	RR = 1.32 (95% CI = 0.30-5.74)	Vaginal	RR = 0.98 (95% CI = 0.89-1.08)
Total	RR = 1.12 (95% CI = 0.74-1.70)	Total	RR = 0.88 (95% CI = 0.64-1.19)
Caesarean section		Spontaneous birth	
Intramuscular	RR = 1.01 (95% CI = 0.94-1.09)	Intramuscular	RR = 0.88 (95% CI = 0.75-1.04)
Vaginal	RR = 0.91 (95% CI = 0.84-0.98)	Vaginal	RR = 1.74 (95% CI = 1.21-2.49)
Total	RR = 0.96 (95% CI = 0.91-1.02)	Total	RR = 1.22 (95% CI = 0.62-2.38)
Assisted birth		Satisfaction with therapy	
Intramuscular	RR = 1.31 (95% CI = 0.86-1.99)	Intramuscular	not estimable
Vaginal	RR = 0.73 (95% CI = 0.44-1.24)	Vaginal	RR = 0.0 (95% CI = -0.35-0.35)
Total	RR = 1.00 (95% CI = 0.57-1.76)	Total	RR = 0.0 (95% CI = -0.35-0.35)
Antenatal tocolysis		Antenatal corticosteroids	
Intramuscular	RR = 0.98 (95% CI = 0.82-1.17)	Intramuscular	RR = 0.91 (95% CI = 0.70-1.17)
Vaginal	RR = 0.75 (95% CI = 0.55-1.03)	Vaginal	RR = 1.68 (95% CI = 0.81-3.49)
Total	RR = 0.94 (95% CI = 0.80-1.10)	Total	RR = 0.98 (95% CI = 0.77-1.26)
Preterm birth (< 37 weeks)		Preterm birth (< 28 weeks)	
Intramuscular	RR = 1.09 (95% CI = 0.96-1.22)	Intramuscular	RR = 1.19 (95% CI = 0.68-2.07)
Vaginal	RR = 0.98 (95% CI = 0.85-1.13)	Vaginal	RR = 1.27 (95% CI = 0.51-3.19)
Total	RR = 1.04 (95% CI = 0.95-1.14)	Total	RR = 1.21 (95% CI = 0.75-1.95)
Infant birthweight (< 2,500 g)		Apgar score < 7 at 5 minutes	
Intramuscular	RR = 1.02 (95% CI = 0.91-1.14)	Intramuscular	RR = 0.98 (95% CI = 0.70-1.38)
Vaginal	RR = 0.86 (95% CI = 0.80-0.94)	Vaginal	RR = 0.59 (95% CI = 0.28-1.23)
Total	RR = 0.95 (95% CI = 0.88-1.03)	Total	RR = 0.89 (95% CI = 0.66-1.21)
Respiratory distress syndrome		Use of assisted ventilation	
Intramuscular	RR = 1.13 (95% CI = 0.91-1.42)	Intramuscular	RR = 0.99 (95% CI = 0.80-1.22)
Vaginal	RR = 1.08 (95% CI = 0.79-1.48)	Vaginal	RR = 0.78 (95% CI = 0.45-1.36)
Total	RR = 1.13 (95% CI = 0.94-1.35)	Total	RR = 0.95 (95% CI = 0.78-1.16)
Intraventricular haemorrhage (grades III or IV)		Intraventricular haemorrhage (all grades)	
Intramuscular	RR = 0.93 (95% CI = 0.45-1.92)	Intramuscular	RR = 1.98 (95% CI = 0.36-10.77)
Vaginal	not estimable	Vaginal	RR = 1.70 (95% CI = 0.62-4.66)
Total	RR = 0.93 (95% CI = 0.45-1.92)	Total	RR = 1.77 (95% CI = 0.75-4.21)
Periventricular leucomalacia		Retinopathy of prematurity	
Intramuscular	RR = 0.37 (95% CI = 0.05-3.02)	Intramuscular	RR = 0.64 (95% CI = 0.20-2.06)
Vaginal	not estimable	Vaginal	RR = 1.02 (95% CI = 0.26-4.07)
Total	RR = 0.37 (95% CI = 0.05-3.02)	Total	RR = 0.79 (95% CI = 0.32-1.91)
Chronic lung disease		Necrotising enterocolitis	
Intramuscular	RR = 1.91 (95% CI = 0.13-27.80)	Intramuscular	RR = 0.98 (95% CI = 0.52-1.88)
Vaginal	not estimable	Vaginal	RR = 0.51 (95% CI = 0.05-5.63)
Total	RR = 1.91 (95% CI = 0.13-27.80)	Total	RR = 0.94 (95% CI = 0.50-1.75)
Neonatal sepsis		Fetal death	
Intramuscular	RR = 1.22 (95% CI = 0.87-1.72)	Intramuscular	RR = 1.55 (95% CI = 0.77-3.12)
Vaginal	RR = 1.14 (95% CI = 0.61-2.13)	Vaginal	RR = 0.83 (95% CI = 0.35-1.95)
Total	RR = 1.20 (95% CI = 0.89-1.62)	Total	RR = 1.22 (95% CI = 0.71-2.09)
Neonatal death		NICU admission	
Intramuscular	RR = 0.81 (95% CI = 0.31-2.10)	Intramuscular	RR = 1.31 (95% CI = 1.05-1.62)
Vaginal	RR = 1.34 (95% CI = 0.36-4.95)	Vaginal	RR = 0.87 (95% CI = 0.71-1.07)
Total	RR = 1.01 (95% CI = 0.48-2.10)	Total	RR = 0.94 (95% CI = 1.05-1.62)

CI confidence interval, NICU neonatal intensive care unit, pPROM preterm spontaneous rupture of membranes, RR risk ratio

Table 28. Pooled data published by Dodd *et al.*⁹⁵⁹ on the effectiveness and safety of progesterone (400 mg) for preventing preterm birth in women with multiple pregnancy compared to placebo/no treatment

Parameter	Progesterone versus placebo	Parameter	Progesterone versus placebo
Perinatal death		Preterm birth (< 34 weeks)	
Intramuscular	RR = 1.06 (95% CI = 0.30-3.71)	Intramuscular	RR = 1.37 (95% CI = 0.73-2.59)
Vaginal	RR = 1.25 (95% CI = 0.67-2.35)	Vaginal	RR = 0.88 (95% CI = 0.65-1.19)
Total	RR = 1.13 (95% CI = 0.61-2.08)	Total	RR = 0.94 (95% CI = 0.71-1.24)
pPROM		Caesarean section	
Intramuscular	RR = 1.11 (95% CI = 0.72-1.71)	Intramuscular	RR = 1.01 (95% CI = 0.94-1.09)
Vaginal	RR = 0.33 (95% CI = 0.03-3.12)	Vaginal	RR = 0.90 (95% CI = 0.84-0.98)
Total	RR = 1.05 (95% CI = 0.69-1.60)	Total	RR = 0.96 (95% CI = 0.91-1.01)
Antenatal tocolysis		Antenatal corticosteroids	
Intramuscular	RR = 0.98 (95% CI = 0.82-1.17)	Intramuscular	RR = 0.91 (95% CI = 0.70-1.17)
Vaginal	RR = 0.77 (95% CI = 0.56-1.05)	Vaginal	RR = 1.58 (95% CI = 0.76-3.31)
Total	RR = 0.94 (95% CI = 0.80-1.10)	Total	RR = 0.97 (95% CI = 0.76-1.24)
Preterm birth (< 37 weeks)		Preterm birth (< 28 weeks)	
Intramuscular	RR = 1.09 (95% CI = 0.96-1.22)	Intramuscular	RR = 1.19 (95% CI = 0.68-2.07)
Vaginal	RR = 0.97 (95% CI = 0.84-1.11)	Vaginal	RR = 1.52 (95% CI = 0.63-3.69)
Total	RR = 1.04 (95% CI = 0.95-1.13)	Total	RR = 1.28 (95% CI = 0.80-2.04)
Infant birthweight (< 2,500g)		Apgar score < 7 at 5 minutes	
Intramuscular	RR = 1.02 (95% CI = 0.91-1.14)	Intramuscular	RR = 0.98 (95% CI = 0.70-1.38)
Vaginal	RR = 0.89 (95% CI = 0.82-0.96)	Vaginal	RR = 0.81 (95% CI = 0.41-1.58)
Total	RR = 0.96 (95% CI = 0.89-1.04)	Total	RR = 0.94 (95% CI = 0.70-1.27)
Use of assisted ventilation		Fetal death	
Intramuscular	RR = 0.99 (95% CI = 0.80-1.22)	Intramuscular	RR = 1.55 (95% CI = 0.77-3.12)
Vaginal	RR = 0.93 (95% CI = 0.55-1.59)	Vaginal	RR = 1.10 (95% CI = 0.49-2.48)
Total	RR = 0.98 (95% CI = 0.81-1.19)	Total	RR = 1.35 (95% CI = 0.79-2.29)
Neonatal death		NICU admission	
Intramuscular	RR = 0.81 (95% CI = 0.31-2.10)	Intramuscular	RR = 1.31 (95% CI = 1.05-1.62)
Vaginal	RR = 1.77 (95% CI = 0.84-3.72)	Vaginal	RR = 0.86 (95% CI = 0.70-1.07)
Total	RR = 1.17 (95% CI = 0.62-2.21)	Total	RR = 0.93 (95% CI = 0.75-1.17)

CI confidence interval, NICU neonatal intensive care unit, pPROM preterm spontaneous rupture of membranes, RR risk ratio

Table 29. Pooled data published by Dodd *et al.*⁹⁵⁹ on the effectiveness and safety of progesterone for preventing preterm birth in women following presentation with threatened preterm labour compared to placebo/no treatment

Parameter	Progesterone versus placebo	Parameter	Progesterone versus placebo
Perinatal death		Use of tocolysis	
Intramuscular	RR = 2.00 (95% CI = 0.16-24.33)	Intramuscular	RR = 1.20 (95% CI = 0.55-2.62)
Vaginal	not estimable	Vaginal	RR = 0.93 (95% CI = 0.50-1.73)
Total	RR = 2.00 (95% CI = 0.16-24.33)	Total	RR = 0.98 (95% CI = 0.58-1.65)
Pregnancy prolongation		Pregnancy prolongation (< 1 week)	
Intramuscular	RR = -3.30 (95% CI = -7.41-0.81)	Intramuscular	RR = 0.40 (95% CI = 0.07-2.37)
Vaginal	RR = 7.21 (95% CI = 2.39-12.03)	Vaginal	not estimable
Total	RR = 1.88 (95% CI = -8.42-12.17)	Total	RR = 0.40 (95% CI = 0.07-2.37)
Pregnancy prolongation (1.0 to 1.9 weeks)		Pregnancy prolongation (≥ 2 weeks)	
Intramuscular	RR = 2.00 (95% CI = 0.16-24.33)	Intramuscular	RR = 2.00 (95% CI = 0.42-9.42)
Vaginal	not estimable	Vaginal	not estimable
Total	RR = 2.00 (95% CI = 0.16-24.33)	Total	RR = 2.00 (95% CI = 0.42-9.42)
Spontaneous birth		Caesarean section	
Intramuscular	RR = 1.09 (95% CI = 0.80-1.49)	Intramuscular	RR = 0.90 (95% CI = 0.51-1.60)
Vaginal	not estimable	Vaginal	not estimable
Total	RR = 1.09 (95% CI = 0.80-1.49)	Total	RR = 0.90 (95% CI = 0.51-1.60)
Preterm birth (< 34 weeks)		Preterm birth (< 37 weeks)	
Intramuscular	RR = 1.00 (95% CI = 0.72-1.39)	Intramuscular	RR = 0.29 (95% CI = 0.12-0.69)
Vaginal	RR = 0.92 (95% CI = 0.37-2.27)	Vaginal	RR = 0.76 (95% CI = 0.55-1.06)
Total	RR = 0.95 (95% CI = 0.55-1.65)	Total	RR = 0.51 (95% CI = 0.20-1.31)
Use of assisted ventilation		Respiratory distress syndrome	
Intramuscular	not estimable	Intramuscular	RR = 0.86 (95% CI = 0.66-1.12)
Vaginal	RR = 0.30 (95% CI = 0.06-1.37)	Vaginal	RR = 10.48 (95% CI = 0.20-1.15)
Total	RR = 0.30 (95% CI = 0.06-1.37)	Total	RR = 0.74 (95% CI = 0.49-1.10)
Infant birthweight (< 2,500 g)		Intraventricular haemorrhage (grades III or IV)	
Intramuscular	not estimable	Intramuscular	RR = 9.00 (95% CI = 0.53-152.93)
Vaginal	RR = 0.52 (95% CI = 0.28-0.98)	Vaginal	not estimable
Total	RR = 0.52 (95% CI = 0.28-0.98)	Total	RR = 9.00 (95% CI = 0.53-152.93)
Necrotizing enterocolitis		Neonatal sepsis	
Intramuscular	RR = 3.06 (95% CI = 0.50-18.69)	Intramuscular	RR = 1.09 (95% CI = 0.39-3.05)
Vaginal	not estimable	Vaginal	RR = 0.26 (95% CI = 0.07-1.00)
Total	RR = 3.06 (95% CI = 0.50-18.69)	Total	RR = 0.54 (95% CI = 0.17-1.68)
Fetal death		Neonatal death	
Intramuscular	RR = 1.09 (95% CI = 0.07-16.75)	Intramuscular	RR = 2.00 (95% CI = 0.16-24.33)
Vaginal	not estimable	Vaginal	RR = 0.17 (95% CI = 0.02-1.40)
Total	RR = 1.09 (95% CI = 0.07-16.75)	Total	RR = 0.54 (95% CI = 0.05-6.24)
Neonatal length of hospital stay		Apgar score < 7 at 5 minutes	
Intramuscular	RR = -2.16 (95% CI = -15.84-11.53)	Intramuscular	not estimable
Vaginal	not estimable	Vaginal	RR = 0.26 (95% CI = 0.03-2.27)
Total	RR = -2.16 (95% CI = -15.84-11.53)	Total	RR = 0.26 (95% CI = 0.03-2.27)
pPROM		Preterm birth (< 28 weeks)	
Intramuscular	not estimable	Intramuscular	not estimable
Vaginal	RR = 0.52 (95% CI = 0.19-1.45)	Vaginal	RR = 0.99 (95% CI = 0.06-15.60)
Total	RR = 0.52 (95% CI = 0.19-1.45)	Total	RR = 0.99 (95% CI = 0.06-15.60)
Apgar score < 7 at 5 minutes		NICU admission	
Intramuscular	not estimable	Intramuscular	not estimable
Vaginal	RR = 0.26 (95% CI = 0.03-2.27)	Vaginal	RR = 1.56 (95% CI = 0.27-9.07)
Total	RR = 0.26 (95% CI = 0.03-2.27)	Total	RR = 1.56 (95% CI = 0.27-9.07)

CI confidence interval, NICU neonatal intensive care unit, pPROM preterm spontaneous rupture of membranes, RR risk ratio

Table 30. Pooled data published by Alfirevic *et al.*¹⁰³⁴ on the effectiveness and safety of cervical cerclage (stitch) for preventing birth in singleton pregnancy compared to expectant management (no treatment)

Parameter	Cerclage versus no treatment	Parameter	Cerclage versus no treatment
All peritoneal losses		Serious neonatal morbidity	
History-indicated	RR = 0.80 (95% CI = 0.58-1.10)	History-indicated	not estimable
One-off ultrasound-indicated (high risk for PTL)	RR = 0.77 (95% CI = 0.14-4.25)	One-off ultrasound-indicated (high risk for PTL)	RR = 0.77 (95% CI = 0.14-4.25)
Serial ultrasound-indicated (high risk for PTL)	RR = 0.66 (95% CI = 0.41-1.06)	Serial ultrasound-indicated (high risk for PTL)	RR = 0.84 (95% CI = 0.51-1.37)
One-off ultrasound-indicated (low/unspecified risk for PTL)	RR = 1.01 (95% CI = 0.46-2.22)	One-off ultrasound-indicated (low/unspecified risk for PTL)	RR = 1.40 (95% CI = 0.61-3.23)
Total	RR = 0.78 (95% CI = 0.61-1.00)	Total	RR = 0.95 (95% CI = 0.63-1.43)
Stillbirths		Neonatal deaths before discharge	
History-indicated	RR = 1.00 (95% CI = 0.45-2.20)	History-indicated	RR = 0.67 (95% CI = 0.33-1.36)
One-off ultrasound-indicated (high risk for PTL)	RR = 0.23 (95% CI = 0.01-4.58)	One-off ultrasound-indicated (high risk for PTL)	RR = 2.31 (95% CI = 0.22-24.01)
Serial ultrasound-indicated (high risk for PTL)	not estimable	Serial ultrasound-indicated (high risk for PTL)	RR = 0.87 (95% CI = 0.13-5.89)
One-off ultrasound-indicated (low/unspecified risk for PTL)	RR = 0.95 (95% CI = 0.20-4.59)	One-off ultrasound-indicated (low/unspecified risk for PTL)	RR = 0.63 (95% CI = 0.18-2.18)
Total	RR = 0.89 (95% CI = 0.45-1.75)	Total	RR = 0.73 (95% CI = 0.42-1.28)
Miscarriages		Preterm birth (< 37 completed weeks)	
History-indicated	RR = 0.86 (95% CI = 0.57-1.30)	History-indicated	RR = 0.86 (95% CI = 0.59-1.27)
One-off ultrasound-indicated (high risk for PTL)	not estimable	One-off ultrasound-indicated (high risk for PTL)	RR = 0.55 (95% CI = 0.30-0.99)
Serial ultrasound-indicated (high risk for PTL)	RR = 0.65 (95% CI = 0.25-1.66)	Serial ultrasound-indicated (high risk for PTL)	RR = 0.78 (95% CI = 0.60-1.02)
One-off ultrasound-indicated (low/unspecified risk for PTL)	RR = 1.72 (95% CI = 0.16-18.22)	One-off ultrasound-indicated (low/unspecified risk for PTL)	RR = 0.80 (95% CI = 0.55-1.16)
Total	RR = 0.84 (95% CI = 0.58-1.22)	Total	RR = 0.80 (95% CI = 0.69-0.95)
Preterm birth (< 28 completed weeks)		Serious intracranial pathology	
History-indicated	RR = 0.82 (95% CI = 0.59-1.13)	History-indicated	RR = 1.02 (95% CI = 0.06-16.09)
One-off ultrasound-indicated (high risk for PTL)	RR = 0.69 (95% CI = 0.18-2.62)	One-off ultrasound-indicated (high risk for PTL)	RR = 0.38 (95% CI = 0.02-9.01)
Serial ultrasound-indicated (high risk for PTL)	RR = 0.71 (95% CI = 0.48-1.04)	Serial ultrasound-indicated (high risk for PTL)	RR = 0.96 (95% CI = 0.05-19.53)
One-off ultrasound-indicated (low/unspecified risk for PTL)	RR = 1.01 (95% CI = 0.55-1.83)	One-off ultrasound-indicated (low/unspecified risk for PTL)	RR = 0.95 (95% CI = 0.06-14.98)
Total	RR = 0.80 (95% CI = 0.64-1.00)	Total	RR = 0.83 (95% CI = 0.2-3.09)
Serious respiratory morbidity		Necrotising enterocolitis	
History-indicated	RR = 3.06 (95% CI = 0.32-28.93)	History-indicated	not estimable
One-off ultrasound-indicated (high risk for PTL)	RR = 0.58 (95% CI = 0.06-6.00)	One-off ultrasound-indicated (high risk for PTL)	not estimable
Serial ultrasound-indicated (high risk for PTL)	RR = 0.98 (95% CI = 0.53-1.81)	Serial ultrasound-indicated (high risk for PTL)	RR = 0.81 (95% CI = 0.16-4.12)
One-off ultrasound-indicated (low/unspecified risk for PTL)	RR = 1.63 (95% CI = 0.39-6.86)	One-off ultrasound-indicated (low/unspecified risk for PTL)	not estimable
Total	RR = 1.11 (95% CI = 0.66-1.88)	Total	RR = 0.81 (95% CI = 0.16-4.12)
Retinopathy of prematurity		Caesarean section	
History-indicated	not estimable	History-indicated	RR = 1.21 (95% CI = 0.96-1.52)
One-off ultrasound-indicated (high risk for PTL)	RR = 0.23 (95% CI = .01-4.58)	One-off ultrasound-indicated (high risk for PTL)	RR = 1.35 (95% CI = 0.52-3.50)
Serial ultrasound-indicated (high risk for PTL)	RR = 0.62 (95% CI = 0.15-2.53)	Serial ultrasound-indicated (high risk for PTL)	RR = 1.10 (95% CI = 0.82-1.46)
One-off ultrasound-indicated (low/unspecified risk for PTL)	RR = 0.32 (95% CI = 0.01-7.69)	One-off ultrasound-indicated (low/unspecified risk for PTL)	RR = 1.31 (95% CI = 0.84-2.04)
Total	RR = 0.46 (95% CI = 0.14-1.48)	Total	RR = 1.19 (95% CI = 1.01-1.40)

CI confidence interval, PTL preterm labour, RR risk ratio

Pooled data published by Alfirevic *et al.*¹⁰³⁴ on the effectiveness and safety of cervical cerclage (stitch) for preventing birth in singleton pregnancy compared to expectant management (no treatment) (continued)

Parameter	Cerclage versus no treatment	Parameter	Cerclage versus no treatment
Preterm birth (< 34 completed weeks)		Pyrexia	
History-indicated	RR = 0.76 (95% CI = 0.40-1.46)	History-indicated	RR = 2.22 (95% CI) 1.22-4.01)
One-off ultrasound-indicated (high risk for PTL)	RR = 0.63 (95% CI = 0.27-1.46)	One-off ultrasound-indicated (high risk for PTL)	RR = 3.44 (95% CI = 0.15-81.09)
Serial ultrasound-indicated (high risk for PTL)	RR = 0.77 (95% CI = 0.55-1.10)	Serial ultrasound-indicated (high risk for PTL)	not estimable
One-off ultrasound-indicated (low/unspecified risk for PTL)	RR = 0.82 (95% CI = 0.55-1.22)	One-off ultrasound-indicated (low/unspecified risk for PTL)	RR = 6.66 (95% CI = 0.35-127.20)
Total	RR = 0.79 (95% CI = 0.68-0.93)	Total	RR = 2.39 (95% CI = 1.35-4.23)
Chorioamnionitis		Maternal side effects	
History-indicated	RR = 2.97 (95% CI = 0.12-72.81)	History-indicated	RR = 1.57 (95% CI = 0.76-3.24)
One-off ultrasound-indicated (high risk for PTL)	not estimable	One-off ultrasound-indicated (high risk for PTL)	not estimable
Serial ultrasound-indicated (high risk for PTL)	RR = 0.41 (95% CI = 0.03-6.21)	Serial ultrasound-indicated (high risk for PTL)	not estimable
One-off ultrasound-indicated (low/unspecified risk for PTL)	RR = 1.29 (95% CI = 0.39-4.23)	One-off ultrasound-indicated (low/unspecified risk for PTL)	RR = 5.95 (95% CI = 1.36-26.06)
Total	RR = 0.84 (95% CI = 0.26-2.72)	Total	RR = 2.25 (95% CI = 0.89-5.69)
pPROM			
History-indicated	RR = 1.63 (95% CI = 0.71-3.70)		
One-off ultrasound-indicated (high risk for PTL)	RR = 0.49 (95% CI = 0.14-1.72)		
Serial ultrasound-indicated (high risk for PTL)	RR = 0.51 (95% CI = 0.18-1.45)		
One-off ultrasound-indicated (low/unspecified risk for PTL)	RR = 1.32 (95% CI = 0.78-2.23)		
Total	RR = 0.96 (95% CI = 0.62-1.48)		

CI confidence interval, pPROM preterm spontaneous rupture of membranes, PTL preterm labour, RR risk ratio

Table 31. Pooled data published by Rafael *et al.*¹⁰⁷⁷ on the effectiveness and safety of cervical cerlage (stitch) for preventing birth in multiple pregnancy compared to expectant management (no treatment)

Parameter	Cerclage versus no treatment	Parameter	Cerclage versus no treatment
All peritoneal losses		Serious neonatal morbidity	
Twin only-indicated	RR = 1.19 (95% CI = 0.47-3.02)	Twin only-indicated	not estimable
Twin and history-indicated	RR = 1.33 (95% CI = 0.20-8.80)	Twin and history-indicated	not estimable
Ultrasound-indicated	RR = 2.66 (95% CI = 0.83-8.54)	Ultrasound-indicated	RR = 2.59 (95% CI = 0.85-7.86)
Triplets	RR = 3.00 (95% CI = 0.38-23.68)	Triplets	RR = 0.11 (95% CI = 0.01-1.80)
Total	RR = 1.74 (95% CI = 0.92-3.28)	Total	RR = 0.96 (95% CI = 0.13-7.10)
Stillbirths		Neonatal deaths	
Twin only-indicated	not estimable	Twin only-indicated	RR = 1.19 (95% CI = 0.47-3.02)
Twin and history-indicated	RR = 0.26 (95% CI = 0.01-5.26)	Twin and history-indicated	not estimable
Ultrasound-indicated	not estimable	Ultrasound-indicated	RR = 5.57 (95% CI = 0.44-70.55)
Triplets	not estimable	Triplets	not estimable
Total	RR = 0.26 (95% CI = 0.01-5.26)	Total	RR = 1.60 (95% CI = 0.69-3.74)
Preterm birth (< 28 completed weeks)		Preterm birth (< 32 completed weeks)	
Twin only-indicated	RR = 0.52 (95% CI = 0.05-5.36)	Twin only-indicated	not estimable
Twin and history-indicated	RR = 1.33 (95% CI = 0.09-19.23)	Twin and history-indicated	RR = 0.33 (95% CI = 0.04-2.61)
Ultrasound-indicated	RR = 2.62 (95% CI = 0.72-9.51)	Ultrasound-indicated	RR = 2.48 (95% CI = 0.96-6.37)
Triplets	RR = 1.00 (95% CI = 0.10-9.61)	Triplets	RR = 1.00 (95% CI = 0.32-3.10)
Total	RR = 1.54 (95% CI = 0.63-3.81)	Total	RR = 1.43 (95% CI = 0.72-2.83)
Preterm birth (< 34 completed weeks)		Preterm birth (< 35 completed weeks)	
Twin only-indicated	not estimable	Twin only-indicated	not estimable
Twin and history-indicated	RR = 0.27 (95% CI = 0.04-1.99)	Twin and history-indicated	RR = 0.22 (95% CI = 0.03-1.61)
Ultrasound-indicated	RR = 2.19 (95% CI = 0.72-6.63)	Ultrasound-indicated	RR = 1.63 (95% CI = 0.88-3.02)
Triplets	RR = 0.71 (95% CI = 0.31-1.66)	Triplets	RR = 0.71 (95% CI = 0.31-1.66)
Total	RR = 1.16 (95% CI = 0.44-3.06)	Total	RR = 1.11 (95% CI = 0.58-2.14)
Preterm birth (< 37 completed weeks)		Mean gestational age at delivery	
Twin only-indicated	RR = 0.95 (95% CI = 0.51-1.78)	Twin only-indicated	not estimable
Twin and history-indicated	RR = 1.33 (95% CI = 0.71-2.51)	Twin and history-indicated	RR = 0.70 (95% CI = -3.50-4.90)
Ultrasound-indicated	RR = 1.18 (95% CI = 0.91-1.53)	Ultrasound-indicated	RR = -1.24 (95% CI = -3.13-0.66)
Triplets	RR = 1.00 (95% CI = 0.59-1.69)	Triplets	RR = -2.00 (95% CI = 11.23-7.23)
Total	RR = 1.13 (95% CI = 0.89-1.43)	Total	RR = -0.95 (95% CI = -2.64-0.75)
Low birthweight (< 2,500 g)		Very low birthweight (< 1,500 g)	
Twin only-indicated	not estimable	Twin only-indicated	not estimable
Twin and history-indicated	RR = 0.91 (95% CI = 0.62-1.34)	Twin and history-indicated	RR = 0.19 (95% CI = 0.03-1.45)
Ultrasound-indicated	RR = 1.39 (95% CI = 1.06-1.83)	Ultrasound-indicated	RR = 3.31 (95% CI = 1.58-6.91)
Triplets	RR = 0.79 (95% CI = 0.54-1.16)	Triplets	RR = 1.00 (95% CI = 0.52-1.92)
Total	RR = 1.10 (95% CI = 0.82-1.48)	Total	RR = 1.42 (95% CI = 0.52-3.85)
Respiratory distress syndrome		Intraventricular hemorrhage	
Twin only-indicated	not estimable	Twin only-indicated	not estimable
Twin and history-indicated	not estimable	Twin and history-indicated	not estimable
Ultrasound-indicated	RR = 5.07 (95% CI = 1.75-14.70)	Ultrasound-indicated	RR = 1.13 (95% CI = 0.27-4.74)
Triplets	RR = 0.11 (95% CI = 0.01-1.80)	Triplets	RR = 0.33 (95% CI = 0.02-7.24)
Total	RR = 1.70 (95% CI = 0.15-18.77)	Total	RR = 0.88 (95% CI = 0.25-3.12)
Sepsis		NICU admission	
Twin only-indicated	not estimable	Twin only-indicated	not estimable
Twin and history-indicated	not estimable	Twin and history-indicated	not estimable
Ultrasound-indicated	RR = 0.23 (95% CI = 0.01-4.58)	Ultrasound-indicated	RR = 0.35 (95% CI = 0.06-2.12)
Triplets	RR = 0.33 (95% CI = 0.02-7.24)	Triplets	not estimable
Total	RR = 0.27 (95% CI = 0.03-2.31)	Total	RR = 0.35 (95% CI = 0.06-2.12)
Caesarian section		Maternal side-effects	
Twin only-indicated	RR = 1.34 (95% CI = 0.61-2.98)	Twin only-indicated	not estimable
Twin and history-indicated	RR = 1.07 (95% CI = 0.36-3.14)	Twin and history-indicated	RR = 3.92 (95% CI = 0.17-88.67)
Ultrasound-indicated	not estimable	Ultrasound-indicated	not estimable
Triplets	not estimable	Triplets	not estimable
Total	RR = 1.24 (95% CI = 0.65-2.35)	Total	RR = 3.92 (95% CI = 0.17-88.67)

CI confidence interval, NICU neonatal intensive care unit, RR risk ratio

12 Clinically occult carcinoma diagnosed after simple hysterectomy

12.1 Summary of available scientific evidence

12.1.1 Reoperation

Three studies¹⁰⁸⁴⁻¹⁰⁸⁶ comparing reoperation with other therapeutic options in patients with occult invasive cervical cancer found after inadvertent simple hysterectomy were identified. In the first identified study¹⁰⁸⁴, the treatment groups (radical parametrectomy, radiation therapy, and CCRT) were similar for age, body mass index (BMI), FIGO stage, tumour diameter, and LVSI. The decision regarding the type of treatment to be used was not made based on patient characteristics (BMI, age), or the disease status (tumour diameter, FIGO stage, pathology). In case of local residual macroscopic disease, concomitant chemoradiation were preferentially performed, if possible. Surgical reoperation effectively decreased the risk of local recurrence (0% versus 37.5%), and secondarily, it significantly increased survival (5-year OS, 100% versus 77% ($p = 0.04$), and 5-year DFS, 86% versus 37% ($p = 0.02$)). It should be noted that complementary treatment was necessary in 38% of the patients, and adjuvant external radiation therapy was required in 30% of the patients in the surgical group.

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The gain in terms of 10-year DFS and 10-year OS in favor of surgical group as compared to radiation therapy group (radiation therapy or CCRT therapy) and observation group (no definitive group) did not reached statistical significance in the second identified study¹⁰⁸⁵ (10-year DFS: 100%, 93% and 63%, respectively ($p = 0.199$); 10-year-OS: 100%, 94%, and 84%, respectively ($p = 0.276$)). The treatment groups were similar notably for age, FIGO stage, tumour diameter, and LVSI. It should be noted that in the study published by Narducci *et al.*¹⁰⁸⁴, there were (1) bigger tumours (22-31 mm versus 11-17 mm) and (2) more LVSI (55-60% versus 3.8-22.7%). That might have explained the significance of the difference observed by Narducci *et al.*¹⁰⁸⁴ with less follow-up. The survival differences reported by Park *et al.*¹⁰⁸⁵ may have become significant for these smaller lesions with a longer follow-up period. After a median follow-up of 116 months, there was no recurrence in the surgical group, versus 6.8% in the radiation therapy group and 34.6% in the observation group.

The third identified study¹⁰⁸⁶ reported a higher 5-year OS rate in case of surgical treatment as compared to radiation therapy (61% versus 30%). It should be noted that these results have to be interpreted cautiously notably due to the obsolescence of the radiation therapy used in this study published almost 50 years ago.

Results from the eighteen other identified studies¹⁰⁸⁷⁻¹¹⁰⁴ evaluating reoperation as therapeutic option are limited notably by the heterogeneity and the number of patients evaluated (seventeen studies^{1087,1088,1090-1104} have accrued less than 40 patients). Among these identified studies, eight reports¹⁰⁸⁷⁻¹⁰⁹⁴ provide data on survival after at least 5-year follow-up period. Five-year OS rates after radical parametrectomy for occult cervical cancer have been found to range from 32% to 100%. Taking into account the only four studies^{1087,1088,1093,1094} published in the last two decades, 5-year OS rates have been found to range from 88.9% to 100%. Seventeen identified studies described perioperative complications up to 40% of patients^{1084-1088,1090-1093,1096-1100,1102-1104}. It should be noted that most complications were easily managed, either intraoperatively or conservatively. The occurrence of long-term morbidity after radical parametrectomy was rare.

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12.1.2 Adjuvant treatment

Eighteen studies^{37,1105-1121} using only a single modality were identified. Results from these

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studies are limited notably by the heterogeneity and the number of patients evaluated (seven studies^{1108,1109,1113,1115,1118-1120} have accrued less than 40 patients), and by the heterogeneity in the radiation therapy protocols used. Five-year OS rates after radiation therapy (EBRT with or without intracavitary radiotherapy or chemoradiation) for occult cervical cancer have been found to range from 54% to 100%. Taking into account the only ten studies^{37,1112-1120} published in the last two decades, 5-year OS rates have been found to range from 59% to 100%. Radio-induced complications were observed from 1% to 27% of patients in the identified studies published in the last two decades reporting such information. Treatment-related complications requiring hospitalization or surgical intervention were ranged from 1% to 6% of patients.

12.1.3 No adjuvant treatment

Based on the pathologic findings, Suh *et al.*¹¹¹⁹ used the following criteria for risk scoring:

- one for depth of invasion is between 3-5 mm, and 2 for depth of invasion greater than 5 mm;
- one for longest diameter is between 0.7-20 mm, and 2 for longest diameter greater than 5 mm;
- one for lymphovascular space invasion positive
- three each for parametrium, resection margin, and LN positive.

The final score was calculated by summing up the risk scores. Patient whose score was 1 to 3, 4 to 5, and 6 or higher was classified into low-risk, intermediate-risk, and high-risk groups, respectively. After a median follow-up of 67 months, all included patients in the low-risk group did not recur without any adjuvant treatment. Among the eleven patients who did not receive any further treatment, no patient died of the disease. One recurrence was observed. Carcinoma in situ at resection margin was newly detected during the slide review, which made the score of the patient 4. However, resection margin had been initially negative on the pathology report after simple hysterectomy. That was the reason why the doctor did not consider any adjuvant treatment.

After a mean follow-up period of 52.7 months, none of the patients with a tumour width ≤ 20 mm and superficial stromal invasion developed recurrence or died of the disease in the study published by Bai *et al.*¹¹²⁰. Taking into account all the patients who did not receive adjuvant treatment, 5-year OS and 5-year PFS were 97.4% and 97.8%, respectively.

12.2 Previous initiatives

One previous initiative⁴²⁴ presenting guidelines for management of patients with clinically occult carcinoma diagnosed after simple hysterectomy was identified.

12.3 Development group comments

Occult cervical cancer lesions are generally asymptomatic small lesions found after simple hysterectomy (e.g. for myoma) and reported outcomes are therefore favourable. However, the few series reported in literature mainly consist of small retrospective series with heterogeneous cohorts consisting of mixed stages, histology and treatment, with inherent bias. The risk of potential disease in the parametria and LNs become relevant from tumour stage pT1a2 LVSI+ and beyond.

Radiotherapy alone or combined with chemotherapy (usually applied in those with gross residual disease or involved LNs at time of radiotherapy) is an effective alternative for radical surgery followed by adjuvant therapy in patients with risk factors (avoiding morbidity of combined radical surgery and radiotherapy). Both treatment options have distinct profiles of treatment related morbidity and the limited literature in occult disease reflects the main findings from non-occult disease with highest morbidity rates in those with combined radical surgery and radiotherapy. Therefore, similar to non-occult

disease, the treatment strategy should aim for the avoidance of combining radical surgery and radiotherapy. Established risk factors and indications for adjuvant radiotherapy based on combinations of tumour size, depth of invasion and the presence of LVSI should be taken into account. General recommendations regarding workup and management follow the same principles to those of non-occult disease.

12.4 Guidelines

12.4.1 General recommendations

- ✓ Management of occult disease should be based on expert pathology review and discussed in a multidisciplinary tumor 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 nonoccult disease (see above).
- B** In general, management of occult disease follows the same principles as that of nonoccult disease. Treatment strategy should aim for the avoidance of combining radical surgery and radiotherapy because of the highest morbidity after combined treatment.

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

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

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

- ✓ In patients with tumor stage pT1a2 LVSI positive or pT1b1 or pT2a1 after simple hysterectomy, potential disease in the parametria and LNs has to be addressed.
- D** Radiotherapy or chemoradiotherapy is recommended as an effective treatment option that avoids further surgery. In absence of residual tumor on imaging (including suspicious LNs), radiotherapy alone is recommended. In case of residual tumor on imaging, including suspicious LNs, chemoradiotherapy is recommended.
- C** PALN dissection, at least up to inferior mesenteric artery, may be considered in patients without suspicious para-aortic nodes on imaging for staging purposes.
- ✓ Debulking of suspicious PLNs may be considered.
- D** Radical surgery is an option in patients without LN involvement on imaging and in the absence of an upfront indication for adjuvant radiotherapy (combination of negative prognostic factors).
- ✓ PLN dissection should be performed as the first step of the surgery. Intraoperative assessment of PLNs may be considered. If intraoperative LN assessment is negative or is not performed, radical parametrectomy with the resection of the upper vagina should be performed preferably using minimally invasive techniques. The type of radical parametrectomy (extent of parametrial resection) should be tailored to the presence of prognostic risk factors of the primary tumor as described above (Figure 3).
- ✓ 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 (Figure 4).

D If LN involvement, including macrometastases or micrometastases, is detected intraoperatively, further surgery (PLN dissection and radical parametrectomy) should be avoided, and chemoradiotherapy is recommended.

C PALN dissection, at least up to inferior mesenteric artery, may be considered for staging purposes.

✓ Debulking of suspicious nodes may be considered.

12.4.4 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 tumor including involved lymph node on imaging, chemoradiotherapy is recommended, and further surgery should be avoided.

C PALN dissection, at least up to inferior mesenteric artery, may be considered for staging purposes in patients with negative PALNs on imaging.

✓ Debulking of suspicious PLNs may be considered.

13 Management of locally advanced cervical cancer

13.1 Summary of available scientific evidence

13.1.1 Neoadjuvant chemotherapy

A systematic review¹¹²² of RCTs assessing the effect of NACT in two comparisons was identified. In the first comparison, NACT followed by radical radiotherapy was compared with the same radiotherapy alone (eighteen studies^{540,1123-1136} including three unpublished data). Cisplatin was the main drug in all the chemotherapy regimens. It should be noted that both the external beam radiation therapy dose and intracavitary radiotherapy dose varied (40-60.8 and 18-80 Gy, respectively), with a total dose in the range 55-80 Gy. Considering all trials together, there was no evidence of an effect of NACT on survival, or any of the other endpoints taken into account. However, there was a very high level of statistical heterogeneity, suggesting strongly that the results should not be combined in this way. A substantial proportion of heterogeneity was explained by prespecified analyses grouping trials according to the way they delivered the chemotherapy. Trials which gave more intensive chemotherapy in terms of shorter cycle length and/or a higher dose intensity tended to show an advantage for NACT, whereas those that delivered chemotherapy in a less intensive and more prolonged manner, with a longer cycle length or a lower dose intensity, tended to show a detrimental effect of chemotherapy. For trials giving cycles greater than 14 days, a detriment was observed in overall and locoregional DFS and metastases-free survival. In contrast, trials using shorter cycle lengths observed an improvement in 5-year OS. Results for overall and locoregional DFS and metastases-free survival similarly suggested a benefit for short-cycle chemotherapy. Trials using less than 25 mg/m²/wk suggested a significant reduction in 5-year survival, with comparable reductions in overall and locoregional DFS and metastases-free survival. On the other hand, trials using dose intensities of cisplatin greater than 25 mg/m²/wk suggested a potential improvement in 5-year survival, but this is not conventionally statistically significant. Similar improvements in overall, locoregional disease-free and metastases-free survival were found, but again these results were not conventionally significant.

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A RCT¹¹³⁷ not included in the systematic review¹¹²² mentioned was also identified. Despite the high response rate of NACT (bleomycin, vincristine, mitomycin and cisplatin chemotherapy: 72%), the combination (NACT plus radiotherapy) failed to improve the 5-year survival rates of patients with LACC when compared with radiotherapy alone. It was also noteworthy that the incidence of distant metastasis was not reduced by the use of NACT.

In the second comparison described in the systematic review¹¹²² mentioned above, NACT followed by surgery was compared with radical radiotherapy alone (five studies^{1125,1126,1138-1140}). Here again, cisplatin was the main drug in all of the chemotherapy regimens. But, contrary to the first comparison, external beam radiation therapy and intracavitary radiotherapy doses in the control arm were very similar across trials (45-60 and 25-40 Gy, respectively). Combining the results of all trials indicated a high significant reduction in the risk of death with NACT. The results for overall DFS and locoregional DFS are very similar to those for survival, although there was a greater degree of heterogeneity. There was no evidence to suggest that the effect of NACT on survival varied across groups of patients defined by age, stage, histology, grade or performance status. It should be noted that (1) there was a greater proportion of stage IB-II patients than in the first comparison, (2) intra-arterial chemotherapy and pelvic radiotherapy were used in the NACT plus surgery arm in one trial¹¹³⁸, (3) almost all patients received pelvic radiotherapy in two trials^{1125,1126}, and (4) pelvic radiotherapy was given to approximately 30% of patients in another two trials^{1138,1139}.

A RCT⁵⁴¹ comparing NACT followed by radical surgery or external-beam radiation therapy

followed by brachytherapy in patients suffering from cervical cancer in stages IB-III was also identified. A 5-year DFS rate for the NACT arm and radiotherapy arm, respectively, of 77.1% and 64.3% in stages IB-IIA ($p < 0.05$), 56.2% and 57.1% in stage IIB ($p > 0.05$) was found. No significant differences in terms of 5-year OS rates were identified between the two treatment arms whatever the stages taken into account.

A systematic review¹¹⁴¹ assessing the effects of NACT in women with LACC compared with planned surgery alone was also identified (six RCTs^{77,540-542,1142,1143}). Both OS and PFS were significantly improved with NACT (HR = 0.76 (95% CI = 0.59-0.99), $p = 0.04$ and HR = 0.72 (95% CI = 0.55-0.95), $p = 0.02$, respectively). A non-significant trend was observed in terms of local recurrence, distant recurrence and rates of radical resection in favour of NACT. There was also no significant differences in the effect of NACT on survival according to total cisplatin dose, chemotherapy cycle length or by cervical cancer stage.

Yang *et al.*¹¹⁴⁴ performed a RCT to evaluate the toxicity and curative effect of NACT for stage IB2, IIA2, and IIB cervical cancer patients. Patients were randomly assigned to received NACT or to be treated directly with surgery. Survival analysis revealed no significant difference in DFS or OS between the two treatment groups. It should be noted that the LVSI and deep stromal invasion rates were significantly lower in the NACT group. Patients in the NACT group were then randomly assigned to be treated with irinotecan plus cisplatin followed by surgery or to be treated with paclitaxel plus cisplatin followed by surgery. Here again, no significant difference in DFS or OS between the two treatment groups were reported. No statistically significant difference in response rate between the two groups was also observed. The irinotecan/cisplatin regimen was associated with higher grade 3-4 neutropenia and grade 3-4 diarrhea compared to paclitaxel/cisplatin combination (16.3% versus 1.7%, $p = 0.005$ and 12.2% versus 0%, $p = 0.008$, respectively).

NACT did not significantly improve long-term PFS and/or OS of patients with LACC compared to primary surgery in seven other identified studies^{543,1145-1150}. It should be noted that (1) when OS rates among patients with stage IB2 squamous cell carcinoma were specifically compared by Abou-Taleb *et al.*¹¹⁴⁵, patients treated with NACT followed by surgery had significantly higher OS rates than those treated with primary surgery ($p = 0.034$), and (2) the gain in OS did not reached statistical significance in the study published by Behtash *et al.*⁵⁴³ probably due to the very small number of patients who received NACT.

LoE 2-

Yamakawa *et al.*¹¹⁵¹ found that neoadjuvant intraarterial chemotherapy was able to improve the prognosis of patients with LACC. The estimated 5-year OS rate was significantly higher for patients who received neoadjuvant intraarterial chemotherapy than for the patients who underwent conventional treatment (80% versus 59.6%, $p = 0.004$). In stage II and III, the 5-year survival rate for patients who received neoadjuvant intraarterial chemotherapy was significantly higher than that in the control group (83.3% versus 68.1%, $p = 0.029$ and 77.8% versus 49.8%, $p = 0.013$, respectively).

Two RCTs^{95,1152} comparing two NACT regimens were identified. The first one¹¹⁵² compared a three-drug combination of paclitaxel, ifosfamide, and cisplatin versus paclitaxel and cisplatin followed by surgery. The three-drug combination confirmed its activity (optimal response rate: 43% versus 25%) but was associated with higher grade 3-4 haematological toxicity than the paclitaxel/cisplatin regimen (78% versus 29%, $p < 0.0001$). The overall optimal response OR showed a significant benefit of three-drug combination over doublet in a logistic multivariate analysis which contained grade and age as covariates (OR = 2.3 (95% CI = 1.1-4.7), $p = 0.027$). It should be noted that the gain in failure rate and OS in favor of the three-drug combination

LoE 1-

did not reach statistical significance.

In the second identified RCT⁹⁵, the optimal pathologic response rate was higher with the paclitaxel/ifosfamide/cisplatin combination than with the ifosfamide/cisplatin doublet (OR = 3.22 (95% CI = 1.69-5.88), $p = 0.0003$) but no difference in survival was observed. Moreover, the triplet was associated with significant higher rates of severe (grade 3-4) neutropenia, thrombocytopenia, and anemia than the ifosfamide/cisplatin schedule (55% versus 41% ($p = 0.02$), 13% versus 7% ($p = 0.02$), and 17% versus 11% ($p = 0.05$), respectively).

Yin *et al.*¹¹⁵³ found that nedaplatin and paclitaxel followed by surgery offers a higher response rate (80.77% versus 68.24%, $p = 0.0267$), lower incidence of grade 3-4 toxic reactions (32.69% versus 85.14%, $p < 0.0001$), and better 5-year DFS (81.41% versus 67.28%, $p = 0.014$) and 5-year OS (93.89% versus 81.54%, $p = 0.0084$) for patients with LACC compared with the NACT regimen of paclitaxel and cisplatin followed by surgery.

LoE 2-

A third systematic review¹¹⁵⁴ (thirty studies^{77,540-542,545,1139,1140,1155-1177}) evaluating the effectiveness of NACT for the management of LACC from stage IB2 to IIIB was identified. Twenty-nine studies^{77,540-542,545,1139,1140,1155-1175,1177} used chemotherapy doublets, or triplets. The most commonly used chemotherapy agents were platinum derivatives (cisplatin^{77,540-542,545,1139,1140,1156,1159-1161,1163-1169,1171-1175,1177}, carboplatin^{1155,1170}, or nedaplatin¹¹⁵⁷). The authors reported an overall response rate of 84%. Trials that included platinum derivatives had an overall response rate of 79%. Trials based on cisplatin had an overall response rate of 76%, whereas studies that did not include cisplatin achieved an overall response rate of 78% ($p = 0.07$). While included studies that did not include platinum derivatives had an overall response rate of 80%.

LoE 1-

Considering survival results (twenty-one studies^{77,541,542,1139,1140,1155,1157-1160,1162,1164-1166,1168,1169,1171-1173,1175,1177}), the mean 5-year PFS was 58.9%, and the mean 5-year OS was 62%. For stage IB2-IIA, the mean 2-year PFS was 79.1% and the 2-year OS was 86%. The mean 5-year PFS was 72% and the mean 5-year OS was 83.4%. For stage IIB-III, the mean 2-year PFS was 69% and the mean 2-year OS was 75%. All the 21 studies that assessed survival reported relapse data. During the 2-year follow-up period, the locoregional pattern occurred in 60% of relapsed patients, whereas a disseminated relapse occurred in 40% of them. For the 5-year follow-up period, locoregional relapse occurred in 52% of the relapsed patients, whereas a disseminated relapse occurred in 28% of them. These 21 included studies also reported data about early toxicities. Leucopenia and neutropenia were the most common grade 3-4 early toxicities and occurred in 18.3% and 33.3% of chemotherapy cycles respectively. No grade 3-4 late toxicities were reported.

A meta-analysis¹¹⁷⁸ (seven studies^{541,1139,1140,1164,1179-1181}) was identified but is not described due to major methodological limitations.

Twenty-nine other studies^{746,1182-1209} not included in the systematic reviews mentioned above, and evaluating combinations of drugs were also identified. Corresponding response rates and survival are summarized in table 32.

LoE 3

13.1.2 Surgery

Two RCTs^{94,95} comparing preoperative radiotherapy and radical hysterectomy versus radiotherapy alone, were identified. In the first one⁶⁸, patients with “bulky” stage IB cervical cancer were randomized to either external and intracavitary irradiation or attenuated irradiation followed by extrafascial hysterectomy. The addition of extrafascial hysterectomy to standardized radiation therapy did not improve PFS or OS. It should be noted that (1) there

LoE 1-

was a lower cumulative incidence of local relapse at five years in the combined treatment regimen (27% versus 14%) and (2) hysterectomy did not increase the frequency of reported grade 3-4 adverse effects. In the second one¹²¹⁰, patients with stage IB-IIA cervical cancer were randomized to either irradiation alone or irradiation and radical hysterectomy. No differences in terms of tumour-free actuarial survival at five years and severe complications were observed.

Another identified RCT¹²¹¹ compared hysterectomy (extrafascial or radical) with no hysterectomy in patients with a (clinical and radiological) complete response after chemoradiotherapy for stage IB2-II cervical cancer. There was no difference in OS or RFS at three years between treatment groups. It should be noted that adverse events and morbidity were not reported.

The fourth identified RCT¹²¹² found no difference in the risk of death, disease progression or severe late complications between women who received standard brachytherapy versus radical hysterectomy after both groups had received identical external beam chemoradiotherapy.

A systematic review¹²¹³ was identified but is not described because it contains only the four RCTs^{68,1210-1212} mentioned above.

As part of a small study, Okame *et al.*¹²¹⁴ compared radiotherapy and surgery as a primary treatment of LACC. Three-year locoregional control rates were significantly better in patients who underwent radical hysterectomy in comparison with patients treated with radiotherapy (79.0% versus 46.2%, $p = 0.03$). The advantage in terms of 5-year OS rates in favour of radical hysterectomy did not reach statistical significance (70.7% versus 38.5%, $p = 0.09$). It should be noted that these results have to be interpreted cautiously notably because (1) NACT and/or adjuvant chemotherapy was conducted in most radical hysterectomy cases, and this might have contributed to the improved results in comparison with radiotherapy, and (2) adjuvant chemotherapy regimens varied between the two groups. As part of another small study, Sarraf *et al.*¹²¹⁵ compared patients treated with EBRT and brachytherapy with EBRT and extrafascial hysterectomy in LACC. There were no significant differences between the two groups in metastasis, recurrence, and survival rates.

LoE 3

Comparing radical hysterectomy after CCRT versus CCRT alone, Fanfani *et al.*¹²¹⁶ observed no difference in terms of DFS or OS at 3 years between the two groups. Additionally, they observed no differences in terms of distant recurrence rate, and a significantly higher rate of local recurrences for patients treated with hysterectomy after CCRT than those treated with CCRT alone (22.1% versus 10.9%, $p < 0.002$).

LoE 2-

In a study¹²¹⁷ comparing outcomes of patients with and without completion surgery after CCRT, survival was not statistically improved by completion surgery, although there was a trend to significance. The gain in terms of recurrence rate for patients who did have a completion surgery did also not reach statistical significance. It should be noted that completion surgery after CCRT improved local disease control in patients with a partial pathologic response, and enhanced survival in the study published by Sun *et al.*¹⁰⁸. In this study¹⁰⁸, the DFS rates among patients who underwent extrafascial hysterectomy, extended hysterectomy, or no completion surgery were 83.2%, 71.7%, and 54.1%, respectively, at three years, and 66.4%, 50.7%, and 37.2% at five years ($p < 0.05$ for all comparisons). The respective OS rates among patients who underwent extrafascial hysterectomy, extended hysterectomy, or no completion surgery were 72.2%, 60.1%, and 45.9% at three years, and 53.5%, 40.7%, and 32.2% at five years ($p < 0.05$ for all comparisons).

Comparing DFS and OS of two groups of patients, with or without additional surgery, Lèguevaque *et al.*¹¹⁶ reported a relative risk of disease progression or death in favor of completion surgery (RR = 0.41 (95% CI = 0.20-0.85), $p = 0.01$). A significant benefit of completion surgery was seen in DFS ($p = 0.01$). However, completion surgery did not improve OS.

Four studies¹²¹⁷⁻¹²²⁰ evaluating the feasibility and safety of different types of hysterectomy in the management of patients affected by LACC were identified. In the first one¹²¹⁸, patients undergoing type C2 total extraperitoneal abdominal radical hysterectomy were compared with a historical control group of patients undergoing intraperitoneal radical hysterectomy. In all patients tumour resection with disease free margins was achieved. No significant differences in terms of surgical data (except concerning the mean operative time in favour of total extraperitoneal abdominal radical hysterectomy: 195 min versus 235 min, $p < 0.05$) or complications were found. The second one¹²¹⁹ showed that the patients treated with type C2/III radical hysterectomy had same sexual activity and sexual enjoyment data compared with patients surgically treated for gynaecological benign disease. It should be noted that oncologic group patients had clinically worse problems with symptom experience, body image, and sexual/vaginal functioning than benign gynaecological disease group ($p < 0.05$). Oncologic group patients also reported more severe lymphedema, peripheral neuropathy, menopausal symptoms, and sexual worry. The third one¹²¹⁷ showed no significant differences in terms of recurrence, survival and late complication rates after radical hysterectomy than after extrafascial hysterectomy.

Panici *et al.*¹²²⁰ evaluated the feasibility and safety of type B radical hysterectomy in the management of patients affected by LACC with favorable prognostic factors (tumour diameter < 4 cm, negative nodes, or LVSI). Patients were compared with historical cohort of patients undergoing type C radical hysterectomy. Type B radical hysterectomy was associated with reduced operative time (105 min versus 206 min, $p < 0.0001$) and hospital stay (4.6 days versus 6.3 days, $p \leq 0.0001$), without detrimental effect on survival or late postoperative morbidity.

Vizza *et al.*¹¹⁵⁹ evaluated the feasibility and morbidity of total laparoscopic radical hysterectomy with pelvic lymphadenectomy in LACC patients (stage IB2-IIB) with complete clinical response after NACT. A conversion to laparotomy was required in 10% of patients. No reoperation was noticed. Pathological evaluation showed complete response in 22.5% of patients, a partial response with microscopic tumour in 22.5% of patients, and a partial response with macroscopic tumour in 37.5% of patients. No response was observed in 7.5% of patients.

Favero *et al.*¹²²¹ evaluated the feasibility and safety of laparoscopic extrafascial hysterectomy and bilateral salpingo-oophorectomy after primary chemoradiotherapy in patients with LACC without evidence of nodal metastasis. No casualty related to surgery, intraoperative complication, or conversion to laparotomy occurred. Significant complication occurred in 12% of the cases. All patients had free margins.

Four studies^{577,1222-1224} assessing laparoscopic hysterectomy after NACT^{577,1222} or CCRT^{1223,1224} in LACC compared to laparotomy, were identified. Considering the two identified studies^{577,1222} assessing laparoscopic hysterectomy after NACT^{577,1222} compared to laparotomy, Cai *et al.*¹²²² reported that median operative time, number of harvested LNs, and rate of positive surgical margins did not differ significantly between the groups, but laparoscopic hysterectomy resulted in less median blood loss (300 ml versus 375 ml, $p = 0.027$). Laparoscopic radical hysterectomy offered less blood loss and lower transfusion rate in the study published by Ghezzi *et al.*⁵⁷⁷ (265 ml versus 400 ml ($p < 0.0001$) and 1.5% versus 11.3% ($p = 0.009$),

LoE 3

respectively). No difference was found between open surgery and laparoscopy in intra- or post-operative complications. No patient had her radical surgery converted to an open procedure in both identified studies^{577,1222}.

In the first identified study¹²²³ assessing laparoscopic hysterectomy after CCRT, there was no difference in operative time, or intra- and post-operative complication rates between the two groups. Intraoperative transfusion and abdominal drain were significantly lower in the laparoscopy group, as well as the duration of hospital stay (0% versus 13% ($p = 0.0446$), 7.5% versus 78.3% ($p < 0.0001$), and 5.7 days versus 7.3 days ($p < 0.001$), respectively). Assessment of quality of life using EORTC QLQ-C30 at one week after surgery was better for patients having undergone laparoscopy compared to laparotomy. At one month, global health and quality of life, physical functioning and role functioning were better in the laparoscopy group ($p = 0.01$, $p = 0.01$, and $p = 0.05$, respectively). At six months, the measurable benefits remained for patients who underwent laparoscopy, in particular they experienced less fatigue than patients who underwent laparotomy ($p = 0.04$). Using the specific cervical cancer questionnaire, CX24, only sexual activity was significantly better at six months for the laparoscopy group ($p = 0.01$). Consistent findings were described in the second identified study¹²²⁴ in terms of duration of hospital stay (5 days versus 8 days, $p < 0.01$), operative time, blood transfusion (2.2% versus 7.1%, $p = 0.02$). However, postoperative complications were significantly reduced in the laparoscopic group (28.3% versus 48.1%, $p = 0.04$). It should be noted that the average estimated blood loss was significantly lower in this group (200 ml versus 400 ml, $p < 0.01$) and the median duration of urinary catheterization was significantly shorter in this group (4 days versus 6 days, $p < 0.01$).

Four studies¹²²⁵⁻¹²²⁸ evaluating the feasibility and safety of robotic radical hysterectomy with pelvic lymphadenectomy for LACC after NACT¹²²⁵⁻¹²²⁷ or chemoradiotherapy¹²²⁸ were also identified (Table 33). In two^{100,101} of them, surgical outcomes were compared to those achieved by women undergoing robotic surgery for an early stage disease during the same temporal interval. In the first one¹²²⁵, all but one of the procedures were successfully completed with robotic surgery in patients with LACC. No intraoperative complications or conversion to emergency laparotomy occurred in this group. No differences were encountered between groups in terms of operative time, blood loss, hospitalization, nodal yield, parametrial and vaginal cuff length, and early postoperative complications. Consistent findings were reported by Minig *et al.*¹²²⁶ in terms of estimated blood loss, length of hospital stay, conversion to laparotomy, intra- and post-operative complications. However, the mean operative time was significantly longer in the robotic surgery group (307.8 min versus 277.4 min, $p \leq 0.001$). No conversion to laparotomy/laparoscopy was also necessary in the third identified study¹²²⁷. The authors experienced one intra-operative complication (1.7%) and nineteen early post-operative complications (31.7%), but no conversion to laparotomy were necessary to manage these complications. The surgical lateral margins of parametria were free of disease in all cases.

As part of a small study, Gallotta *et al.*¹²²⁸ reported a feasibility rate of robotic radical surgery in patients with LACC who received chemoradiotherapy of 97.5%. No intraoperative complications were recorded. During the observation period, 22.5% of patients experienced postoperative complications.

A study⁶¹³ comparing the surgical outcome of robotic radical hysterectomy versus laparoscopic radical hysterectomy for the treatment of LACC after NACT, was also identified. No differences in terms of median operative time, median length, and intra- and post-operative complications were observed between the two groups. However, the median estimated blood loss was statistically significant in favour of robotic radical hysterectomy group (160 ml versus 240 ml,

p ≤ 0.05).

Corrado *et al.*¹²²⁹ compared the surgical and oncological results of robotic surgery with a historical cohort of patients undergoing laparoscopic or abdominal hysterectomy plus pelvic lymphadenectomy for LACC after NACT. Significant differences were found between the robotic surgery group and the two other groups in terms of operative time (180 min versus 220 min versus 290 min, p < 0.001), estimated blood loss (150 ml versus 250 ml versus 480 ml, p < 0.001), median hospital stay (4 days versus 6 days versus 8 days, p < 0.001), and major late postoperative complications (5 versus 13 versus 28, p < 0.001). No conversion to laparotomy in the robotic group was necessary. The median number of removed PLNs was statistically higher in the abdominal surgery group compared with the laparoscopic surgery group (25 versus 20, p < 0.05), whereas no differences were observed between the abdominal surgery group and robotic surgery group and between the laparoscopic surgery group and the robotic surgery group. It should be noted that there were no significant differences between the 3-year OS and DFS rates in the minimally invasive groups.

13.1.3 Radiotherapy

Meta-analysis¹²¹³ of three RCTs^{1139,1140,1180} comparing NACT and hysterectomy versus radiotherapy alone, found that women who received NACT plus hysterectomy had less risk of death than those who received radiotherapy alone (HR = 0.71 (95% CI = 0.55-0.93)). However, no difference in the risk of disease progression or recurrence between the two groups were reported. It should be noted that a significant number of the participants who received NACT plus hysterectomy had radiotherapy as well. In terms of acute toxicity, only one¹¹³⁹ of the three^{1139,1140,1180} included RCTs provided data, and described no significant difference between the two groups. None of the two^{1139,1140} included RCTs reporting data on long-term complications and toxicity described significant difference between the two treatment groups.

LoE 1-

A meta-analysis¹²³⁰ evaluating the impact of the extension of the radiotherapy field cranially toward PALNs in LACC was also identified. All patients had undergone pelvic radiotherapy and the same systemic therapy (or not) in both treatment arms. The radiotherapy technique was conventional in three included RCTs¹²³¹⁻¹²³⁴ and conformational in the last one^{399,1235}. Extended-field irradiation significantly reduced the rate of para-aortic failure (HR = 0.35 (95% CI = 0.19-0.64), p < 0.01) and the incidence of other distant metastases (HR = 0.69 (95% CI = 0.50-0.96), p = 0.03). Locoregional failure and cancer-related death were not significantly altered. The increase number of treatment-related death due to extended-field irradiation reported by two included RCTs¹²³¹⁻¹²³³ did not statistically significant. More bone fractures were recorded in the extended-field irradiation arm of one RCT¹²³⁴ but not in the second RCT¹²³¹ reporting such events. It should be noted (1) the absence of included RCTs that directly compared pelvic versus extended-field radiation with standard cisplatin chemotherapy in both treatment arms and (2) older radiotherapy techniques likely achieved the proximity to abdominal organs at risk, which might have caused the limiting high-grade toxicity events, such as bone fractures.

Dobrowsky *et al.*¹²³⁶ randomized patients with stage IIIA or IIIB cervical cancer to either radical radiotherapy alone or radical radiotherapy and additional administration of AK-2123. The addition of AK-2123 to radical radiotherapy significantly increased local tumour control (61% versus 46%, p = 0.006) and 5-year actuarial survival (57% versus 41%, p = 0.01). AK-2123 did neither increase local toxicity nor was it attributed to haematological toxicity. A mild peripheral toxicity, usually completely reversible, was infrequently seen after AK-2123 administration.

13.1.4 Brachytherapy

A meta-analysis¹²³⁷ (four studies¹²³⁸⁻¹²⁴¹) showed no significant differences between high dose rate and low dose rate intracavity brachytherapy in combination with EBRT when considering OS, DSS, RFS, local control rate, recurrence, metastasis and treatment related complications for women with LACC. However, increased small bowel complications with high dose rate intracavity brachytherapy were described (RR = 3.37 (95% CI = 1.06-10.72), p = 0.04)). It should be noted that (1) there were broad differences in trial design, particularly with regard to the timing and total dose of EBRT and the fractionation schedules, (2) in one RCT¹²⁴⁰ the subgroup radiotherapy schedules were based on tumour volume and local cervical anatomy rather than on disease stage^{1238,1239,1241}.

LoE 1-

One previously published meta-analysis¹²⁴² showed also no differences between high dose-rate and low dose-rate intracavity brachytherapy in the survival and complication rates. It should be noted that four¹²³⁸⁻¹²⁴¹ of the five RCTs^{1238-1241,1243} included in this meta-analysis¹²⁴² were also included in the meta-analysis published by Liu *et al.*¹²³⁷. The results mentioned above have been confirmed with a more recently published meta-analysis¹²⁴⁴ including fifteen studies^{1240,1241,1245-1257}, which also showed no difference in terms of OS, DFS, local recurrence, and complication rates.

Investigating whether high dose-rate intracavitary brachytherapy dose ratios can predict treatment outcomes in patients with stage IIB cervical cancer, Cho *et al.*¹²⁵⁸ found that the 5-year DSS and PFS rates were significantly lower in the group with low high-dose rate intracavitary brachytherapy ratio compared to the group with the high high-dose rate intracavitary brachytherapy ratio (5-year DSS: 78.3% versus 93.1%, p = 0.003 and 5-year PFS: 72.7% versus 90.7%, p = 0.007, respectively). A high high-dose rate intracavitary brachytherapy was confirmed as an independent prognostic factor for PFS (HR = 0.25 (95% CI = 0.06-0.96), p = 0.043) after controlling for age, pathological subtype, tumour size, PLN involvement, squamous cell carcinoma antigen/haemoglobin levels, overall treatment durations, and total dose.

LoE 2-

Comparing radiotherapy with chemoradiotherapy with high-dose-rate brachytherapy, the pooled analysis published by Mayadev *et al.*¹²⁵⁹ (eighty studies^{11,98,114,1238,1239,1246,1260-1335}) reported an improvement in pelvic control and DFS in favour of chemoradiotherapy with high-dose-rate brachytherapy whereas the OS of the groups were similar, whatever the study type taken into account:

LoE 1-

- Prospective studies: pelvic control: 81.27% versus 73.49%, DFS: 65.44% versus 55.23, OS: 70.15% versus 66.06%
- Retrospective studies: pelvic control: 80.51% versus 74.82%, DFS: 63.02% versus 55.72%, OS: 66.19% versus 54.05%

Comparing patients receiving CCRT and image-based brachytherapy to traditional Point A dose specification, significant improvements in pelvic control (86.00% versus 83.84%, p < 0.01) and DFS (72.46% versus 69.51%, p < 0.01) were described with image-based brachytherapy. The OS of the groups were statistically different, with the mean OS better in the Point A dose group versus the image-based brachytherapy group (73.36% versus 64.33%, p < 0.01).

As part of a systematic review, Mendez *et al.*¹³³⁶ evaluated local control and toxicities of perineal-based interstitial brachytherapy in patients treated with three-dimensional image-based planning. All patients received EBRT (45-50.4 Gy) as a first phase of treatment and 77.8% of patients that had chemotherapy information available received concomitant chemotherapy with EBRT. Sixty per cent of patients treated with perineal-based interstitial

brachytherapy had stage IIIB disease or higher and yet a local control rate of 79% was found (eleven studies^{1270,1289,1309,1337-1344}). Patients receiving equivalent 2 Gy dose ≥ 76 Gy and > 76 Gy had local control of 84% and 67%, respectively (fifteen studies^{1289,1309,1337,1339-1341,1343,1345-1352}). Only grade 3-4 gastro-intestinal, genitourary and vaginal late toxicities were described (eleven studies^{1270,1289,1309,1337-1344}). Three quarters of these related to gastrointestinal toxicity. Genitourinary and vaginal late toxicities were 21.3% and 4.3%, respectively. It should be noted (1) that the majority of the included studies^{1270,1289,1309,1337-1340,1344-1346,1348-1350} based their treatment on computed tomography imaging, (2) an observed heterogeneity of the template types used (Syed-Neblett^{1289,1309,1340,1341,1344-1347,1350,1351}, custom-made^{1342,1348,1349,1352}, Martinez universal perineal interstitial template^{1270,1338}, free hand¹³³⁹, Benidorm template¹³⁴³, unspecified template type¹³³⁷), and (3) the small sample size of the majority of the enrolled studies^{1270,1289,1337-1342,1344,1346-1352}.

All the fourteen identified studies^{1260,1285,1353-1364} of image-guided adaptive brachytherapy reporting outcomes according to Groupe européen de curiethérapie - European society for radiotherapy and oncology (GEC-ESTRO) recommendations^{10,11} published in 2005 reported high local control rates with a low radiation-induced morbidity (Table 34). At the exception of the study published by Charra-Brunaud *et al.*¹³⁶⁴ which reported the lowest doses, the local control rates at 2-3 years ranged between 86.4 and 100%, whereas the severe morbidity rates remained below or close to 10%.

LoE 2-

Three^{1310,1355,1358} of the four identified studies^{1310,1355,1358,1364} describing comparisons with historical cohorts of patients treated with radiographs-based brachytherapy reported a significant improvement of OS rates with the use of image-guided adaptive brachytherapy at 3 years (64% versus 53% ($p = 0.03$)¹³¹⁰, 79% versus 63% ($p = 0.005$)¹³⁵⁵, 86% versus 43% ($p < 0.01$)¹³⁵⁸). In addition, the severe morbidity rates were decreased in the image-guided adaptive brachytherapy cohorts, by 8 to 18% (7% versus 15% ($p = 0.002$)¹³⁵⁵, 3% versus 21.4% ($p < 0.01$)¹³⁵⁸, 2.6% versus 22.7% ($p = 0.004$)¹³⁶⁴). It should be noted unbalanced uses of concomitant chemotherapy in the groups of these studies. Several identified studies¹³⁶⁵⁻¹³⁷⁰ have shown dose-effect relationships for the rectum¹³⁶⁵⁻¹³⁶⁹ and the bladder^{1365,1367,1370}. It should be noted that they are based on limited samples of patients, and evaluations relied on heterogeneous methods (eligibility, endpoint, and scoring systems).

13.1.5 Chemoradiotherapy

On the basis of thirteen RCTs^{67,1261,1266,1267,1269,1371-1378} that compared chemoradiotherapy versus the same radiotherapy, a meta-analysis¹³⁷⁹ found that there was a 19% relative reduction in the risk of death with chemoradiotherapy and translated to an absolute survival benefit of 6% at five years. A larger survival benefit was seen for the two further RCTs^{721,1380} in which chemotherapy was administered after chemoradiotherapy (HR = 0.46 (95% CI = 0.32-0.66)). The authors found no evidence of a difference in the size of the effect of chemoradiotherapy when RCTs were grouped according to the type of chemotherapy they had used (platinum based or non platinum based), the planned radiotherapy dose or the total planned duration of radiation. Similarly, for the ten RCTs^{67,1261,1266,1269,1372,1374-1378} that used cisplatin-based chemoradiotherapy, the authors found no evidence that the effect of chemoradiotherapy differed according to the cycle length or the dose intensity of cisplatin used (Table 35).

LoE 1+

An absolute DFS benefit of 8% at 5 years was also reported ($p = 0.000005$). There were similar and significant absolute benefits of chemoradiotherapy on 5-year locoregional DFS (9%, $p < 0.001$), time to locoregional recurrence/progression (6%, $p = 0.00009$) and metastase-free survival (7%, $p < 0.001$). A smaller improvement in time to metastases at five years was also described (4%, $p = 0.04$). There was a suggestion of trend in the relative effect of

chemoradiotherapy by tumour stage ($p = 0.017$), with the benefit of chemoradiotherapy decreasing with increasing stage (stage IB-IIA: 10%, stage IIB: 7%, stage III-IVA: 3%). It should be noted that there was no significant trend for the analysis of DFS by stage. This meta-analysis described no evidence to suggest that the effect of chemoradiotherapy differed in groups of women defined by age, histology, tumour grade or whether they had PLN involvement.

A second identified meta-analysis¹³⁸¹ (eighteen RCTs^{67,721,1129,1269,1382-1395}) comparing the effectiveness and safety of chemoradiotherapy with radiotherapy alone in LACC reported significant differences in terms of response rate, 3-year OS rates, and 5-year OS rates in favour of patients in the chemoradiotherapy group (RR = 1.17 (95% CI = 1.11-1.23), RR = 1.13 (95% CI = 1.04-1.24), and RR = 1.22 (95% CI = 1.13-1.31), respectively).

Evaluating the efficacy and safety of cisplatin-based CCRT in patients with high-risk cervical carcinoma compared with exclusive radiotherapy, the meta-analysis published by Meng *et al.*¹³⁹⁶ revealed a statistically significant difference in OS in favor of cisplatin-based CCRT over exclusive radiotherapy (eight studies^{721,1269,1273,1279,1387,1388,1397,1398}, HR = 0.68 (95% CI = 0.57-0.80)). Similar results were observed for PFS (six studies^{721,1269,1273,1388,1397,1398}, HR = 0.63 (95% CI = 0.50-0.76)). It should be noted that a minor heterogeneity among the included six studies was observed. Their pooled analysis showed significantly enhanced treatment-related grade 3-4 adverse events in the CCRT group compared with the exclusive radiotherapy group (five studies^{67,721,1387,1397,1398}, OR = 3.13 (95% CI = 2.37-4.13)). Data on tumour response (five studies^{1387,1397-1400}) and treatment failures (five studies^{1273,1279,1387,1388,1397}) were also reported. The pooled analysis showed that statistical significance was reached in none of the different comparisons.

Fully consistent data are also provided by Uppal *et al.*¹⁴⁰¹ with respect to decreased OS rate with radiotherapy alone as compared to CCRT (HR = 1.47 (95% CI = 1.4-1.56)).

LoE 2-

A meta-analysis¹⁴⁰² of twenty-two randomized comparisons^{727,1123,1125-1130,1133-1137,1261,1267,1269,1373,1397,1403-1406} of chemotherapy plus radiotherapy versus the same radiotherapy alone in advanced cervical cancer found no statistically significant overall benefit from chemotherapy. Analyses according to the type of regimen showed a significant benefit only for non-platinum regimens (HR = 0.73 (95% CI = 0.57-0.95)). There was no evidence for any survival benefit in trials of platinum monotherapy plus radiotherapy versus radiotherapy alone and in trials of combinations of platinum plus non-platinum agents plus radiotherapy versus radiotherapy alone. It should be noted that significant between-study heterogeneities were described.

LoE 1+

A marginally significant survival benefit was found in trials using cisplatin-based regimens with short length cycles (HR = 0.80 (95% CI = 0.66-0.97)), while a marginally significant deterioration of survival was observed in trials using platinum-based regimens with longer cycles (HR = 1.18 (95% CI = 1.02-1.38)). It should be noted that the survival benefit with short length cisplatin cycles was driven largely by a trial¹¹²⁵ that had reported only preliminary interim analysis results.

CCRT did also not result in a significant improvement in pelvic control rate, response rate, and/or survival compared to standard conventional radiotherapy in two studies^{115,1407} not included in the meta-analyses^{1379,1381,1402} mentioned above.

LoE 2-

As part of another meta-analysis of RCTs^{67,721,1267,1269,1373,1374,1383,1397,1408-1421} comparing concomitant chemotherapy and radiation therapy for LACC, Green *et al.*¹⁴²² reported statistically significant increases in the rate of grade 1-2 haematological (unspecified), white blood cell, haemoglobin, platelet, gastrointestinal, skin and neurological toxicities with CCRT

LoE 1+

and grade 1-2 nausea and vomiting. These ranged from a 29% increase in the risk of white blood cell toxicity up to a greater than three-fold increase in the risk of nausea and vomiting on the CCRT arm compared with that on control. Rates of grade 3-4 haematological, white blood cell, haemoglobin, platelet and gastrointestinal toxicity and nausea and vomiting toxicity were also significantly increased with CCRT. These ranged from around a two-fold increase in gastrointestinal toxicity up to more than four times the risk of nausea and vomiting. Late effects of treatment were not well reported and so the impact of chemoradiotherapy on these effects could not be determined adequately (Table 36).

Kirwan *et al.*¹⁴²³ described fully consistent toxicity pooled data with those reported in the meta-analysis¹⁴²² mentioned above. It should be noted that thirteen^{67,721,1383,1397,1409-1411,1413,1415,1416,1418,1420,1421} of the nineteen RCTs^{67,721,1371,1383,1397,1409-1411,1413,1415,1416,1418,1420,1421,1424-1428} from which these analyses are based on have also been taken into account by Green *et al.*¹⁴²².

A RCT¹⁴²⁹ not included in the meta-analyses^{19,1379,1381,1402,1422,1423} mentioned above and comparing chemoradiotherapy versus radiotherapy, was also identified. Their results showed that compared with control group, the overall short-term outcomes, 1- and 3-year survival rates of experimental group were significantly higher (88.57% versus 70.77%, $p < 0.05$ and 82.14% versus 57.69%, $p < 0.05$, respectively), which was similar to the results presented above. Stage-based stratified analysis showed that in stage III patients, the differences in short-term efficacy, 1-year survival and local control rates between experimental group and control group were significant (76.47% versus 45.45%, $p < 0.05$ and 61.76% versus 36.36%, $p < 0.05$, respectively), whereas the differences in 3-year survival and local control rates were not significant. It should be noted that there was no significant difference on short-term efficacy in stage II patients between the two treatment groups. For the stage II patients who had followed up for over three years, the difference of 3-year survival and local control rates between the two groups were significant (93.75% versus 64.29%, $p < 0.05$ and 93.75% versus 64.29%, $p < 0.05$, respectively). The quality of life of patients in both the control group and the experimental group was significantly improved after treatment ($p < 0.05$). However, it should be noted that the difference between the two groups was not significant.

Using the technique of meta-analysis (nineteen studies^{1261,1265,1269,1273,1279,1371,1397,1399,1418,1420,1430-1438}), Fu *et al.*¹⁴³⁹ compared different CCRT regimens in the treatment of advanced cervical cancer (radiotherapy, CCRT (cisplatin), CCRT (vinorelbine), CCRT (paclitaxel), CCRT (hydroxyurea), CCRT (cisplatin + 5 fluorouracil), CCRT (cisplatin + gemcitabine), CCRT (cisplatin + docetaxel), CCRT (cisplatin + paclitaxel), CCRT (cisplatin + amifostine), CCRT (cisplatin + 5 fluorouracil + hydroxyurea), and CCRT (cisplatin + vincristine + bleomycin)). In terms of efficacy, pairwise meta-analyses showed that the 5-year OS rates of CCRT (cisplatin) and CCRT (cisplatin + 5 fluorouracil + hydroxyurea) were higher than CCRT (hydroxyurea). There were no significant differences in (1) the 5-year OS rates among the other CCRT regimens tested and (2) the overall response rates and 5-year DFS rate among the evaluated CCRT regimens (Table 37). The network meta-analyses showed that the overall response rates of CCRT (cisplatin + docetaxel) was higher than radiotherapy (OR = 23.63 (95% CI = 1.29-433.02)). Compared with CCRT (hydroxyurea), the 5-year OS rate of CCRT (cisplatin + 5 fluorouracil + hydroxyurea) was higher (OR = 2.36 (95% CI = 1.54-3.63)). Compared with radiotherapy and CCRT (cisplatin), the 5-year OS rate of CCRT (hydroxyurea) was lower (OR = 0.49 (95% CI = 0.28-0.87) and OR = 0.44 (95% CI = 0.29-0.68), respectively). It should be noted that there was no significant difference of 5-year DFS rate among the evaluated CCRT regimens).

As for hematotoxicity, compared with CCRT (cisplatin), the incidences of anemia, neutropenia,

and thrombocytopenia with CCRT (cisplatin + gemcitabine) were higher (Table 38). The addition of 5 fluorouracil to CCRT (cisplatin) was associated with higher incidence of leucopenia. The same increase was reported in case of addition of cisplatin to radiotherapy. Compared with CCRT (cisplatin + 5 fluorouracil), the incidences of leucopenia with CCRT (hydroxyurea) and CCRT (cisplatin + paclitaxel) were higher (Table 38). As far as gastrointestinal toxicity, compared with CCRT (cisplatin), the incidence of diarrhea with CCRT (cisplatin + gemcitabine) was higher, and the incidence of nausea with CCRT (cisplatin + 5 fluorouracil) was higher. It should be noted that there was no significant difference of the incidence of vomiting among the evaluated CCRT regimens. The network meta-analyses showed that compared with CCRT (cisplatin), the incidences of leucopenia with CCRT (hydroxyurea), CCRT (cisplatin + 5 fluorouracil) and CCRT (cisplatin + paclitaxel) were higher (OR = 21.30 (95% CI = 6.44-70.45), OR = 2.42 (95% CI = 1.08-5.44), OR = 73.59 (95% CI = 17.86-303.31), respectively), and the incidence of thrombocytopenia with CCRT (cisplatin + gemcitabine) was higher (OR = 4.44 (95% CI = 1.63-12.07)). In terms of gastrointestinal toxicity, the incidence of diarrhea and vomiting with CCRT (cisplatin + gemcitabine) was higher than CCRT (cisplatin) (OR = 3.80 (95% CI = 2.08-6.95), OR = 2.94 (95% CI = 1.26-6.86), respectively). Compared with radiotherapy, the incidence of nausea with CCRT (cisplatin + 5 fluorouracil) was higher (OR = 2.53 (95% CI = 1.13-5.66)). It should be noted that there was no significant difference among the evaluated CCRT regimens in terms of anemia and neutropenia.

Another meta-analysis¹⁴⁴⁰ (fifteen RCTs^{1266,1430,1431,1441-1452}) comparing the efficacy and safety between different single-agent regimens (cisplatin, nedaplatin, docetaxel, paclitaxel, paclitaxel liposome, 5 fluorouracil, vinorelbine, and irinotecan) in the chemoradiation system was identified. When the research focused on OS or local recurrent rate, no significant advantage existed when the other single-agent regimen was used in the concurrent chemoradiotherapy compared with cisplatin. It should be noted that when aimed at distant metastasis rate, fluoropyrimidine showed a disadvantage to cisplatin, whereas others showed equal efficacy. With regard to the response rate, only nedaplatin showed a significant improvement compared with cisplatin. Docetaxel, fluoropyrimidine, paclitaxel, paclitaxel liposome, and irinotecan did not show any advantages. Nedaplatin, docetaxel, paclitaxel, and fluoropyrimidine showed a better effect on reducing chemotherapy toxicity than cisplatin (Table 39).

Sebastiao *et al.*¹⁴⁵³ and Nam *et al.*¹⁴⁵⁴ found also that patients treated with CCRT (carboplatin) had survival and response rate when compared to CCRT (cisplatin). Similarly, with postoperative CCRT, Kagabu *et al.*¹⁴⁵⁵ described no significant differences in recurrence rate, PFS, and OS between patients treated with CCRT (nedaplatin) compared with those treated with CCRT (cisplatin).

LoE 2-

Pooled survival rates published by Lukka *et al.*¹⁴⁵⁶ from six RCTs^{1383,1397,1413,1416,1418,1420} that evaluated the role of cisplatin, alone or in combination with other chemotherapy agents, administered concurrently with EBRT, showed a statistically significant effect in favour of cisplatin-based chemoradiotherapy compared with radiotherapy without cisplatin (RR = 0.78 (95% CI = 0.67-0.90)).

LoE 1+

Petrelli *et al.*¹⁴⁵⁷ evaluated whether cisplatin-based doublet therapy improved survival compared to weekly cisplatin plus radiotherapy in patients with cervical cancer. Meta-analysis of eight studies^{726,1265,1433,1437,1458-1461} showed that for LACC, CCRT and with cisplatin-based doublet chemotherapy significantly improved the OS (OR = 0.65 (95% CI = 0.51-0.81), $p = 0.0002$), PFS (OR = 0.71 (95% CI = 0.55-0.91), $p = 0.006$), and rate of locoregional relapse (OR = 0.64 (95% CI = 0.47-0.89), $p = 0.008$), compared to radiotherapy with concurrent weekly cisplatin alone. However, the rate of distant metastases was similar between the study arms. It should be noted that toxicities were largely underreported in the included studies.

Thrombocytopena and neutropenia were worse in the experimental arms ($p = 0.01$ and $p = 0.02$, respectively). Acute gastrointestinal toxicity, including grade 3 or 4 vomiting or nausea plus diarrhea, occurred more frequently in the polychemotherapy arms ($p = 0.016$).

A systematic review¹⁴⁶² aiming to assess the effectiveness of concomitant radiation and hydroxyurea compared with radiotherapy alone in treating LACC was identified but is not described because the authors did not find studies meeting their inclusion criteria.

Seven RCTs¹⁴⁶³⁻¹⁴⁶⁹ not included in the systematic reviews/meta-analyses^{1379,1381,1402,1422,1423,1439,1440,1456,1457,1462} mentioned above was also identified.

Kim *et al.*¹⁴⁶³ designed a RCT for prophylactic para-aortic irradiation on the basis of hypoxia marker, CA9, to test whether concomitant cisplatin and extended-field irradiation can reduce para-aortic recurrences and increase disease-free survival rate in LACC. Patients were randomized to either extended-field irradiation or pelvic radiotherapy in each CA9 group. Para-aortic recurrence-free survival was significantly higher for extended-field irradiation compared to pelvic radiotherapy in CA9-positive group (100% versus 81.7%, $p = 0.007$), while there was non such difference in CA9-negative group. There was no significant benefit in terms of DFS by extended-field irradiation in CA9-positive groups, while DFS was significantly higher in patients who received extended-field irradiation in CA9-negative groups (100% versus 70.7%, $p = 0.018$). It should be noted that the number of CA9-negative patients was too small to compare the effect of extended-field irradiation against the CA9-positive group.

In the second one¹⁴⁶⁴, patients were randomized to receive cisplatin with concurrent EBRT, followed by brachytherapy or gemcitabine with the same radiation therapy. Although it was observed more frequent complete pathological response in the study arm (gemcitabine) than in the control arm (96% versus 88%), no difference in terms of DFS or OS was reported between the two treatment groups. Occurrence of toxicities were significantly high in the study group compared to the control group in the case of leucopenia ($p = 0.015$), skin reaction ($p = 0.03$), and bleeding ($p = 0.019$).

The third one¹⁴⁶⁵ randomly assigned patients to receive weekly (cisplatin 40 mg/m², six cycles) or triweekly (cisplatin 75 mg/m², three cycles) chemotherapy during concurrent radiotherapy. The 5 year-OS rate was significantly higher in the triweekly arm than in the weekly arm (HR = 0.375 [95% CI = 0.154-0.914], $p = 0.03$). In this trial, despite the survival difference, the recurrence rate and PFS were almost identical in both arms. Grade 3-4 neutropenia was more frequent in the weekly arm than in the triweekly arm (39.2% versus 22.6%, $p = 0.03$). No statistical differences in gastrointestinal, renal, and neurosensory toxicities between the two arms.

As part of another trial¹⁴⁶⁶, FIGO stage IIB-IIIB cervical cancer patients were randomized to have tegafur-uracil plus carboplatin concurrent with radiotherapy or carboplatin alone concurrent with radiotherapy. CCRT by tegafur-uracil and carboplatin did not show any significant advantage in tumour response rate, PFS, OS or treatment toxicity over CCRT with carboplatin alone.

The RCT¹⁴⁶⁷ comparing, showed that treatment with interferon alpha-2b plus 13-cis-retinoic acid with radiation did not demonstrate survival or response rate advantage over cisplatin plus radiation despite being less toxic.

In a small RCT¹⁴⁶⁸ aiming to compare three-dimensional conformal radiotherapy and intensity-modulated radiotherapy combined with concurrent chemotherapy, no significant difference was observed in OS and DFS in first, second, and third years in both groups.

Another small identified RCT¹⁴⁶⁹ concerned the feasibility of concurrent chemotherapy and interspacing brachytherapy during the course of external radiotherapy to reduce the overall treatment time and compare the normal tissue toxicity and locoregional control with a conventional schedule. Arm I treatment consisted of irradiation of the whole pelvis, and weekly cisplatin. High-dose intracavitary brachytherapy was performed after one week of completion of EBRT. Arm II treatment consisted of irradiation of the whole pelvis. Cisplatin was administered from day 1-5 and day 24-28. Overall treatment time was taken from first day of EBRT to last day of high-dose rate brachytherapy. In this RCT interspacing brachytherapy with EBRT and concurrent chemotherapy resulted in significantly shorter treatment duration as compared to the standard practice (48 days versus 65 days, $p = 0.001$). The response rates and toxicities were comparable.

A study^{1470,1471} exploring the safety and efficacy of the addition of bevacizumab to standard CCRT in LACC was identified. This study included patients with stage FIGO IIB-IIIB, or with FIGO stage IB-IIA with biopsy-proven PLN metastases and/or tumour size ≥ 5 cm (but with negative PALN). There were no treatment-related serious adverse events, and protocol-specified treatment related adverse events within 90 days of treatment start were reported in 31% of patients (most common were hematologic: 80%). Two years later, the same authors published data concerning secondary efficacy endpoints. These were OS, locoregional failure, para-aortic failure, distant failure, and DFS in the same patients who participated in the trial. Three-year OS and DFS were 81.3% and 68.7%, respectively. Three-year locoregional failure was 23.2%, while 3-year para-aortic node failure was 8.4%.

LoE 3

13.1.6 Hyperthermia

Using the technique of meta-analysis (six RCTs^{1374,1472-1476}), Datta *et al.*¹⁴⁷⁷ assessed whether adding hyperthermia to standard (chemo)radiotherapy had an impact on outcomes for patients with LACC. Patients treated with thermoradiotherapy had superior outcomes in terms of complete response (OR = 2.67 (95 CI = 1.57-4.54), $p < 0.001$) and long-term locoregional control (OR = 2.61 (95% CI = 1.55-4.39), $p < 0.001$) when compared with radiotherapy for patients surviving at the end of follow-up without improvement of grade 3-4 acute and late toxicities. The survival advantage observed with thermoradiotherapy did not reach statistical significance.

LoE 1-

It should be noted that the outcomes of thermochemoradiotherapy compared to radiotherapy could only be computed from one small RCT¹³⁷⁴. A total of 83.3% of the patients treated with thermochemoradiotherapy achieved a complete response compared with 46.7% of the patients treated with radiotherapy alone (OR = 5.71 (95% CI = 1.72-18.94), $p = 0.004$). No other parameters were reported in this study.

Network meta-analyses, allowing both direct and indirect comparisons of various treatment approaches, were also performed for two endpoints (complete response and patients alive at the end of the study period). For the first one (thirteen RCTs^{1374,1472-1474,1478,1479}), a significant advantage of thermochemoradiotherapy was found over radiotherapy (OR = 4.52 (95% CI = 1.93-11.78)) and over chemoradiotherapy (OR = 2.91 (95% CI = 1.97-4.31)). Thermoradiotherapy also demonstrated a significantly higher probability of a complete response over radiotherapy alone (OR = 2.85 (95% CI = 1.63-5.08)). There were no significant differences observed for the remaining three comparisons (thermochemoradiotherapy versus thermoradiotherapy, thermoradiotherapy versus chemoradiotherapy, and chemoradiotherapy versus radiotherapy). The network meta-analysis for patients remaining alive at the end of the study follow-up period was performed with data from twelve RCTs^{1472-1474,1476,1478,1479} showed that thermochemoradiotherapy provided a significant advantage over chemoradiotherapy (OR = 2.65 (95% CI = 1.51-4.87)) or radiotherapy (OR = 5.57 (95% CI = 1.22-23.42)). There were

no significant differences for the remaining four comparisons between therapies (thermoradiotherapy versus radiotherapy, thermoradiotherapy versus chemoradiotherapy, thermochemoradiotherapy versus thermoradiotherapy, and chemoradiotherapy versus radiotherapy).

Another identified meta-analysis¹⁴⁷⁸ (nine RCTs^{NA}) showed that, compared with the chemoradiotherapy alone, thermochemoradiotherapy had significant increased 1-year survival rates (OR = 3.05 (95% CI = 1.70-6.68), p = 0.005), 2-year survival rates (OR = 2.29 (95% CI = 1.19-4.38), p = 0.01), and overall effective rates (OR = 3.66 (95% CI = 2.31-5.81), p < 0.00001). The incidence of adverse reactions was no statistically significant between the two treatment groups. A third identified systematic review¹⁴⁸⁰ is not described because it contains no additional studies beyond those already captured by the meta-analysis¹⁴⁷⁷ mentioned above. It should be noted that Datta *et al.*¹⁴⁷⁷ replaced (1) the original reports published by van der Zee *et al.*¹⁴⁸¹ and by Harima *et al.*¹⁴⁸² in 2001, included in this third identified systematic review¹⁴⁸⁰, by updated reports published by Franckena *et al.*¹⁴⁷² and by Harima *et al.*¹⁴⁷³ in 2009, respectively.

A RCT¹⁴⁸³ not included in the systematic reviews/meta-analyses^{1477,1478,1480} mentioned above, and evaluating the effectiveness of hyperthermia added to standard chemoradiotherapy, was also identified. Consistently with the network meta-analyses' results described by Datta *et al.*¹⁴⁷⁷, complete response was significantly more likely to be achieved in patients treated with thermochemoradiotherapy than in the chemoradiotherapy group (OR = 3.993 (95% CI = 1.018-15.67), p = 0.047). It should be noted that (1) the advantages in terms of 5-year OS, DFS and local relapse-free survival in favor of patients treated with thermochemoradiotherapy compared to those who underwent chemoradiotherapy did not reach statistical significance and (2) the addition of hyperthermia was well tolerated and caused no additional acute or long-term toxicity compared with chemoradiotherapy alone.

A recently reported RCT¹⁴⁸⁴ comparing brachytherapy versus brachytherapy and hyperthermia following priori chemoradiotherapy in patients with stage II-III cervical cancer failed to demonstrate any therapeutic benefit in terms of DFS or local control with the addition of hyperthermia.

In a single arm study^{1485,1486} including patients treated with thermochemoradiotherapy, 89.7% of patients achieved a complete response. A locoregional control was observed in 58.8% of patients while 69.1% of patients were surviving at the end of the study period (median follow-up: 81 months). A total of 33% of the patients experienced grade 3-4 acute toxicities in the form of leucopenia, fatigue, nausea, emesis and diarrhea but these did not result in withholding hyperthermia treatment.

LoE 2-

As part of a single arm study^{1487,1488}, a complete response was achieved in 78% of patients treated with thermoradiotherapy. At five years, pelvic tumour control, DSS, and incidence of grade 3-4 acute and late hyperthermia-related toxicity were 65%, 47%, 11%, and 12%, respectively.

Sreenivasa *et al.*¹⁴⁸⁹ evaluated preoperative chemoradiotherapy combined with hyperthermia in patients with nonresectable stage \geq IIB "bulky" cervical cancer. Preoperative thermochemoradiotherapy induced a response rate of 75% and enabled curative surgery in 62.5% of patients.

LoE 3

13.1.7 Adjuvant/consolidation chemotherapy

Two RCTs^{1267,1435,1490-1492} evaluating the effect of adjuvant chemotherapy after concurrent

LoE 1-

chemoradiotherapy on outcomes of women with LACC compared with concurrent chemoradiotherapy alone, were identified. In the first identified RCT¹²⁶⁷, the patients were randomized into four arms (conventional radiotherapy, conventional radiotherapy and adjuvant chemotherapy, conventional radiotherapy plus concurrent chemotherapy, conventional radiotherapy plus concurrent chemotherapy and adjuvant chemotherapy). Concurrent chemotherapy consisted of mitomycin C and 5-FU. Adjuvant chemotherapy consisted of 5-FU. There was no significant difference in survival when comparing radiotherapy alone with radiotherapy and adjuvant chemotherapy. There was also no significant difference in survival when comparing radiotherapy plus concurrent chemotherapy with conventional radiotherapy plus concurrent chemotherapy and adjuvant chemotherapy. Moreover, this RCT¹²⁶⁷ did not demonstrate that the addition of chemotherapy could decrease total failure rate or locoregional or distant failure after concurrent chemoradiotherapy. It should be noted that at the time of analysis, there were no increases in late side effects.

The second one^{1435,1490-1492} showed significant improvement in PFS and OS among those who received concurrent chemoradiotherapy plus adjuvant chemotherapy compared with those given concurrent chemoradiotherapy alone (HR = 0.68 (95 % CI = 0.49-0.95), p = 0.027 and HR = 0.68 (95% CI = 0.49-0.95), p = 0.022, respectively). Subsequent analyses¹⁴⁹² showed that benefit from adjuvant chemotherapy, PFS in particular, was greater in women with more advanced disease, larger tumour size and age younger than 55 years. Response rates and rates of local failure were similar. However, distant failure rate was lower in the study arm (8.1% versus 16.4%, p = 0.005). More women who had concurrent chemoradiotherapy plus adjuvant chemotherapy were hospitalised (30 versus 11, p = 0.003), had a greater number of grade 3-4 overall toxicities (87% versus 46%, p < 0.001), and/or received one or more blood transfusions (49.2% versus 27.5%, p < 0.001). It should be noted that chemotherapy used concurrently with radiotherapy included cisplatin plus gemcitabine in the study arm and only cisplatin in the control arm.

A systematic review¹⁴⁹³ was identified but is not described because it contains only the two RCTs^{1267,1435,1490-1492} mentioned above.

A part of another RCT¹⁴⁹⁴, incorporating adjuvant chemotherapy into chemoradiotherapy was associated with a significantly longer disease-free, cumulative survival and long-term local tumour control but it should be noted that NACT was given along with additional chemotherapy after concurrent chemoradiotherapy.

As the second identified RCT mentioned above, Choi *et al.*¹⁴⁹⁵ found that (1) the complete response rate was similar between the two groups and (2) the addition of the adjuvant chemotherapy was associated with an increased OS after a median follow-up period of 35 months without significant additional toxicities (92.7% versus 69.9%, p = 0.042). However, it should be noted that the difference in PFS did not reach statistical significance.

LoE 2-

Six other studies¹⁴⁹⁶⁻¹⁵⁰³ evaluating adjuvant chemotherapy after concurrent chemoradiotherapy were also identified. Corresponding response rates and survival are summarized in table 40.

LoE 3

A RCT¹⁵⁰⁴ comparing four versus six courses of adjuvant chemotherapy (cisplatin) after NACT plus radical surgery was identified. The two chemotherapy regimens showed similar results in terms of recurrence rate, OS and DFS, with a favorable toxicity profile in favour of the first one.

LoE 1-

13.2 Previous initiatives

Eleven previous initiatives^{419,422-425,529,531,1505-1510} presenting guidelines on the management of LACC were identified.

13.3 Development group comments

There was uniform agreement in the development group based on level 1 evidence (meta-analyses and phase III chemoradiotherapy trials) that combined chemoradiotherapy and brachytherapy is the method of choice for the management of stage T2b-T4a cervical cancer and also for stage T1b2/T2a2 with involved LNs on radiological staging (iN1). Therefore the management recommendation in the guidelines has become a grade A recommendation.

There was considerable discussion in the development group as to the management of stage T1b2/T2a2 with negative LNs on radiological staging (iN0), in particular in regard to the options of chemoradiotherapy and brachytherapy and of surgery. Finally, agreement was reached allocating chemoradiotherapy and brachytherapy to the “preferred treatment” whereas an “alternative option” was seen for radical surgery, in particular for patients with negative risk factors (tumor size, LVSI, stromal invasion) and in centers where high quality surgery is available in regard to parametrectomy and LN dissection. This statement has to be seen in comparison with the recommendations for the management of stage T1b1/T2a1 iN0 allocating radical surgery to the “preferred treatment” and whereas an “alternative option” was seen for radiotherapy, in particular in patients with risk factors (compare 10.3).

There was unconfined agreement in the development group that for management of patients with localized cervical cancer combination of radical surgery and postoperative external beam radiotherapy has to be avoided as - according to widespread clinical evidence - this combination mainly contributes to a significant increase in morbidity and has no evident impact on survival. Such combination occurs in a considerable proportion of patients with stage T1b1/T2a1 iN0 and stage T1b2/T2a2 iN0 because risk factors detected in these stages during radical surgery often lead to the addition of postoperative external beam radiotherapy (based on evidence from multiple clinical trials). Therefore the development group discussed in depth the necessity of upfront multidisciplinary communication on tumour extent and staging using MRI - within a multidisciplinary tumour board - in order to reduce the amount of patients undergoing combined radical surgery and postoperative external beam radiotherapy (compare staging guidelines and 10.3).

The discovery that cervical cancer cells were sensitive to chemotherapy led to the initiation of studies investigating the efficacy of NACT before surgery in patients with LACC over the past two decades. The potential advantage of NACT is to potentially decrease tumour volume, eliminate distant metastasis, to increase the tumour vascularization, reduce the number of hypoxic cells and to increase the possibility of obtaining a wider uninvolved resection margins, thereby avoiding adjuvant radiotherapy. On the opposite, the delay in surgery, the prolonged duration of treatment with potentially an accelerated repopulation of resistant cancer cells and the toxicity have been considered as disadvantages of NACT.

But up to now there are no RCTs comparing NACT plus surgery versus primary chemoradiotherapy which is considered the standard of care for locally advanced cervical cancer all over the world. Two recently concluded phase III trials ((EORTC 55994) will hopefully delineate the impact of NACT followed by radical surgery versus chemoradiotherapy in women with LACC.

Adjuvant chemotherapy may be beneficial because a significant proportion of patients experience disease progression after chemoradiotherapy. Although this is included in routine practice in some patients with cervical cancer at very high risk of recurrence, there are only limited data from controlled studies with small numbers of patients. Future large trials are therefore required to demonstrate its efficacy, toxicities and quality of life.

13.4 Guidelines

13.4.1 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 because of the significant increase in morbidity and no evident impact on survival.
- A** Definitive platinum-based chemoradiotherapy and brachytherapy are the preferred treatment (see Principles of radiotherapy).
- C** PALN dissection, at least up to inferior mesenteric artery, may be considered before chemoradiotherapy and brachytherapy. PLN dissection is not required.
- ✓ Radical surgery is an alternative option, in particular in patients without negative risk factors (combinations of tumor size, LVSI, and/or depth of stromal invasion). Quality of surgery, both parametrectomy and LN dissection, is, however, of key importance in the management of large tumors. Intraoperative assessment of LN status (frozen section) is recommended as the first step. If LN involvement is detected intraoperatively, including macrometastases or micrometastases, further PLN dissection and radical hysterectomy should be avoided, and patients should be referred for definitive chemoradiotherapy and brachytherapy. PALN dissection, at least up to inferior mesenteric artery, may be considered for staging purposes. If intraoperative LN assessment is negative or is not done, systematic PLN dissection should be performed. Type C2 radical hysterectomy is recommended.
- C** NACT followed by radical surgery is a controversial alternative. The benefit of tumor downsizing with regard to prognosis has not been proven.

13.4.2 Stage T1b2/T2a2 and involved lymph nodes on radiological staging

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

13.4.3 Stage T2b, T3a/b, T4a

- A** Definitive platinum-based chemoradiotherapy and brachytherapy are recommended (see Principles of radiotherapy).
- C** An additional radiation boost to the involved LNs should be applied (see Principles of radiotherapy).
- C** PALN dissection, at least up to inferior mesenteric artery, may be considered before treatment in patients with negative PALNs on imaging.
- ✓ Debulking of suspicious PLNs may be considered. Pelvic exenteration is an option in selected cases with stage T4 N0 M0 disease.

13.4.4 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.

Table 32. Original studies presenting survival and response rates data according to NACT regimens administered in patients with LACC

Author ^{reference}	Year	N	Drugs	Response	Survival (%)	
				rate (%)	PFS	OS
Abou-Taleb <i>et al.</i> ¹¹⁴⁵	2016	48	Irinotecan/nedaplatin	75	nr	nr
Shimada <i>et al.</i> ¹²⁰⁷	2016	52	Docetaxel/carboplatin	69	2-year: 67.9	2-year: 85.9
Yang <i>et al.</i> ¹¹⁴⁴	2016	49	Irinotecan/cisplatin	67.3	nr	3-year: 96
Yang <i>et al.</i> ¹¹⁴⁴	2016	58	Paclitaxel/cisplatin	75.7	nr	3-year: 89.5
Benedetti Panici <i>et al.</i> ¹¹⁸²	2015	22	Paclitaxel/cisplatin	52.6	nr	nr
Li <i>et al.</i> ¹¹⁸³	2015	72	Paclitaxel/cisplatin	86.1	nr	nr
Yang <i>et al.</i> ¹¹⁴⁸	2015	116	Paclitaxel/carboplatin	71.3	5-year: 86	5-year: 85
Angioli <i>et al.</i> ¹¹⁸⁴	2014	35	Carboplatin/paclitaxel	78.3	nr	nr
McCormack <i>et al.</i> ¹¹⁸⁵	2013	46	Paclitaxel/carboplatin	70	5-year: 68	5-year: 67
Singh <i>et al.</i> ¹¹⁸⁶	2013	28	Paclitaxel/carboplatin	67.8	nr	nr
Mousavia <i>et al.</i> ¹¹⁸⁷	2013	19	Paclitaxel/cisplatin	79	nr	nr
Ferrandina <i>et al.</i> ¹¹⁸⁸	2013	75	Paclitaxel/epirubicin/cisplatin	56.1	5-year: 51	5-year: 53
Shoji <i>et al.</i> ^{1155,a}	2013	18	Carboplatin/paclitaxel/docetaxel	78.3	5-year: 60	5-year: 68
Heijkoop <i>et al.</i> ¹¹⁸⁹	2012	43 ^b	Cisplatin/paclitaxel (N = 25) Cisplatin/etoposide (N = 8) Carboplatin/paclitaxel (N = 6) Carboplatin/5 fluorouracil (N = 1) Methotrexate/vinblastin/doxorubicin/cisplatin (N = 3)	83.7	5-year: 45	5-year: 55
Moioli <i>et al.</i> ¹¹⁹⁰	2012	14	Cisplatin/paclitaxel	85.7	nr	nr
Gong <i>et al.</i> ¹¹⁴⁷	2012	202	Cisplatin/bleomycin (or pingyangmycin) (N = 159) 5 fluorouracil/cisplatin (N = 12) 5 fluorouracil/cisplatin/ifosfamide/mesna (N = 11) Paclitaxel/cisplatin/carboplatin (N = 9) Cisplatin/vincristine/bleomycin (N = 6)	90	2-year: 93	2-year: 95.5
Yamaguchi <i>et al.</i> ^{1157,a}	2012	66	Nedaplatin/irinotecan	75.8	2-year: 73.8	2-year: 76
Yin <i>et al.</i> ¹¹⁵³	2012	104	Nedaplatin/paclitaxel	80.77%	nr	5-year: 93.89
Yin <i>et al.</i> ¹¹⁵³	2012	148	Paclitaxel/cisplatin	68.24%	nr	5-year: 81.54
Ren <i>et al.</i> ¹¹⁹¹	2011	52	Irinotecan/cisplatin	78.8	nr	nr
Pinheiro <i>et al.</i> ^{1158,a}	2011	27	Mitomycin-C/methotrexate/bleomycin	81	5-year: 59	5-year: 67
Manci <i>et al.</i> ¹¹⁹²	2011	46	Topotecan/cisplatin	89.5	2-year: 70	2-year: 81
Huang <i>et al.</i> ¹¹⁹³	2011	52	Docetaxel/cisplatin	86.5	2-year: 87.2	2-year: 94.4
Vizza <i>et al.</i> ^{1159,a}	2011	40	Cisplatin/paclitaxel/ifosfamide	82.5	2-year: 87.5	2-year: 90
McCaffrey <i>et al.</i> ⁷⁴⁶	2011	42	Cisplatin/bleomycin/methotrexate/5 fluorouracil	79%	nr	nr
Raspagliesi <i>et al.</i> ¹¹⁹⁴	2010	71	Irinotecan/cisplatin	73.2	nr	4-year: 87
Mori <i>et al.</i> ¹¹⁹⁵	2010	30	Paclitaxel/carboplatin	87	5-year: 79.2	5-year: 83.1
Mossa <i>et al.</i> ^{1160,a}	2010	153	Cisplatin/vincristine/bleomycin	nr	5-year: 65.4	5-year: 70.4
Kumar <i>et al.</i> ¹¹⁹⁶	2009	56	Paclitaxel/ifosfamide/cisplatin	87.5	nr	nr
Bae <i>et al.</i> ¹¹⁹⁷	2008	99	Cisplatin/etoposide	69.7	5-year: 60.5	5-year: 88.1
Benedetti Panici <i>et al.</i> ¹¹⁹⁸	2007	18	Paclitaxel/cisplatin	66.7	nr	5-year: 31.6
Eddy <i>et al.</i> ^{542,a}	2007	145	Cisplatin/vincristine	52	5-year: 71	5-year: 78
Kokawa <i>et al.</i> ^{1162,a}	2007	33	Mitomycin-C/irinotecan	85.7	5-year: 69	5-year: 72
Choi <i>et al.</i> ^{1164,a}	2006	94	Cisplatin/ 5 fluorouracil	66	5-year: 71	5-year: 76.4
Cai <i>et al.</i> ^{77,a}	2006	52	Cisplatin/ 5 fluorouracil	84.6	5-year: 72.7	5-year: 84.7
Behtash <i>et al.</i> ⁵⁴³	2006	22	Cisplatin/vincristine	nr	nr	5-year: 28
Termrungruanglert <i>et al.</i> ^{1165,a}	2005	27	Cisplatin/gemcitabine	88.9	2-year: 81	2-year: 88.9

^a study included in the systematic review published by Osman *et al.*¹¹⁵⁴ (2014), OS overall survival, nr not reported, PFS progression-free survival

Original studies presenting survival and response rates data according to NACT regimens administered in patients with LACC (continued)

Author ^{reference}	Year	N	Drugs	Response	Survival (%)	
				rate (%)	PFS	OS
Taneja <i>et al.</i> ^{1166,a}	2005	22	Cisplatin/bleomycin/vincristine	nr	5-year: 62	5-year: 69
Buda <i>et al.</i> ⁹⁵	2005	100	Ifosfamide/cisplatin	23	nr	nr
Buda <i>et al.</i> ⁹⁵	2005	89	Paclitaxel/ifosfamide/cisplatin	48	nr	nr
Motoyama <i>et al.</i> ¹¹⁹⁹	2004	23	Cisplatin/mitomycin C/peplomycin	87	5-year: 47	5-year: 74
Huang <i>et al.</i> ^{1177,a}	2003	102	Cisplatin/bleomycin/vincristine	nr	5-year: 65	5-year: 69
Napolitano <i>et al.</i> ^{541,a}	2003	106	Cisplatin/bleomycin/vincristine	nr	5-year: 71.7	5-year: 76.4
Kobayashi <i>et al.</i> ¹²⁰⁰	2003	34	Cisplatin/mitomycin C/bleomycin (N = 11) Cisplatin/doxorubicin/5 fluorouracil/mitomycin C (or cyclophosphamide) (N = 23)	82	nr	nr
Di Vagno <i>et al.</i> ¹²⁰¹	2003	58	Cisplatin/vinorelbine	85	nr	nr
D'Agostino <i>et al.</i> ^{1169,a}	2002	42	Cisplatin/epirubicin/paclitaxel	78.5	5-year: 85	5-year: 90
Benedetti Panici <i>et al.</i> ^{1140,a}	2002	152	Cisplatin/vincristine/bleomycin	nr	5-year: 56.5	5-year: 61
Duenas-Gonzalez <i>et al.</i> ^{1171,a}	2002	41	Cisplatin/gemcitabine	95	2-year: 65	2-year: 69
MacLeod <i>et al.</i> ^{1173,a}	2001	106	Cisplatin/vinblastine/bleomycin (N = 97) Cisplatin/epirubicin (N = 4) Etoposide/vincristine/cyclophosphamide/adriamycin (N = 5)	58.5	5-year: 54	5-year: 60
Costa <i>et al.</i> ^{1172,a}	2001	16	Cisplatin/epirubicine/etoposide/bleomycin	66.7	5-year: 67	5-year: 71
Hwang <i>et al.</i> ^{1168,a}	2001	80	Cisplatin/vinblastine/bleomycin	93.7	5-year: 78.7	5-year: 82
Lopez-Graniel <i>et al.</i> ¹²⁰⁸	2001	41	Cisplatin/gemcitabine	95	nr	2-year: 91
Chang <i>et al.</i> ^{1139,a}	2000	68	Cisplatin/vincristine/bleomycin	82.4	5-year: 68	5-year: 70
Etcheverry <i>et al.</i> ¹²⁰²	2000	47	Cisplatin/5 fluorouracil/ifosfamide/mesna	85	nr	nr
Yamakawa <i>et al.</i> ¹¹⁵¹	2000	26	Bleomycin/mitomycin C/cisplatin	73.1	nr	5-year: 80
Sugiyama <i>et al.</i> ¹⁵¹¹	1999	23	Cisplatin/irinotecan	78	nr	nr
Zanetta <i>et al.</i> ^{1175,a}	1998	32	Cisplatin/paclitaxel/ifosfamide	84.2	2-year: 76	2-year: 90
Sugiyama <i>et al.</i> ¹²⁰³	1998	48	Cisplatin (or carboplatin)/peplomycin (± doxorubicin)	77.1	nr	nr
Giardina <i>et al.</i> ¹²⁰⁴	1997	23	Cisplatin	85	nr	nr
Lai <i>et al.</i> ^{1205,1512}	1997	59	Cisplatin/vincristine/bleomycin	81.4	nr	5-year: 69.7
Toita <i>et al.</i> ¹²⁰⁹	1997	51	Cisplatin	47.6	nr	5-year: 47.1
Eddy <i>et al.</i> ¹²⁰⁶	1995	34	Cisplatin/vincristine	88	nr	nr

^a study included in the systematic review published by Osman *et al.*¹¹⁵⁴ (2014), OS overall survival, nr not reported, PFS progression-free survival

Table 33. Original data on the perioperative outcomes of laparoscopic or robotic radical hysterectomy after NACT or CCRT in patients with LACC

Author ^{reference}	Year	N	Previous treatment	Operative time (min)	Blood loss loss (ml)	Transfusion (N)	Conversion to laparotomy (N)	Removed PLNs (N)	Hospital stay (d)
Laparoscopic surgery									
Corrado <i>et al.</i> ¹²²⁹	2016	41	NACT	Median: 220	Median: 250	2	2	Median: 20	Median: 6
Cai <i>et al.</i> ¹²²²	2016	99	NACT	Median: 240	Median: 300	nr	0	nr	nr
Vizza <i>et al.</i> ⁶¹³	2015	25	NACT	Median: 188	Median: 220	2	0	Median: 21	Median: 6
Ghezzi <i>et al.</i> ⁵⁷⁷	2013	68	NACT	217	265	1	0	nr	nr
Vizza <i>et al.</i> ¹¹⁵⁹	2011	40	NACT	Median: 305	Median: 250	4	4	Median: 25	Median: 6
Favero <i>et al.</i> ¹²²¹	2014	33	CCRT	Mean: 104	Mean: 80	nr	0	nr	Mean: 1.7
Baffert <i>et al.</i> ¹²²³	2016	39	CCRT	Mean: 258	nr	0	3	nr	Mean: 5.7
Colombo <i>et al.</i> ¹²²⁴	2009	46	CCRT	Mean: 157	Median: 200	1	7	Mean: 11	Mean: 5
Robotic surgery									
Siesto <i>et al.</i> ¹⁵¹³	2016	32	NACT	Median: 264	Median: 100	3	0	Median: 28	Median: 4
Corrado <i>et al.</i> ¹²²⁹	2016	41	NACT	Median: 180	Median: 150	3	0	Median: 23	Median: 4
Minig <i>et al.</i> ¹²²⁶	2016	30	NACT	Mean: 307.8	Mean: 111	3	0	Mean: 22.8	Mean: 4.1
Vizza <i>et al.</i> ⁶¹³	2015	25	NACT	Median: 190	Median: 160	3	0	Median: 23	Median: 4
Vizza <i>et al.</i> ¹²²⁷	2014	60	NACT	Median: 225	Median: 150	6	0	Median: 23	Median: 4
Vitobello <i>et al.</i> ¹²²⁵	2013	18	NACT	Median: 260	Median: 100	0	0	Median: 26	Median: 4
Gallotta <i>et al.</i> ¹²²⁸	2017	40	CCRT	Median: 185	Median: 100	0	1	Median: 21	Median: 2

CCRT concurrent chemoradiotherapy, NACT neoadjuvant chemotherapy, nr not reported, PLNs pelvic lymph nodes

Table 34. Original studies of image-guided adaptive brachytherapy reporting outcomes according to GEC - ESTRO recommendations^{135,244}

Author ^{reference}	Year	N	Dose rate	Image guidance Modality	Median follow-up (months)	Local control rate (%)	OS (%)	Actuarial grade 3-4 Morbidity rate (%)
Ribeiro <i>et al.</i> ¹³⁶²	2016	154	PDR: 100%	MRI: 100%	37	95.5	nr	11
Sturdza <i>et al.</i> ¹³⁶³	2016	731	HDR: 58.7% PDR: 40.4% LDR: 1%	MRI: 80.9% CT: 19.1%	43	91	74	11
Lakosi <i>et al.</i> ¹³⁶¹	2015	85	PDR: 100%	MRI: 100%	36	94	81	nr
Castelnau-Marchand <i>et al.</i> ¹³⁶⁰	2015	225	PDR: 100%	MRI: 89.3% CT: 10.7%	38.8	86.4	76.1	6.6
Simpson <i>et al.</i> ¹³⁵⁹	2015	76	HDR: 100%	CT: 100%	10	94.2	75	2.2
Gill <i>et al.</i> ¹²⁸⁵	2015	128	HDR: 100%	MRI: 100%	24.4	91.6	87.7	0.9
Rijkmans <i>et al.</i> ¹³⁵⁸	2014	83	HDR: 100%	MRI: 86.7% CT: 13.3%	42.3	93	86	8.4
Kharofa <i>et al.</i> ¹³⁵⁷	2014	18	HDR: 100%	MRI: 100%	20	100	93	11.1
Tharavichitkul <i>et al.</i> ¹³⁵⁶	2013	17	HDR: 100%	CT: 100%	19	100	94.1	11.8
Lindegaard <i>et al.</i> ¹³⁵⁵	2013	140	PDR: 100%	MRI: 98% CT: 2%	36	91	79	7
Nomden <i>et al.</i> ¹³⁵⁴	2013	46	HDR: 10.9% PDR: 84.8% PDR + HDR: 4.3%	MRI: 100%	41	93	65	9.5
Mahantshetty <i>et al.</i> ¹³⁵³	2011	24	HDR: 100%	MRI: 100%	24	87.5	96	4.1
Potter <i>et al.</i> ¹²⁶⁰	2011	156	HDR: 100%	MRI: 100%	42	95	68	5.6

CT computed tomography, HDR high-dose rate, LDR low-dose rate, MRI magnetic resonance imaging, nr not reported, PDR pulsed-dose rate

Table 35. Pooled data published by the chemoradiotherapy for cervical cancer meta-analysis collaboration¹³⁷⁹ regarding the efficacy of chemoradiotherapy for patients with LACC

Parameter	CCRT versus radiotherapy
Planned chemotherapy type	
Platinum based	HR = 0.84 (95% CI = 0.72-0.98)
Non-platinum based	HR = 0.76 (95% CI = 0.62-0.94)
Planned radiotherapy dose	
> 45 Gy + brachytherapy	HR = 0.78 (95% CI = 0.68-0.89)
< 45 Gy + brachytherapy	HR = 0.93 (95% CI = 0.70-1.24)
Planned chemotherapy cycle length	
< 1 week	HR = 0.74 (95% CI = 0.60-0.92)
> 1 week	HR = 0.95 (95% CI = 0.72-1.25)
Planned cisplatin dose intensity	
< 25 mg/m ² /week	HR = 0.93 (95% CI = 0.70-1.24)
> 25 mg/m ² /week	HR = 0.76 (95% CI = 0.62-0.96)
Cisplatin regimen	
Single agent	HR = 0.75 (95% CI = 0.63-0.88)
Combination	HR = 0.86 (95% CI = 0.71-1.04)

CCRT concurrent chemoradiotherapy, CI confidence interval, HR hazard ratio

Table 36. Pooled data published by Green *et al.*¹⁴²² on the safety of chemoradiotherapy in patients with LACC

Outcome	CCRT versus radiotherapy
Acute haematological toxicity (<i>non-specified</i>)	
Grade 1-2	OR = 1.60 (95% CI = 1.26-2.03)
Grade 3-4	OR = 3.42 (95% CI = 2.59-4.51)
Acute haemoglobin toxicity	
Grade 1-2	OR = 1.71 (95% CI = 1.33-2.21)
Grade 3-4	OR = 3.66 (95% CI = 1.72-7.77)
Acute gastrointestinal toxicity	
Grade 1-2	OR = 1.33 (95% CI = 1.11-1.58)
Grade 3-4	OR = 1.98 (95% CI = 1.49-2.63)
Acute genitourinary toxicity	
Grade 1-2	OR = 1.14 (95% CI = 0.90-1.45)
Grade 3-4	OR = 1.08 (95% CI = 0.57-2.04)
Acute neurologic toxicity	
Grade 1-2	OR = 1.82 (95% CI = 1.16-2.85)
Grade 3-4	OR = 0.95 (95% CI = 0.29-3.08)
Acute white blood cell toxicity	
Grade 1-2	OR = 1.29 (95% CI = 1.08-1.53)
Grade 3-4	OR = 2.20 (95% CI = 1.72-2.80)
Acute platelet toxicity	
Grade 1-2	OR = 2.30 (95% CI = 1.81-2.94)
Grade 3-4	OR = 2.44 (95% CI = 1.18-5.06)
Acute nausea/vomiting	
Grade 1-2	OR = 3.09 (95% CI = 2.27-4.21)
Grade 3-4	OR = 4.09 (95% CI = 2.34-7.16)
Acute skin toxicity	
Grade 1-2	OR = 1.37 (95% CI = 1.05-1.78)
Grade 3-4	OR = 1.36 (95% CI = 0.74-2.50)

CCRT concurrent chemoradiotherapy, CI confidence interval, OR odd ratio

Table 37. Pooled data published by Fu *et al.*¹⁴³⁹ regarding the efficacy of different concurrent chemoradiotherapy regimens in the treatment of advanced cervical cancer

Author ^{reference}	Year	Treatment 1	Treatment 2	Pairwise meta-analysis
Overall response rate				
Ke <i>et al.</i> ¹³⁹⁹	2012	Radiotherapy	CCRT (cisplatin + docetaxel)	OR = 0.70 (95% CI = 0.33-1.55)
Sol <i>et al.</i> ¹⁴³⁶	2009	CCRT (cisplatin + 5 fluorouracil)	CCRT (cisplatin + paclitaxel)	OR = 1.00 (95% CI = 0.56-1.78)
Kim <i>et al.</i> ¹²⁶⁵	2008	CCRT (cisplatin)	CCRT (cisplatin + 5 fluorouracil)	OR = 1.00 (95% CI = 0.61-1.65)
Tseng <i>et al.</i> ¹³⁹⁷	1997	Radiotherapy	CCRT (cisplatin + vincristine + bleomycin)	OR = 0.84 (95% CI = 0.49-1.43)
Wong <i>et al.</i> ¹⁴²⁰	1989	Radiotherapy	CCRT (cisplatin)	OR = 0.84 (95% CI = 0.46-1.55)
5-year OS rate				
Zuliani <i>et al.</i> ¹²⁷³	2014	Radiotherapy	CCRT (cisplatin)	OR = 0.95 (95% CI = 0.70-1.30)
Garipagaoglu <i>et al.</i> ¹²⁶¹	2004	Radiotherapy	CCRT (cisplatin)	
Pearcey <i>et al.</i> ¹²⁶⁹	2002	Radiotherapy	CCRT (cisplatin)	
Kong <i>et al.</i> ¹⁴³⁴	2012	CCRT (cisplatin)	CCRT (cisplatin + 5 fluorouracil)	OR = 1.08 (95% CI = 0.73-1.58)
Geara <i>et al.</i> ¹⁴³⁰	2010	CCRT (cisplatin)	CCRT (paclitaxel)	OR = 1.41 (95% CI = 0.40-4.91)
Sol <i>et al.</i> ¹⁴³⁶	2009	CCRT (cisplatin + 5 fluorouracil)	CCRT (cisplatin + paclitaxel)	OR = 0.98 (95% CI = 0.54-1.81)
Rose <i>et al.</i> ¹⁴³⁷	2007	CCRT (cisplatin)	CCRT (hydroxyurea)	OR = 1.50 (95% CI = 1.04-2.16)
Rose <i>et al.</i> ¹⁴³⁷	2007	CCRT (cisplatin)	CCRT (cisplatin + 5 fluorouracil + hydroxyurea)	OR = 0.98 (95% CI = 0.70-1.38)
Rose <i>et al.</i> ¹⁴³⁷	2007	CCRT (hydroxyurea)	CCRT (cisplatin + 5 fluorouracil + hydroxyurea)	OR = 0.65 (95% CI = 0.45-0.94)
5-year DFS rate				
Zuliani <i>et al.</i> ¹²⁷³	2014	Radiotherapy	CCRT (cisplatin)	OR = 0.76 (95% CI = 0.48-1.19)
Garipagaoglu <i>et al.</i> ¹²⁶¹	2004	Radiotherapy	CCRT (cisplatin)	OR = 0.76 (95% CI = 0.48-1.19)
Sol <i>et al.</i> ¹⁴³⁶	2009	CCRT (cisplatin + 5 fluorouracil)	CCRT (cisplatin + paclitaxel)	OR = 0.84 (95% CI = 0.45-1.58)
Thomas <i>et al.</i> ¹³⁷¹	1998	Radiotherapy	CCRT (cisplatin + 5 fluorouracil)	OR = 0.68 (95% CI = 0.35-1.30)

CCRT concurrent chemoradiotherapy, CI confidence interval, DFS disease-free survival, OR odd ratio, OS overall survival

Table 38. Pooled data published by Fu *et al.*¹⁴³⁹ regarding the toxicity of different concurrent chemoradiotherapy regimens in the treatment of advanced cervical cancer

Author ^{reference}	Year	Treatment 1	Treatment 2	Pairwise meta-analysis
Anemia				
Wang <i>et al.</i> ¹⁴³²	2015	CCRT (cisplatin)	CCRT (cisplatin + gemcitabine)	OR = 0.33 (95% CI = 0.15-0.75)
Duenas-Gonzalez <i>et al.</i> ¹⁴³⁵	2011	CCRT (cisplatin)	CCRT (cisplatin + gemcitabine)	
Coronel <i>et al.</i> ¹⁴³¹	2013	CCRT (cisplatin)	CCRT (vinorelbine)	OR = 0.95 (95% CI = 0.06-16.29)
Kong <i>et al.</i> ¹⁴³⁴	2012	CCRT (cisplatin)	CCRT (cisplatin + 5 fluorouracil)	OR = 0.29 (95% CI = 0.07-1.15)
Sol <i>et al.</i> ¹⁴³⁶	2009	CCRT (cisplatin + 5 fluorouracil)	CCRT (cisplatin + paclitaxel)	OR = 1.07 (95% CI = 0.20-5.56)
Gallardo <i>et al.</i> ¹⁴³⁸	1999	CCRT (cisplatin)	CCRT (cisplatin + amifostine)	OR = 2.00 (95% CI = 0.16-25.75)
Leucopenia				
Wang <i>et al.</i> ¹⁴³²	2015	CCRT (cisplatin)	CCRT (cisplatin + gemcitabine)	OR = 0.73 (95% CI = 0.30-1.78)
Coronel <i>et al.</i> ¹⁴³¹	2013	CCRT (cisplatin)	CCRT (vinorelbine)	OR = 0.19 (95% CI = 0.01-4.22)
Nedovic <i>et al.</i> ¹⁴³³	2012	CCRT (cisplatin)	CCRT (cisplatin + 5 fluorouracil)	OR = 0.44 (95% CI = 0.20-0.99)
Kong <i>et al.</i> ¹⁴³⁴	2012	CCRT (cisplatin)	CCRT (cisplatin + 5 fluorouracil)	
Sol <i>et al.</i> ¹⁴³⁶	2009	CCRT (cisplatin + 5 fluorouracil)	CCRT (cisplatin + paclitaxel)	OR = 0.14 (95% CI = 0.05-0.39)
Whitney <i>et al.</i> ¹⁴¹⁸	1999	CCRT (hydroxyurea)	CCRT (cisplatin + 5 fluorouracil)	OR = 6.89 (95% CI = 2.87-16.54)
Tseng <i>et al.</i> ¹³⁹⁷	1997	Radiotherapy	CCRT (cisplatin + vincristine + bleomycin)	OR = 0.70 (95% CI = 0.26-1.87)
Wong <i>et al.</i> ¹⁴²⁰	1989	Radiotherapy	CCRT (cisplatin)	OR = 0.06 (95% CI = 0.01-0.47)
Neutropenia				
Wang <i>et al.</i> ¹⁴³²	2015	CCRT (cisplatin)	CCRT (cisplatin + gemcitabine)	OR = 0.15 (95% CI = 0.09-0.24)
Duenas-Gonzalez <i>et al.</i> ¹⁴³⁵	2011	CCRT (cisplatin)	CCRT (cisplatin + gemcitabine)	
Coronel <i>et al.</i> ¹⁴³¹	2013	CCRT (cisplatin)	CCRT (vinorelbine)	OR = 0.19 (95% CI = 0.01-4.22)
Gallardo <i>et al.</i> ¹⁴³⁸	1999	CCRT (cisplatin)	JCCRT (cisplatin + amifostine)	OR = 2.00 (95% CI = 0.30-13.51)
Thrombocytopenia				
Wang <i>et al.</i> ¹⁴³²	2015	CCRT (cisplatin)	CCRT (cisplatin + gemcitabine)	OR = 0.24 (95% CI = 0.09-0.64)
Duenas-Gonzalez <i>et al.</i> ¹⁴³⁵	2011	CCRT (cisplatin)	CCRT (cisplatin + gemcitabine)	
Coronel <i>et al.</i> ¹⁴³¹	2013	CCRT (cisplatin)	CCRT (vinorelbine)	OR = 9.50 (95% CI = 0.41-217.61)
Nedovic <i>et al.</i> ¹⁴³³	2012	CCRT (cisplatin)	CCRT (cisplatin + 5 fluorouracil)	OR = 0.33 (95% CI = 0.07-1.50)
Kong <i>et al.</i> ¹⁴³⁴	2012	CCRT (cisplatin)	CCRT (cisplatin + 5 fluorouracil)	

CCRT concurrent chemoradiotherapy, CI confidence interval, OR odd ratio

Pooled data published by Fu *et al.*¹⁴³⁹ regarding the toxicity of different concurrent chemoradiotherapy regimens in the treatment of advanced cervical cancer (continued)

Author ^{reference}	Year	Treatment 1	Treatment 2	Pairwise meta-analysis
Thrombocytopenia (continued)				
Sol <i>et al.</i> ¹⁴³⁶	2009	CCRT (cisplatin + 5 fluorouracil)	CCRT (cisplatin + paclitaxel)	OR = 0.36 (95% CI = 0.01-8.95)
Whitney <i>et al.</i> ¹⁴¹⁸	1999	CRT (hydroxyurea)	CCRT (cisplatin + 5 fluorouracil)	OR = 2.70 (95% CI = 0.11-66.67)
Gallardo <i>et al.</i> ¹⁴³⁸	1999	CCRT (cisplatin)	CCRT (cisplatin + amifostine)	OR = 1.00 (95% CI = 0.05-18.30)
Tseng <i>et al.</i> ¹³⁹⁷	1997	Radiotherapy	CCRT (cisplatin + vincristine + bleomycin)	OR = 0.48 (95% CI = 0.09-2.74)
Wong <i>et al.</i> ¹⁴²⁰	1989	Radiotherapy	CCRT (cisplatin)	OR = 0.77 (95% CI = 0.10-5.75)
Diarrhea				
Wang <i>et al.</i> ¹⁴³²	2015	CCRT (cisplatin)	CCRT (cisplatin + gemcitabine)	OR = 0.30 (95% CI = 0.16-0.54)
Duenas-Gonzalez <i>et al.</i> ¹⁴³⁵	2011	CCRT (cisplatin)	CCRT (cisplatin + gemcitabine)	
Coronel <i>et al.</i> ¹⁴³¹	2013	CCRT (cisplatin)	CCRT (vinorelbine)	OR = 0.95 (95% CI = 0.06-16.29)
Nedovic <i>et al.</i> ¹⁴³³	2012	CCRT (cisplatin)	CCRT (cisplatin + 5 fluorouracil)	OR = 0.32 (95% CI = 0.10-1.04)
Kong <i>et al.</i> ¹⁴³⁴	2012	CCRT (cisplatin)	CCRT (cisplatin + 5 fluorouracil)	
Geara <i>et al.</i> ¹⁴³⁰	2010	CCRT (cisplatin)	CCRT (paclitaxel)	OR = 0.70 (95% CI = 0.20-2.51)
Sol <i>et al.</i> ¹⁴³⁶	2009	CCRT (cisplatin + 5 fluorouracil)	CCRT (cisplatin + paclitaxel)	OR = 1.19 (95% CI = 0.44-3.18)
Tseng <i>et al.</i> ¹³⁹⁷	1997	Radiotherapy	CCRT (cisplatin + vincristine + bleomycin)	OR = 1.61 (95% CI = 0.55-4.71)
Wong <i>et al.</i> ¹⁴²⁰	1989	Radiotherapy	CCRT (cisplatin)	OR = 0.77 (95% CI = 0.10-5.75)
Nausea				
Wang <i>et al.</i> ¹⁴³²	2015	CCRT (cisplatin)	CCRT (cisplatin + gemcitabine)	OR = 0.57 (95% CI = 0.23-1.42)
Duenas-Gonzalez <i>et al.</i> ¹⁴³⁵	2011	CCRT (cisplatin)	CCRT (cisplatin + gemcitabine)	
Coronel <i>et al.</i> ¹⁴³¹	2013	CCRT (cisplatin)	CCRT (vinorelbine)	OR = 2.85 (95% CI = 0.11-74.34)
Kong <i>et al.</i> ¹⁴³⁴	2012	CCRT (cisplatin)	CCRT (cisplatin + 5 fluorouracil)	OR = 0.44 (95% CI = 0.20-0.97)
Sol <i>et al.</i> ¹⁴³⁶	2009	CCRT (cisplatin + 5 fluorouracil)	CCRT (cisplatin + paclitaxel)	OR = 2.29 (95% CI = 0.85-6.12)
Vomiting				
Wang <i>et al.</i> ¹⁴³²	2015	CCRT (cisplatin)	CCRT (cisplatin + gemcitabine)	OR = 0.36 (95% CI = 0.15-0.84)
Coronel <i>et al.</i> ¹⁴³¹	2013	CCRT (cisplatin)	CCRT (vinorelbine)	OR = 1.90 (95% CI = 0.16-22.72)
Kong <i>et al.</i> ¹⁴³⁴	2012	CCRT (cisplatin)	CCRT (cisplatin + 5 fluorouracil)	OR = 0.43 (95% CI = 0.16-1.15)
Sol <i>et al.</i> ¹⁴³⁶	2009	CCRT (cisplatin + 5 fluorouracil)	CCRT (cisplatin + paclitaxel)	OR = 7.46 (95% CI = 0.37-148.48)

CCRT concurrent chemoradiotherapy, CI confidence interval, OR odd ratio

Table 39. pooled data published by Zhang *et al*¹⁴⁴⁰ regarding the efficacy and toxicity of different concurrent single-agent chemotherapy and radiotherapy in the treatment of LACC

Outcome	Pooled data
Nedaplatin versus cisplatin	
OS	OR = 1.27 (95% CI = 0.73-2.22)
Response rate	OR = 3.71 (95% CI = 0.66-8.29)
Local recurrent rate	OR = 0.46 (95% CI = 0.20-1.06)
Distant metastasis rate	OR = 0.34 (95% CI = 0.12-1.01)
Nausea and vomiting	OR = 0.21 (95% CI = 0.13-0.36)
Leucopenia	OR = 0.84 (95% CI = 0.48-1.49)
Thrombocytopenia	OR = 1.84 (95% CI = 1.14-2.97)
Renal dysfunction	OR = 0.41 (95% CI = 0.23-0.74)
Liver dysfunction	OR = 0.40 (95% CI = 0.19-0.86)
Diarrhea	OR = 0.41 (95% CI = 0.19-0.91)
Docetaxel versus cisplatin	
OS	OR = 2.142 (95% CI = 0.789-5.820)
Response rate	OR = 1.928 (95% CI = 0.396-9.379)
Local recurrent rate	OR = 0.602 (95% CI = 0.163-2.227)
Distant metastasis rate	OR = 0.783 (95% CI = 0.164-3.741)
Myelosuppression	OR = 0.21 (95% CI = 0.09-0.47)
Gastrointestinal toxicity	OR = 0.19 (95% CI = 0.08-0.44)
Renal dysfunction	OR = 0.46 (95% CI = 0.10-2.20)
Paclitaxel versus cisplatin	
OS	OR = 0.653 (95% CI = 0.285-1.496)
Response rate	OR = 0.892 (95% CI = 0.290-2.743)
Local recurrent rate	OR = 0.850 (95% CI = 0.320-2.260)
Distant metastasis rate	OR = 1.008 (95% CI = 0.335-3.033)
Myelosuppression	OR = 0.37 (95% CI = 0.17-0.81)
Nausea and vomiting	OR = 0.40 (95% CI = 0.17-0.92)
Diarrhea	OR = 1.07 (95% CI = 0.46-2.50)
5 fluorouracil	
OS	OR = 0.705 (95% CI = 0.467-1.065)
Response rate	OR = 1.190 (95% CI = 0.242-5.844)
Local recurrent rate	OR = 0.873 (95% CI = 0.471-1.625)
Distant metastasis rate	OR = 1.858 (95% CI = 1.094-3.154)
Myelosuppression	OR = 0.24 (95% CI = 0.14-0.43)
Nausea and vomiting	OR = 0.70 (95% CI = 0.43-1.14)
Overall grade 3-4 toxicity	OR = 0.34 (95% CI = 0.22-0.52)
Paclitaxel liposome versus cisplatin	
Response rate	OR = 2.760 (95% CI = 0.277-27.483)
Vinorelbine versus cisplatin	
OS	OR = 1.607 (95% CI = 0.373-6.919)
Irinotecan versus cisplatin	
Response rate	OR = 1.625 (95% CI = 0.408-6.469)

OR odd ratio, OS overall survival

Table 40. Original studies presenting survival and response rates data according to adjuvant chemotherapy after chemoradiotherapy in patients with LACC

Author ^{reference}	Year	N	Adjuvant chemotherapy	Response rate (%)	Survival (%)
Jelavic <i>et al.</i> ^{1496,1497}	2015	118	Cisplatin/ifosfamide	100	8-year OS: 74.6
Angioli <i>et al.</i> ¹⁵⁰⁴	2015	95	Cisplatin (4 courses) Cisplatin (6 courses)		4-year OS: 84.21 4-year OS: 83.87 4-year DFS: 80 4-year DFS: 79.56
Duenas-Gonzalez <i>et al.</i> ^{1435,1490-1492}	2012	259	Cisplatin/gemcitabine	95.8	3-year OS: 78 3-year PFS: 74.4
Tang <i>et al.</i> ¹⁴⁹⁴	2012	440	Cisplatin/paclitaxel	100	DFS: 71.4
Kim <i>et al.</i> ¹⁴⁹⁸	2012	19	Paclitaxel/carboplatin	77.8	3-year OS : 90.9 3-year PFS : 62.7
Choi <i>et al.</i> ¹⁴⁹⁵	2011	39	Cisplatin/5 fluorouracil	92.3	OS: 92.7 PFS: 70.1
Zhang <i>et al.</i> ¹⁴⁹⁹	2010	34	Paclitaxel/nedaplatin	100	2-year OS:93 2-year PFS: 82
Domingo <i>et al.</i> ¹⁵⁰⁰	2009	60	Capecitabine	88	1-year OS: 95 1-year PFS: 86
Choi <i>et al.</i> ¹⁵⁰¹	2007	30	Cisplatin/5 fluorouracil	87	3-year OS: 91 3-year PFS: 83
Vrdoljak <i>et al.</i> ^{1502,1503}	2006	62	Cisplatin/ifosfamide	100	OS: 88.7 DFS: 88.7
Lorvidhaya <i>et al.</i> ¹²⁶⁷	2003	230	5 fluorouracil	nr	3-year OS: 79 5-year OS: 73.6 3-year PFS: 63 5-year PFS: 59.7

DFS disease-free survival, nr not reported, OS overall survival, PFS progression-free survival

14 Distant metastatic disease at presentation & recurrent disease

14.1 Summary of available scientific evidence

14.1.1 Neoadjuvant chemotherapy

A study published by Landoni *et al.*¹⁵¹⁴ investigated the role of preoperative chemotherapy prior to pelvic exenteration in patients presenting with poor prognostic factors such as tumour size larger than 5 cm, lateral pelvic extension of tumour and recurrence less than a year after initial treatment. The chemotherapy was prescribed as 3 cycles of paclitaxel, ifosfamide and cyclophosphamide. All patients had either pelvic radiotherapy or concurrent chemotherapy and pelvic radiotherapy prior to their exenteration or NACT followed by exenteration. Tumour shrinkage was observed in 61% of patients with a rate of uninvolved margins, complications, OS and DFS comparable to patients who initially presented with a better prognosis.

LoE 2-

As part of a small previous study¹⁵¹⁵, 17 patients with recurrent or persistent disease and no evidence of systemic disease, considered not be candidates for pelvic exenteration because of the extent of pelvic tumour, received courses of platinum-based chemotherapy for a maximum of 6 courses. Nine responses to chemotherapy were observed, including 4 pathological complete responses. At a median follow-up of 11 months, the median survival for the whole group was 11 months, 3 months for those who did not responded to chemotherapy and 32 months for those who underwent exenteration.

LoE 3

14.1.2 Pelvic exenteration

As part of a systematic review, Sardain *et al.*^{1516,1517} reported that 7-36% of exenterations performed with a curative intent after preoperative radiation, were found to have tumour present at the surgical resection margin after thorough pathological evaluation (ten studies¹⁵¹⁸⁻¹⁵²⁷). The authors described a rate of early postoperative complications (within 30 days of the surgery) ranging from 16 to 83% (eight studies^{1519,1520,1522-1527}). The most frequent complications were gastrointestinal fistulas with connections to the skin, urinary system or vagina, blood clots and leaking anastomoses. The rate of late postoperative complications (occurring more than 30 days after surgery) ranged from 36 to 61%, including notably enterocutaneous and vaginal fistulas, ureteral obstruction, bowel obstruction and pyelonephritis (five studies^{1519,1520,1522,1523,1527}). For patients where exenteration was the final therapeutic option, the 5-year OS rate varied from 24.7 to 64% (seven studies^{1518,1522-1524,1527-1529}). It should be noted that these results have to be interpreted with caution notably because there is a large heterogeneity among included studies with respect to the type of procedure that was performed and the type of cancer that is being investigated (cervical, endometrial, vulvar or ovarian). Studies rarely focused uniquely on cervical cancer and even more rarely on cervical cancer recurrences. Moreover, the authors rarely explained how and/or why anterior, posterior, total, supra or infralevator exenterations with or without perineal resection were chosen.

LoE 1-

A systematic review¹⁵³⁰ aiming to evaluate the effectiveness and safety of exenterative surgery versus other treatment modalities for women with recurrent gynaecological cancer was identified but is not described because the authors did not found studies meeting their inclusion criteria.

The outcomes of patients who underwent pelvic exenteration for recurrent and/or persistent cervical cancer, assessed by the nine other identified studies^{93,1531-1538}, are summarized in the table 41.

LoE 3

14.1.3 Intraoperative radiotherapy

Barney *et al.*¹⁵³⁹ assessed the outcomes of women with recurrent cervical cancer who received intraoperative radiation therapy (IORT) as a component of therapy. Of the 86 patients who met criteria for inclusion in this study, 73 had locally recurrent cervical cancer. To date, this represents the largest series evaluating the role of IORT in the treatment of recurrent cervical carcinoma. For this group of patients, the 3-year cumulative incidences of central relapse, locoregional relapse and distant relapse were 23, 39 and 44%, respectively. The authors noted an OS of 25% at 3 years.

LoE 2-

Mahe *et al.*^{1540,1541} reported their experience with IORT in 70 patients with recurrent cervical carcinoma. Mean follow-up after IORT was 11 months. Treatment modalities consisted of IORT alone in 40 out of 70 patients. Thirty of the women also received external-beam radiation therapy. Additional chemotherapy in the form of 5-FU and cisplatin or a cisplatin-containing regimen was given to 20 of the patients. With a mean follow-up of 15 months, the authors found median survival to be 11 months and local control to be 21%. At 3 years, the reported OS was 8%. Local and distant relapses were seen in 75% and 33% of the women, respectively (Table 42). It should be noted that (1) 40 of these patients did not receive external-beam radiation therapy and 37 of them had gross residual tumour and (2) the results documented may be a reflection of inclusion of all patients without selecting for tumour volume and site of recurrence.

The Mayo Clinic¹⁵⁴²⁻¹⁵⁴⁴ published data concerning a documented series that included 36 patients with recurrent cervical cancer. At five years, local relapse was seen in 50%, central relapse in 40%, and distant relapse in 58%. Median survival was 15 months. Five-year survival was 25%, with a reported DFS at 5 years of 21%.

LoE 3

As part of another small studies^{10,11}, 38 patients with recurrent cervical cancer were treated with both chemotherapy (cisplatin and 5-FU) and external-beam radiation therapy followed by surgery with or without IORT to high-risk areas for recurrence. Complete and quasi-complete response was documented pathologically in 74% of the surgical specimen. A partial response was noted in 26%. Median follow-up was 27 months, with an actuarial DFS of 80% and a locoregional control rate of 93.4%.

Stelzer *et al.*¹⁵⁴⁵ evaluated also the contribution of IORT in the management of recurrent cervical cancer. Twenty-two patients were treated with IORT for recurrent cervical cancers that were confined to the pelvis but were too extensive to be adequately treated by radical surgery alone. The 5-year disease-specific survival was 43%, with a median survival of 26 months. The 5-year local control was 48%, with a median time to local failure of 22 months. Comparison of the 15 patients who received previous pelvic radiation with those who did not showed no difference in disease-specific survival ($p = 0.46$). Likewise, there was no significant difference in disease-specific survival between those patients who underwent total pelvic exenteration and those who had less than exenterative surgery ($p = 0.18$).

In an older small study¹⁵⁴⁶, local relapse in the field of IORT was observed in 18% of patients. At 4 years, the authors reported an OS of 32%. Results of other identified studies¹⁵⁴⁷⁻¹⁵⁵⁸ are limited notably due to the very small number of patients evaluated, the heterogeneity in the IORT modality used (orthovoltage, high-dose rate brachytherapy, intraoperative electron beam radiation therapy), and/or the absence of data taking into account specifically patients with cervical cancer.

14.1.4 Chemotherapy

Single agent chemotherapy: Bonomi *et al.*¹⁵⁵⁹ conducted a RCT comparing 3 cisplatin single agent chemotherapy regimens (50 mg/m² every 21 days, 100 mg/m² every 21 days, 20 mg/m² for five consecutive days repeated every 21 days) in patients who were considered incurable with surgery or radiation therapy. The regimen consisting of a 100 mg/m² single dose produced a statistically significant higher response rate than the 50 mg/m² regimen (31.4% versus 20.7%, $p = 0.015$). However, higher dose produced no appreciable differences in complete remission rate, response duration, PDF or OS. In addition, the higher dose regimen was associated with greater myelosuppression and nephrotoxicity. As part of another RCT¹⁵⁶⁰, the 24-hour continuous infusion of cisplatin (50 mg/m²) offered an advantage over more rapid infusions (1 mg/min) in terms of reduced gastrointestinal toxicity in patients with advanced or recurrent cervical cancer no longer amenable to control with surgery or radiation therapy. There were significantly more patients who experienced no nausea and vomiting on the continuous infusion regimen (34% versus 18%, $p = 0.002$). However, no differences in terms of response to treatment or survival were observed between the two treatment regimens.

LoE 1-

McGuire *et al.*¹⁵⁶¹ studied two alternative platinum agents (carboplatin, iproplatin) in patients with advanced or recurrent cervical cancer. Both platinum analogs were given every 28 days with starting doses of 400 mg/m² for carboplatin (340 mg/m² if the patient underwent prior radiation) and 270 mg/m² for iproplatin (230 mg/m² if the patient underwent prior radiation). These doses were equivalent to cisplatin doses of 75 to 100 mg/m². Although this RCT was not designed to compare either analog with cisplatin, the authors noted that overall response rates and complete response rates for both carboplatin and iproplatin were not superior and possibly inferior to those previously reported for the parent, cisplatin.

Many other single agent chemotherapies¹⁵⁶²⁻¹⁶²¹ were also evaluated in patients with advanced, persistent, or recurrent cervical cancer during the last five decades. Corresponding response rates and survival are summarized in table 43. The identified studies evaluating single agents in patients who have progressed after first-line chemotherapy have reported rather modest efficacy. Overall, the responses were partial and had short duration, with a median OS not exceeding 16 months. It should be noted that higher response rates have been reported for lesions in previously unirradiated areas.

LoE 3

As part of a subgroup meta-analysis (ten studies^{1568,1622-1631}) Scatchard *et al.*¹⁶³² did not find statistically significant difference in response rate between women who received single-agent chemotherapy and those who received combination therapy (RR = 0.94 (95% CI = 0.57-1.55)). It should be noted that (1) there was a wide variety of chemotherapy agents and doses used across trials and (2) many of the trials were from an era when activity of agents was not known and so included inactive agents. However, the authors found that the proportion of women who responded to treatment was significantly lower in the group who received chemotherapy as a single agent than in the group who received combination chemotherapy (RR = 0.60 (95% CI = 0.44-0.81), 5 studies^{1622,1624,1628-1630,1633-1635}).

LoE 1-

Other subgroup analyses found that there was significantly less risk of severe neutropenia (four studies^{1622,1628-1630,1633-1635}, RR = 0.04 (95% CI = 0.02-0.12)), severe thrombocytopenia (three studies^{1622,1628-1630,1633-1635}, RR = 0.16 (95% CI = 0.05-0.48)), and severe infection (two studies^{1628,1629,1633-1635}, RR = 0.42 (95% CI = 0.22-0.81)) in women who received chemotherapy as a single agent than those who received combination chemotherapy. However, they did not find any statistically significant difference in the risk of severe renal dysfunction (three studies^{1628-1630,1633-1635}, RR = 0.81 (95% CI = 0.46-1.41)) and severe neuropathy (two studies^{1628,1629,1633-1635}, RR = 1.39 (95% CI = 0.45-4.33)) between women who received single-agent chemotherapy and those who received combination chemotherapy.

Combination chemotherapy: Scatchard *et al.*¹⁶³² did also not find any statistically significant difference in response rate between women who received platinum-based chemotherapy and those who received non-platinum chemotherapy (three studies^{1623,1633-1637}, RR = 1.33 (95% CI = 0.50-3.54)). The authors found that the proportion of women who responded to treatment was statistically significantly lower in the group who received platinum plus paclitaxel than in the group who received combination platinum-containing regimens that did not include paclitaxel (RR = 1.47 (95% CI = 1.01-2.15)). It should be noted that in one¹⁶³⁸ of the two studies^{1638,1639} included in this subgroup analysis a paclitaxel triplet was compared with a non-paclitaxel doublet. The authors performed another subgroup meta-analysis to compare in-radiotherapy-field versus out-of-field responses rates and found that the proportion of women who responded to treatment was significantly lower for recurrences within the pelvic field compared with disease outside of the pelvic radiotherapy field (six studies^{1561,1624,1628,1629,1640-1642}, RR = 0.62 (95% CI = 0.46-0.83)). Of note the majority of patients had not received prior chemotherapy (77.2%) with their radiotherapy. Where patients had had previous chemotherapy this was generally cisplatin as part of chemoradiotherapy, rather than chemotherapy alone with palliative intent.

Lorusso *et al.*¹⁶⁴³ performed a systematic review of the literature (seventeen studies^{1629,1638,1644-1658}) comparing cisplatin and carboplatin based chemotherapy for recurrent, persistent or metastatic cervical cancers. Objective response rates ranged from 33% to 67.9% for carboplatin studies and from 29.1% to 67% for cisplatin/paclitaxel studies, resulting in combined objective response rates of 48.5% (95% CI = 37.9-59.3) for carboplatin and 49.3% (95% CI = 41.1-57.5) for cisplatin-based chemotherapy. After exclusion of studies that used a triple combination the results were slightly better for carboplatin combinations (50.3% versus 43%) but it may be related to the greater number of patients exposed to chemotherapy in carboplatin-doublets arms (median: 55% versus 24%). The response rates for patients previously treated with cisplatin-based chemoradiation were 42.3% and 43.9% in carboplatin and cisplatin arms respectively ($p = 0.54$). In the same way, the response rates for patients not previously treated with cisplatin-based therapy were 68.3% and 59.1% for carboplatin-based chemotherapy and cisplatin-based chemotherapy, respectively ($p = 0.73$).

Twelve RCTs^{1629,1630,1633-1635,1640,1644,1659-1668} evaluating combination of drugs that have demonstrated single agent-activity in order to improve response rates and potentially survival were also identified.

Following the demonstration of activity of ifosfamide and mitolactol, a RCT¹⁶³⁰ evaluated cisplatin alone or with each of these two agents. Including patients not suitable for curative treatment with surgery and/or radiotherapy, the addition of ifosfamide to cisplatin led to higher response rate (31.1% versus 17.8%, $p = 0.004$) and PFS (4.6 months versus 3.2 months, $p = 0.003$) compared with cisplatin alone. The addition of mitolactol to cisplatin showed no significant improvement in these parameters compared with cisplatin alone. There was also no significant difference in OS between cisplatin and either of the combinations. Another identified RCT¹⁶⁴⁰ reported that the addition of bleomycin to the cisplatin/ifosfamide combination in this category of patients had no benefit in terms of response rate, PFS or OS compared with the cisplatin/ifosfamide regimen.

As shown by Bloss *et al.*¹⁶⁴⁰, the addition of bleomycin in the cisplatin/ifosfamide doublet did not improve outcome in terms of response rates, PFS and OS in patients with histologically confirmed, advanced (FIGO stage IVB), recurrent, or persistent squamous cell carcinoma of the cervix not suitable for curative treatment with surgery and/or radiotherapy.

Moore *et al.*¹⁶²⁹ assessed if adding paclitaxel to cisplatin improve outcomes of patients with

FIGO stage IVB, recurrent, or persistent cervical cancer compared with cisplatin alone. Objective responses occurred in 19% of patients receiving cisplatin alone versus 36% receiving cisplatin + paclitaxel ($p = 0.002$). The median PFS was 2.8 and 4.8 months, respectively, for cisplatin versus combined regimen ($p < 0.001$). However, no OS difference was noted.

In a RCT^{1633,1635} enrolling patients with FIGO stage IVB, recurrent, or persistent cervical cancer, topotecan plus cisplatin was compared with cisplatin monotherapy. Median OS was 9.5 months in the combined regimen, compared to 6.5 months with cisplatin alone. The unadjusted HR for OS between treatments arms was 0.76 (95% CI = 0.59-0.98, $p = 0.033$) favoring the combination arm. It should be noted that there were no statistically significant differences in quality of life up to 9 months after randomization despite more hematologic toxicity in the combination arm.

Long *et al.*¹⁶³⁴ undertook a RCT comparing methotrexate, vinblastine, doxorubicin, and cisplatin or topotecan plus cisplatin versus cisplatin alone in patients with FIGO stage IVB recurrent or persistent cervical cancer who were unsuitable candidates for curative treatment with surgery and/or radiotherapy. Patients receiving cisplatin plus topotecan had statistically superior outcomes to those receiving cisplatin alone, with median OS of 9.4 and 6.5 months ($p = 0.017$), median PFS of 4.6 and 2.9 months ($p = 0.014$), and response rates of 27% and 13% ($p = 0.004$), respectively. It should be noted that the third arm (methotrexate, vinblastine, doxorubicin, and cisplatin) was closed after treatment-related deaths occurred among 6% of patients.

Vermorken *et al.*¹⁶⁶⁷ found that the addition of bleomycin, vindesine, and mitomycin C to cisplatin had no impact in survival as compared to cisplatin alone in patients who had histologically confirmed advanced (FIGO stage IVB) or recurrent cervical cancer not suitable for curative treatment with surgery and/or radiotherapy even if the combination regimen induced a significantly higher response rate than cisplatin alone (42% versus 25%, $p = 0.006$).

Based on these results, Monk *et al.*^{1644,1659} undertook a RCT comparing four cisplatin-containing doublet combinations in FIGO stage IVB, recurrent, or persistent cervical cancer (paclitaxel/cisplatin, vinorelbine/cisplatin, gemcitabine/cisplatin, topotecan/cisplatin). The different combinations were not superior to paclitaxel/cisplatin regimen in terms of OS. However, trends in favor of paclitaxel/cisplatin regimen were noted in terms of OR, PFS and response rate. Patients receiving experimental doublets did not report significant differences in health-related quality of life, neuropathy, or pain from those who received the control doublet (paclitaxel/cisplatin). Patients receiving paclitaxel/cisplatin doublet tended to report worse neuropathy during treatment than patients who received other doublets (especially gemcitabine/cisplatin and topotecan/cisplatin), but the differences were not statistically significant. It should be noted that this result was potentially compromised by reduced power due to earlier termination of study.

Kitagawa *et al.*^{1660,1661} published results from a RCT evaluating the clinical benefits of carboplatin plus paclitaxel compared with cisplatin plus paclitaxel for patients with FIGO stage IVB, persistent or recurrent cervical cancer. After a median follow-up of 17.6 months, both PFS and OS were similar. It should be noted that the interim analysis demonstrated that the substitution of carboplatin for cisplatin did not result in inferior outcomes. Observed toxicities were similar in severity and frequency based on previous experiences with these compounds. In a secondary analysis of patients that had not received prior platinum, the cisplatin/paclitaxel doublet appeared to be superior to carboplatin/paclitaxel with a median OS of 23.2 versus 13.0 months (HR = 1.57 (95% CI = 1.06-2.32)).

Using a 2-by-2 factorial design, Tewari *et al.*^{1662,1663} randomly assigned patients with recurrent,

persistent, or metastatic cervical cancer to chemotherapy (cisplatin plus paclitaxel or topotecan plus paclitaxel) with or without bevacizumab. With the data for the two chemotherapy regimens combined, the addition of bevacizumab to chemotherapy was associated with an increased OS (HR = 0.71 (98% CI = 0.54-0.95), $p = 0.004$), an increased PFS (HR = 0.67 (95% CI = 0.54-0.82), $p = 0.002$), and higher response rates (48% versus 36%, relative probability of a response: 1.35 (95% CI = 1.08-1.68), $p = 0.008$). Treatment with cisplatin/paclitaxel/bevacizumab, as compared with cisplatin/paclitaxel alone, was associated with a HR for death of 0.68 (95% CI = 0.48-0.97, $p = 0.04$). The response rates were 50% and 45%, respectively ($p = 0.51$). Topotecan/paclitaxel/bevacizumab, as compared with topotecan/paclitaxel alone, was associated with a HR for death of 0.74 (95% CI = 0.53-1.05, $p = 0.09$). The response rates were 47% and 27%, respectively ($p = 0.002$). It should be noted that as compared with cisplatin/paclitaxel (either with or without bevacizumab) topotecan/paclitaxel was associated with (1) a significantly higher risk of progression (HR = 1.39 (95% CI = 1.09-1.77)) and (2) a non significant risk of death (HR = 1.20 (99% CI = 0.82-1.76)). There was also no significant difference in mortality between the chemotherapy regimens in the subgroup of patients with previous exposure to platinum (HR = 1.18 (95% CI = 0.84-1.65)) and in the subgroup with no previous exposure to platinum (HR = 1.35 (95% CI = 0.68-2.69)). In terms of quality of life, FACT-Cx-TOI and Brief pain inventory scores indicated that the addition of bevacizumab did not adversely affect health-related quality of life. It should also be noted that hypertension of grade 2 or higher was significantly more common with bevacizumab containing regimens than with regimens that did not contain the anti-angiogenic drug (25% versus 2%, $p < 0.001$), but no patients discontinued bevacizumab because of hypertension. Gastrointestinal or genitourinary fistulas of grade 3 or higher were significantly increased with the bevacizumab-containing regimens (6% versus 0%, $p = 0.002$), as were thromboembolic events of grade 3 or higher (8% versus 1%, $p = 0.001$).

As part of another RCT, Symonds *et al.*¹⁶⁶⁴ assessed the effect of the addition of cediranib to carboplatin and paclitaxel chemotherapy in patients with metastatic carcinoma or who subsequently developed metastatic disease or local pelvic recurrence after radical treatment that was not amenable to exenterative surgery. It should be noted that the trial closed prematurely owing to withdrawal of drug supply. After a median follow-up of 24.2 months, median PFS was longer in the cediranib group (8.1 months) than in the placebo group (6.7 months) with a HR of 0.58 (80% CI = 0.40-0.85, $p = 0.032$). Median OS did not differ significantly between the two treatment groups. The authors suggested that the effect of cediranib on OS might depend on disease site. Patients with extra-pelvic metastatic disease only had derive a greater benefit compared to those with local relapse (with or without metastatic disease). The proportion of patients with an overall response in the cediranib group was 64% compared with 45% in the placebo group. Using the EORTC QLQ-C30, the authors reported a significantly worse quality of life associated with diarrhoea in the cediranib group ($p = 0.030$). No other scales derived from the EORTC QLQ-C30 or EORTC QLQX24 questionnaires had significant differences between the study groups.

Monk *et al.*^{1665,1666} reported on a head-to-head RCT comparing an oral multitargeted antivasculature agent (pazopanib) with an oral dual anti-EGFR and anti-HER2/neu tyrosine kinase inhibitor (lapatinib) among women with advanced and recurrent cervical cancer. At the time of interim analysis, Pazopanib improved PFS (HR = 0.66 (95% CI = 0.48-0.91), $p = 0.013$) and OS (HR = 0.67 (95% CI = 0.46-0.99), $p = 0.045$). It should be noted that (1) response rates were 9% and 5% for pazopanib and lapatinib, respectively, and (2) the final analysis¹⁶⁶⁶ confirmed the improvement in PFS with pazopanib compared with lapatinib but the improvement in OS lost its statistical significance (HR = 0.96 (95% CI = 0.71-1.30), $p = 0.407$).

Including women with histologically confirmed, advanced (FIGO stage IVB) recurrent or

persistent carcinoma of the uterine cervix who were unsuitable candidates for curative treatment with surgery and/or radiotherapy, Coronel *et al.*¹⁶⁶⁸ found a significant advantage in PFS (10 months versus 6 months, $p = 0.0384$) for epigenetic therapy with hydralazine valproate over a combination chemotherapy (cisplatin plus topotecan). No significant differences in terms of response to treatment or incidence of grades 3-4 toxicity was described between the two treatment arms.

Forty-one small studies^{1511,1669-1708} not included in the systematic reviews^{1632,1643} mentioned above, and evaluating combinations of drugs that have demonstrated single-agent activity were also identified. Corresponding response rates and survival are summarized in table 44 and table 45.

LoE 3

14.1.5 (chemo)radiotherapy

As part of a small study, Marnitz *et al.*¹⁷⁰⁹ evaluated the use of extended-field chemoradiation with concomitant chemotherapy in patients with histologically confirmed para-aortic metastases after laparoscopic para-aortic and pelvic lymphadenectomy. In all, 93% of the patients underwent intensity-modulated radiotherapy-based treatment. All patients underwent brachytherapy based on MRI planning encompassing the residual tumour at the time of brachytherapy planning and received cisplatin-based chemotherapy, except for five patients (11%) who received carboplatin and one patient who received radiation only (2%). There was no grade 4 or 5 acute radiation toxicity. In all, 11% of the patients had grade 3 gastrointestinal late toxicities, and 19% of the patients had grade 3 genitourinary late toxicities. Para-aortic control rate was 98%. The estimated distant metastases-free survival rates were 63.8 and 34% after 2 and 5 years and correspond to disease-free survival rates of 61.4 and 29.1% after 2 and 5 years, respectively. The 2 and 5 years OS rates were 68.4% and 54.1%, respectively.

LoE 3

In a study published by Jeon *et al.*¹⁷¹⁰, 22 cervical cancer patients with LN recurrence who had previously undergone radical hysterectomy and PLN dissection were treated with salvage radiotherapy with or without chemotherapy. Various chemotherapy regimens were used (5-FU/cisplatin, paclitaxel/carboplatin). Treatment failure after salvage radiotherapy occurred in 63.6% of patients. A significant longer PFS was observed for patients treated with concurrent chemotherapy (64.8% versus 8.3%, $p = 0.01$).

Ng *et al.*¹⁷¹¹ reviewed the outcomes of extended field radiotherapy and concurrent chemotherapy with extended field radiotherapy in patients with positive PALN at diagnosis. Patients were treated with a combination of EBRT and intracavitary brachytherapy. Concurrent chemotherapy consisted of cisplatin. The 5-year OS were 40% for patients who underwent concurrent chemotherapy and extended field radiotherapy as compared to 18% for patients who had extended field radiotherapy alone, with median survival of 29 months and 13 months, respectively. The 5-year PFS for patients who underwent concurrent chemotherapy and extended field radiotherapy was 32% and 18% for those who had extended field radiotherapy alone. Acute toxicities were observed in 69.7% of patients who underwent extended field radiotherapy alone and 89.5% who underwent concurrent chemotherapy and extended field radiotherapy.

Kim *et al.*¹⁷¹² aimed to determine whether CCRT is efficient for improving prognosis compared to chemotherapy in patients with FIGO stage IVB cervical cancer who have distant lymphatic metastasis. Radiation therapy consisted of external-beam radiotherapy to the whole pelvis and intra-cavitary irradiation. Depending on the decision by radiation oncologists, additional radiation was applied to the parametrium, PALNs, and supraclavicular LNs. Chemotherapeutic regimens consisted of paclitaxel/carboplatin, 5-FU/cisplatin, cisplatin or carboplatin. Although

no difference was observed in the overall response rate (80% versus 50%, $p = 0.21$), the complete response rate was higher in patients treated with CCRT (60% versus 0%, $p < 0.01$). It should be noted that chemotherapy using paclitaxel/carboplatin was administered more frequently in patients who received CCRT than in those who received systemic chemotherapy (70% versus 28.6%, $p = 0.04$). Grade 3 or 4 leucopenia was more common in patients treated with CCRT (24.4% versus 9.1%, $p = 0.03$), whereas grade 3 or 4 neutropenia was more frequent in those treated with systemic chemotherapy (28.4% versus 11.1%, $p = 0.03$). However, no differences in grade 3 or 4 anemia and thrombocytopenia were observed between the two treatments. Concurrent chemotherapy was favorable prognostic factor for the improvement of PFS (HR = 0.12 (95% CI = 0.03-0.61), $p = 0.01$) and OS (HR = 0.15 (95% CI = 0.02-0.90), $p = 0.04$). It should be noted that no differences in the site and pattern of disease recurrence were observed between the two treatments.

Another identified study¹⁷¹³ evaluated the efficacy of CCRT with curative intent in patients with FIGO stage IVB cervical cancer initially presenting with para-aortic and left supraclavicular LN metastases (groupe I) and compared these findings with those in patients with PALN without left supraclavicular LN metastases who received extended-field CCRT (group II). All patients were prescribed external beam radiation therapy, high-dose rate brachytherapy and platinum-based chemotherapy (cisplatin, 5-FU/cisplatin, paclitaxel/cisplatin, or paclitaxel/carboplatin). The authors found that 52% of patients in group I and 78% of patients in group II achieved overall complete response ($p < 0.01$). The 3-year OS rates were similar for patients who achieved overall complete response in both groups (68% versus 76%, $p = 0.98$). Group II had significantly better 3-year local recurrence-free survival (53% versus 70%, $p = 0.03$) and distant metastasis-free survival (41% versus 73%, $p < 0.01$) rates than group I. The 3-year DFS rate was significantly higher in group II than in group I (33% versus 57%, $p < 0.01$), but the difference in 3-year OS rate did not reach statistical significance (49% versus 69%, $p = 0.24$).

In a study¹⁷¹⁴ evaluating the role of paclitaxel and cisplatin chemotherapy concurrent with extended-field irradiation in women with cervical cancer metastatic to the PALNs, there were 27 patients evaluable for survival, of which fifteen were alive (56%) after a median follow-up of 46 months.

Grigsby *et al.*¹⁷¹⁵ evaluated outcomes in 36 patients initially treated with a radical hysterectomy and LN dissection who developed a pelvic recurrence and were subsequently treated with irradiation (pelvic irradiation and brachytherapy). Ten patients developed recurrent disease after irradiation. The sites of failure in these patients were pelvis only in two, pelvis and distant metastases in five, and distant metastases only in three. Severe complications occurred in 11% of the patients. In this study, pelvic irradiation and brachytherapy resulted in a 5-year OS of 74%.

As part of a study evaluating the efficacy of radiation therapy in patients treated for pelvic recurrence after hysterectomy, Ijaz *et al.*¹⁷¹⁶ reported a 5-year OS rate of 33% for all 50 enrolled patients, 39% for the patients treated with curative intent, and 25% for patients with isolated sidewall recurrences treated with curative intent. Only 3 patients had major, late, treatment complications. It should be noted that chemoradiation was used in 20% of patients.

14.2 Previous initiatives

Eight previous initiatives^{419,422-426,529,531,1717} presenting guidelines on the management of primary metastatic disease and/or recurrent disease were identified.

14.3 Development group comments

Many of the trials in advanced and metastatic disease were undertaken prior to the adoption of concomitant chemotherapy into radiotherapy protocols and therefore the response rates to single agent cisplatin may differ according to whether patients received prior chemoradiotherapy or not. Furthermore, there was considerable heterogeneity between the trials precluding meaningful analysis. Many of the drugs used in the older combinations (doublet/triplet) are more toxic than the current recommended regimens. Widespread use of the platinum/taxane combination in other gynaecological cancers means that there is considerable experience in both recognising and managing the associated toxicities. The outcome of curative treatment for recurrent disease depends on type of recurrence (central/lateral), primary treatment received, patient symptoms and performance, thorough workup and a multidisciplinary approach.

Curative treatments especially surgical should be carried out in a super-specialty hospital and high volume centers for optimal oncological outcome and complications. In patients with central recurrence after primary surgery, definitive chemoradiotherapy including brachytherapy is offered. Although there are no RCTs reported in the literature, the understanding is that the recurrent tumours are still relatively radio-sensitive and achieve good response rates and outcome. Also, brachytherapy allows for radiation dose escalation and improves the therapeutic ratio.

Extended pelvic surgery in highly selected patients has been reported. Mono-institutional series have been reported for surgery, however, these series report a very high margin positivity rates and severe post operative complications. To improve the surgical margin positivity rates, preoperative radiotherapy or chemotherapy has been tried. Although the response rates were better, the oncological outcomes still remain dismal. Moreover, the early and late postoperative severe complications were very high.

Intraoperative radiotherapy was also attempted in small mono-institutional series with limited success. Exenterative surgeries when performed result in optimal outcome. However, the severe complication rates still remain a concern. Hence, these should be restricted to a highly specialized and high volume centers. There are limited series reported on reirradiation for local recurrences after definitive radiation therapy or postoperative radiation scenarios. This is increasingly being explored in modern radiation era with possibility of reducing doses to critical organs and achieving reasonably adequate doses to the recurrent gross disease.

Palliative care clinics and holistic approach plays a vital role in patients deemed for palliative treatment only. The role of specialist palliative care physicians (where available) in contributing to the overall management of the patient with recurrent and metastatic disease must be emphasized. Their involvement alongside the oncologist can contribute to overall excellent care and even enhance the potential benefits of radiotherapy /chemotherapy in this setting. The evidence for palliative radiotherapy schedules for effective palliation for pain and bleeding is robust and may not be specific for metastatic disease from cervical cancer.

14.4 Guidelines

14.4.1 Distant metastatic disease at presentation



Patients with distant metastatic disease at presentation should have a full diagnostic workup (see Staging) to assess extent of disease, suitability for active treatment, and treatment modality including best supportive care.



In medically fit patients with widespread distant metastatic disease at presentation (visceral +/- nodal), combination chemotherapy is recommended. Carboplatin/paclitaxel and 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 PALN region, should be treated with curative intent with definitive extended field chemoradiotherapy including brachytherapy. Treatment algorithm may also include surgical debulking of enlarged LN and additional chemotherapy.

✓ Patients with supraclavicular LN as the 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 LN, or LVSI-positive tumors.

✓ The role of radiotherapy in palliating symptoms such as bleeding and pain must be considered especially in radiotherapy naive patients.

14.4.2 Recurrent disease

14.4.2.1 *Curative intent treatment*

✓ Treatment of recurrent disease with curative intent requires centralization and involvement of a broad multidisciplinary team including gynecologic oncologist, radiation oncologist, radiologist, pathologist, medical oncologist, urologist, and plastic surgeon. A structured program for multidisciplinary diagnostic workup, treatment, and follow-up must be present in centers responsible for the treatment.

✓ Each center 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 specialized units.

✓ Participation in clinical trials is encouraged to improve the clinical evidence for the effect of curative treatment of recurrent disease.

14.4.2.1.1 Diagnostic workup

✓ The aim of the diagnostic workup is to exclude distant metastases and locoregional tumor 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 counseled regarding not only treatment options but also the involved risks and consequences.

14.4.2.1.2 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 (ie, < 5-mm thickness) in the vagina may be treated using a vaginal cylinder, ovoids, or mold, whereas other lesions usually require combined intracavitary-interstitial techniques.

14.4.2.1.3 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 tumor does not invade extensively into the pelvic sidewall.

D Combined operative-radiotherapy procedures using intraoperative radiotherapy or brachytherapy are 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 is an emerging option.

14.4.2.1.4 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 sidewall and extrapelvic nodes.

✓ Laterally extended endopelvic resection may be considered for a recurrence that extends close to or involves the pelvic sidewall.

✓ 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 specialized centers.

14.4.2.1.5 Role of chemotherapy

✓ If further surgery or radiotherapy is considered, no more than 2 to 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.

14.4.2.1.6 Nodal and oligometastatic recurrences

✓ Localized para-aortic, mediastinal, and/or periclavicular recurrences above previously irradiated fields may be treated by radical EBRT if possible in combination with concomitant chemotherapy. It is recommended to electively irradiate the immediate regional nodal stations below and upstream.

✓ 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.

14.4.2.2 *Palliative treatment*



Recommendations for palliative treatment should be made only after a thorough review of the case by a specialist multidisciplinary team and taking into account the performance status, comorbidities, 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, neurosurgical intervention or short-course fractionated radiotherapy schedule should be considered.



Surgical interventions including diversion stoma and/or stenting should be considered as appropriate, for example, in case of obstructive symptomatic disease.

Table 41. Original studies presenting data in oncologic outcomes in patients treated with pelvic exenteration

Author ^{reference}	Year	N	Preop	Surgeries (%)		Recurrence before	Types of	Positive surgical	Complications (%)		Perioperative	Follow-up	Survival
			RT (%)	cur.	pal.	exenteration (months)		margins (%)	Early	Late	death (%)		
Capilna <i>et al.</i> ¹⁵³²	2015	Cervix: N = 9 Other: N = 6	nr	nr	nr	nr	Total: N = 6 Anterior: N = 4 Posterior: N = 5	nr	40	nr	13	nr	OS: 53
Moreno-Palacios <i>et al.</i> ¹⁵³⁸	2015	Cervix: N = 3 Other: N = 7	50	nr	nr	Average: 43.4	Total: 80 Anterior: 10 Posterior: 10	nr	80	80	0	Median: 14	OS: 60
Tanaka <i>et al.</i> ^{1525,*}	2014	Cervix: N = 12	100	100	0	nr	Total: 25 Anterior: 67 Posterior: 8	33	83	nr	0	Median: 22	nr
Chiantera <i>et al.</i> ^{1526,*}	2014	Cervix: N = 177 Other: N = 53	70.3	97	3	Median: 14	Total: 57 Anterior: 29.6 Posterior: 13.5	27.8	21.3	nr	3	Median: 68	nr
Chiantera <i>et al.</i> ¹⁵³⁴	2014	Cervix: N = 167	nr	nr	nr	nr	Total: 61.1 Anterior: 28.1 Posterior: 10.8	27.5	nr	nr	nr	Median: 68	5-year OS: 38
Sardain <i>et al.</i> ¹⁵³⁷	2014	Cervix: N = 13 Other: N = 3	nr	100	0	nr	Total: 68.75 Anterior: 12.5 Posterior: 18.75	0	75	68.75	0	Median: 11.5	5-year OS: 34.1
Jager <i>et al.</i> ¹⁵³⁵	2013	Cervix: N = 10 Other: N = 18	71	96	4	nr	Total: 39 Anterior: 7 Posterior: 54	18	100	79	0	Median: 27	5-year OS: 70
Kaur <i>et al.</i> ^{1527,*}	2012	Cervix: N = 18 Other: N = 18	89	100	0	Median: 34.8	Total: 88 Anterior: 12	16	58	50	2	Median: 78	5-year OS: 38
Baiocchi <i>et al.</i> ^{1522,*}	2012	Cervix: N = 73 Other: N = 34	nr	100	0	Median: 18.8	Total: 52.3 Anterior: 29.3 Posterior: 9.3	7.9	53.3	44.8	12	Median: 23.7	5-year OS: 24.7
Yoo <i>et al.</i> ^{1523,*}	2012	Cervix: N = 61	98	100	0	Median: 34.1	Total: 69 Anterior: 28 Posterior: 3	14.7	16	36	0	Median: 22	5-year OS: 56
Schmidt <i>et al.</i> ^{1524,*}	2012	Cervix: N = 282	73.5	50	50	Median: 18	Total: 93 Anterior: 5 Posterior: 2	36	51	nr	5	Median: 17	5-year OS: 64

* study included in the systematic review published by Sardain *et al.*^{1516,1517} (2015), cur. curative, nr not reported, OS overall survival, pal. palliative, Preop RT preoperative radiation therapy

Original studies presenting data in oncologic outcomes in patients treated with pelvic exenteration (continued)

Author ^{reference}	Year	N	Preop	Surgeries (%)		Recurrence before	Types of	Positive surgical	Complications (%)		Perioperative	Follow-up	Survival
			RT (%)	cur.	pal.	exenteration (months)	exenteration (%)	margins (%)	Early	Late	death (%)	(months)	(%)
Benn <i>et al.</i> ^{1520,*}	2011	Cervix: N = 40 Other: N = 14	87	96	4	Median: 32	Total: 67 Anterior: 25 Posterior: 10	13	50	61	0	Median: 12.5	nr
McLean <i>et al.</i> ^{1521,*}	2011	Cervix: N = 29 Other: N = 15	100	100	0	Average: 74	Total: 77 Anterior: 11.5 Posterior: 11.5	7	nr	nr	2	nr	nr
Jurado <i>et al.</i> ¹⁵³⁶	2010	Cervix: N = 48	100	nr	nr	Average: 16	nr	56.3	nr	nr	nr	Median: 114.6	10-year DSS: 20.5
Maggioni <i>et al.</i> ^{1519,*}	2009	Cervix: N = 62 Other: N = 43	97	97	3	Median: 16.7	Total: 45 Anterior: 49 Posterior: 6	7	44.8	48.5	0	Median: 22.3	OS: 52
Spahn <i>et al.</i> ¹⁵³¹	2010	Cervix: N = 41 Other: N = 2	51	nr	nr	Median: 16	Total: 14 Anterior: 86	21	51	35	0	Median: 30.5	5-year DSS: 36.5
Park <i>et al.</i> ⁹³	2007	Cervix: N = 33 Other: N = 11	86.4	nr	nr	nr	Total: 68.2 Anterior: 27.3 Posterior: 4.5	16	nr	nr	0	Median: 24	5-year OS: 54
Golberg <i>et al.</i> ^{1528,*}	2006	Cervix: N = 97 Other: N = 8	95	95	0	nr	Total: 100	nr	nr	nr	0.9	nr	5-year OS: 48
Teran-Porcayo <i>et al.</i> ¹⁵³³	2006	Cervix: N = 42	100	100	0	Average: 8.5	Total: 47.6 Anterior: 52.4	6.6	9.5	14.3	4.8	Average: 56.3	5-year OS: 65.8
Berek <i>et al.</i> ^{1518,*}	2005	Cervix: N = 53 Other: N = 22	nr	100	0	Average: 45.5	Total: 61 Anterior: 31 Posterior: 8	12	nr	nr	4	Median: 50	5-year OS: 54 3-year OS : 57
Shingleton <i>et al.</i> ^{1529,*}	1989	Cervix: N = 143	nr	nr	nr	nr	Total: 54.5 Anterior: 44.1 Posterior: 1.4	nr	nr	nr	6.3	nr	5-year OS: 50

* study included in the systematic review published by Sardain *et al.*^{1516,1517} (2015), cur. curative, DSS disease-specific survival, nr not reported, OS overall survival, pal. palliative, Preop RT preoperative radiation therapy

Table 42. Original studies presenting data in oncologic outcomes in patients with recurrent cervical cancer treated with IORT

Author ^{reference}	Year	N	Local relapse	Central relapse	Distant relapse	Survival (months)
Barney <i>et al.</i> ¹⁵³⁹	2013	73	3-year: 39%	3-year: 23%	3-year: 44%	Median: 17 3-year: 23%
Mahe <i>et al.</i> ^{1540,1541}	1997	70	3-year: 75%	nr	3-year: 33%	Median: 11 3-year: 8%
Garton <i>et al.</i> ¹⁵⁴²⁻¹⁵⁴⁴	1997	36	5-year: 50%	5-year: 40%	5-year: 58%	Median: 15 5-year: 25%
Martinez Monge <i>et al.</i> ^{1718,1719}	1997	14 ¹ 24 ²	4-year: 60% 4-year: 16%	4-year: 22% 4-year: 5%	4-year: 20% 4-year: 11%	Median: 7 ¹ , 38 ² 4-year: 7% ¹ , 47% ²
Stelzer <i>et al.</i> ¹⁵⁴⁵	1995	22	5-year: 27%	nr	5-year: 9%	Median: 26 5-year: 43%
Gerard <i>et al.</i> ¹⁵⁴⁶	1994	34	4-year: 18%	nr	nr	Median: nr 4-year: 32%

¹ prior external-beam radiation therapy, ² no prior external-beam radiation therapy, nr not reported

Table 43. Response rates and survival according to single agent chemotherapy administered in patients with advanced, persistent, or recurrent cervical cancer

Author ^{reference}	Year	N	Drugs	Response rate (%)	Survival (months)
Platinum compounds					
Long <i>et al.</i> ¹⁶³⁴	2005	146	Cisplatin	13	6.5
Moore <i>et al.</i> ¹⁶²⁹	2004	134	Cisplatin	19	8.8
Omura <i>et al.</i> ¹⁶³⁰	1997	140	Cisplatin	17.8	8.0
Thigpen <i>et al.</i> ¹⁵⁶⁰	1989	164	Cisplatin ¹	17	6.2
		156	Cisplatin ²	18	6.4
Lele <i>et al.</i> ¹⁷²⁰	1989	67	Cisplatin	27	nr
Potter <i>et al.</i> ¹⁷²¹	1989	74	Cisplatin	40.2	nr
Bonomi <i>et al.</i> ¹⁵⁵⁹	1985	150	Cisplatin ¹	20.7	7.1
		166	Cisplatin ³	31.4	7.0
		128	Cisplatin ⁴	25	6.1
Thigpen <i>et al.</i> ¹⁷²²	1981	34	Cisplatin	38	nr
Weiss <i>et al.</i> ¹⁷²³	1990	41	Carboplatin	15	nr
McGuire <i>et al.</i> ¹⁵⁶¹	1989	175	Carboplatin	15.4	6.2
Arseneau <i>et al.</i> ¹⁷²⁴	1986	39	Carboplatin	28.2	nr
McGuire <i>et al.</i> ¹⁵⁶¹	1989	177	Iproplatin	10.8	5.5
Fracasso <i>et al.</i> ¹⁵⁶²	2003	28	Oxaliplatin	8.3	nr
Anthracyclines					
Chauvergne <i>et al.</i> ¹⁵⁷²	1993	31	Pirarubicin	31	nr
Muss <i>et al.</i> ¹⁵⁷¹	1985	25	Mitoxantrone	8	nr
van der Burg <i>et al.</i> ¹⁵⁷⁰	1992	24	Epidoxorubicin	4	nr
Hakes <i>et al.</i> ¹⁵⁷³	1986	18	Idarubicin	0	nr
McGuire <i>et al.</i> ¹⁵⁷⁴	1989	28	Esorubicin	0	nr
Rose <i>et al.</i> ¹⁶¹¹	2006	26	Doxil	11	nr
Alkylating agents					
Sutton <i>et al.</i> ¹⁵⁶⁵	1993	51	Ifosfamide	15.7	nr
Sutton <i>et al.</i> ¹⁵⁶⁶	1989	27	Ifosfamide	11.1	nr
Meanwell <i>et al.</i> ¹⁵⁶⁴	1986	30	Ifosfamide	33	nr
Omura <i>et al.</i> ¹⁵⁶⁸	1981	30	Cyclophosphamide	7	6.5
Smith <i>et al.</i> ¹⁵⁶⁷	1967	76	Cyclophosphamide	20	15
Stehman <i>et al.</i> ¹⁵⁹⁶	1989	60	Mitolactol	29	5.3
Rose <i>et al.</i> ¹⁶¹²	1996	29	Altretamine	0	4.6
Camptothecins					
Lorusso <i>et al.</i> ¹⁶²¹	2011	18	Topotecan	0	7
Coronel <i>et al.</i> ¹⁶¹⁰	2009	18	Topotecan	nr	7.0
Fiorica <i>et al.</i> ¹⁵⁹⁵	2009	27	Topotecan	0	nr
Muderspach <i>et al.</i> ¹⁵⁹⁴	2001	43	Topotecan	18.6	6.4
Bookman <i>et al.</i> ¹⁵⁹³	2000	41	Topotecan	12.5	6.6
Abu-Rustum <i>et al.</i> ¹⁶⁰⁹	2000	12	Topotecan	17	nr
Lhomme <i>et al.</i> ¹⁶⁰⁰	1999	51	Irinotecan	15.7	8.2
Irvin <i>et al.</i> ¹⁵⁹⁷	1998	16	Irinotecan	0	nr
Look <i>et al.</i> ¹⁵⁹⁸	1998	54	Irinotecan	13.3	nr
Verschraegen <i>et al.</i> ¹⁵⁹⁹	1997	42	Irinotecan	21	nr
Takeuchi <i>et al.</i> ¹⁶⁰⁴	1991	55	Irinotecan	23.6	nr

¹ 50 mg/m²/ 3 wk, ² 50 mg/m²/24h/3 wk, ³ 100 mg/m²/3 wk, ⁴ 20 mg/m²/d x 5/3 wk, Doxil pegylated liposomal doxorubicin, nr not reported

Response rates and survival according to single agent chemotherapy administered in patients with advanced, persistent, or recurrent cervical cancer (continued)

Author ^{reference}	Year	N	Drugs	Response rate (%)	Survival (months)
Epidodophylotoxins					
Morris <i>et al.</i> ¹⁵⁸³	1998	44	Etoposide	9.1	7.7
Rose <i>et al.</i> ¹⁵⁸⁴	1998	17	Etoposide	11.8	nr
Pfeiffer <i>et al.</i> ¹⁵⁸⁵	1990	32	Teniposide	22	28
Vinca alkaloids					
Muggia <i>et al.</i> ¹⁵⁸²	2005	30	Vinorelbine	7.1	nr
Muggia <i>et al.</i> ¹⁵⁸¹	2004	44	Vinorelbine	13.7	nr
Lhomme <i>et al.</i> ¹⁵⁷⁹	2000	41	Vinorelbine	17	nr
Morris <i>et al.</i> ¹⁵⁸⁰	1998	33	Vinorelbine	18.2	11
Sutton <i>et al.</i> ¹⁵⁷⁸	1990	30	Vinblastine	0	nr
Kavanagh <i>et al.</i> ¹⁵⁷⁷	1985	20	Vinblastine	10	nr
Rhomberg <i>et al.</i> ¹⁵⁷⁵	1986	20	Vindesine	30	7
Antimetabolites					
Lorusso <i>et al.</i> ¹⁶⁰²	2010	43	Pemetrexed	13.9	nr
Miller <i>et al.</i> ¹⁵⁷⁶	2008	29	Pemetrexed	15	7.4
Schilder <i>et al.</i> ¹⁵⁸⁷	2005	22	Gemcitabine	4.5	6.5
Schilder <i>et al.</i> ¹⁵⁸⁶	2000	24	Gemcitabine	8.4	4.9
de Palo <i>et al.</i> ¹⁵⁸⁸	1973	23	Methotrexate	16	nr
Lorvidhaya <i>et al.</i> ¹⁶⁰³	2010	37	Capecitabine	13	9.3
Look <i>et al.</i> ¹⁶⁰⁸	2008	21	Capecitabine	0	nr
Garcia <i>et al.</i> ¹⁶⁰⁷	2007	26	Capecitabine	15.4	5.9
Katsumata <i>et al.</i> ¹⁶⁰⁶	2011	37	S-1	30.6	15.4
Vermorken <i>et al.</i> ¹⁶¹³	1991	15	Decitabine	0	nr
Taxanes					
Curtin <i>et al.</i> ¹⁵⁹⁰	2001	42	Paclitaxel	31	nr
Kudelka <i>et al.</i> ¹⁵⁹²	1997	32	Paclitaxel	26	nr
McGuire <i>et al.</i> ¹⁵⁸⁹	1996	43	Paclitaxel	17	nr
Kudelka <i>et al.</i> ¹⁵⁹¹	1996	24	Paclitaxel	21	7.3
Minion <i>et al.</i> ¹⁶²⁰	2016	12	NAB-paclitaxel	nr	8.9
Garcia <i>et al.</i> ¹⁵⁶⁹	2007	27	Docetaxel	8.7	7
Angiogenesis inhibitors					
Monk <i>et al.</i> ¹⁶⁰¹	2009	46	Bevacizumab	10.9	7.3
Santin <i>et al.</i> ¹⁶¹⁶	2011	38	Cetuximab	0	6.7
Hertlein <i>et al.</i> ¹⁶¹⁷	2011	5	Cetuximab	0	8.6
Monk <i>et al.</i> ^{1665,1666}	2015	74	Pazopanib	9	13
Monk <i>et al.</i> ^{1665,1666}	2015	78	Lapatinib	5	10
Candelaria <i>et al.</i> ¹⁶⁰⁵	2009	12	Imatinib mesylate	0	6.4
Schilder <i>et al.</i> ¹⁶¹⁴	2009	28	Erlotinib	0	4.96
Goncalves <i>et al.</i> ¹⁶¹⁵	2008	28	Gefitinib	0	3.56
Mackay <i>et al.</i> ¹⁶¹⁸	2010	19	Sunitinib	0	nr
Tinker <i>et al.</i> ¹⁶¹⁹	2013	38	Temsirolimus	3	nr
Mitomycins					
Thigpen <i>et al.</i> ¹⁵⁶³	1995	56	Mitomycin-C	12	4.9
NAB-paclitaxel nano-particule albumin bound paclitaxel, nr not reported					

Table 44. Response rates and survival according to doublet combination chemotherapy administered in patients with advanced, persistent, or recurrent cervical cancer

Author ^{reference}	Year	N	Drugs	Response rate (%)	Survival (months)
Ghaemmaghami <i>et al.</i> ^{1708,*}	2003	10	Cisplatin/5 Fluorouracil	30	nr
Kaern <i>et al.</i> ¹⁶⁷¹	1996	37	Cisplatin/5 Fluorouracil	49	16
Kaern <i>et al.</i> ¹⁶⁷⁰	1990	72	Cisplatin/5 Fluorouracil	68	18
Bonomi <i>et al.</i> ¹⁶⁷²	1989	55	Cisplatin/5 Fluorouracil	22	6.4
Daghestani <i>et al.</i> ¹⁶⁷³	1983	24	Cisplatin/bleomycin	54	6
Cervellino <i>et al.</i> ¹⁶⁷⁴	1995	30	Cisplatin/ifosfamide	50	25
Coleman <i>et al.</i> ¹⁶⁷⁵	1990	44	Cisplatin/ifosfamide	38	8
Omura <i>et al.</i> ¹⁶³⁰	1997	151	Cisplatin/ifosfamide	31.1	8.3
Bloss <i>et al.</i> ¹⁶⁴⁰	2002	146	Cisplatin/ifosfamide	32	8.5
Duenas-Gonzalez <i>et al.</i> ¹⁶⁷⁶	2001	40	Cisplatin/gemcitabine	57	nr
Duenas-Gonzalez <i>et al.</i> ¹⁶⁷⁷	2001	11	Cisplatin/gemcitabine	37	6
Burnett <i>et al.</i> ¹⁶⁷⁸	2000	17	Cisplatin/gemcitabine	41	nr
Monk <i>et al.</i> ^{1644,1659}	2009	112	Cisplatin/gemcitabine	22.3	10.3
Pignata <i>et al.</i> ¹⁶⁷⁹	1999	50	Cisplatin/vinorelbine	64	nr
Morris <i>et al.</i> ¹⁶⁸⁰	2004	67	Cisplatin/vinorelbine	30	nr
Monk <i>et al.</i> ^{1644,1659}	2009	108	Cisplatin/vinorelbine	25.9	10.0
Rose <i>et al.</i> ¹⁶⁵⁵	1999	41	Cisplatin/paclitaxel	46.3	10
Papadimitriou <i>et al.</i> ¹⁶⁵⁴	1999	34	Cisplatin/paclitaxel	7	9
Piver <i>et al.</i> ¹⁶⁸¹	1999	20	Cisplatin/paclitaxel	45	7
Moore <i>et al.</i> ¹⁶²⁹	2004	130	Cisplatin/paclitaxel	35	9.7
Monk <i>et al.</i> ^{1644,1659}	2009	103	Cisplatin/paclitaxel	29.1	12.9
Kitagawa <i>et al.</i> ^{1660,1661}	2015	123	Cisplatin/paclitaxel	58.8	18.3
Tewari <i>et al.</i> ^{1662,1663}	2014	114	Cisplatin/paclitaxel	45	14.3
Suprasert <i>et al.</i> ¹⁷⁰⁶	2010	21	Cisplatin/topotecan	28.6	11
Fiorica <i>et al.</i> ¹⁶⁸⁵	2002	32	Cisplatin/topotecan	28	10
Monk <i>et al.</i> ^{1644,1659}	2009	111	Cisplatin/topotecan	23.4	10.3
Long <i>et al.</i> ¹⁶³⁴	2005	147	Cisplatin/topotecan	26.7	9.4
Shimada <i>et al.</i> ¹⁶⁶⁹	2016	15	Cisplatin/topotecan	27	nr
Sugiyama <i>et al.</i> ¹⁵¹¹	1999	23	Cisplatin/irinotecan	78	nr
Sugiyama <i>et al.</i> ¹⁶⁸⁶	2000	29	Cisplatin/irinotecan	59	nr
Chitapanarux <i>et al.</i> ¹⁶⁹⁵	2003	30	Cisplatin/irinotecan	66.7	16.9
Malviya <i>et al.</i> ¹⁶⁸⁷	1989	20	Cisplatin/mitomycin-C	35	10.3
Wagenaar <i>et al.</i> ¹⁶⁸⁸	2001	33	Cisplatin/mitomycin-C	42	11.2
Omura <i>et al.</i> ¹⁶³⁰	1997	147	Cisplatin/mitolactol	21.1	7.3
Mannel <i>et al.</i> ¹⁶⁹⁷	2000	44	Cisplatin/pentoxifylline	9	6
Farley <i>et al.</i> ¹⁶⁹⁸	2011	44	Cisplatin/cetuximab	9	nr
Nezhat <i>et al.</i> ¹⁷⁰³	2004	14	Cisplatin/bryostatin-1	0	nr
Maluf <i>et al.</i> ¹⁷⁰⁷	2006	36	Cisplatin/tirapazamine	27.8	nr
Takekuma <i>et al.</i> ¹⁷⁰⁴	2012	45	Paclitaxel/nedaplatin	44.4	15.7
Li <i>et al.</i> ¹⁶⁸²	2017	27	Nab-paclitaxel/nedaplatin	50	16.6
Tinker <i>et al.</i> ¹⁶⁵⁶	2005	25	Carboplatin/paclitaxel	40	21

* two patients with impaired renal function were treated with carboplatin followed by 5 Fluorouracil, nab-paclitaxel nanoparticle albumin-bound paclitaxel, nr not reported

Response rates and survival according to doublet combination chemotherapy administered in patients with advanced, persistent, or recurrent cervical cancer (continued)

Author ^{reference}	Year	N	Drugs	Response rate (%)	Survival (months)
Pectasides <i>et al.</i> ¹⁶⁸³	2009	51	Carboplatin/paclitaxel	53	13
Kitagawa <i>et al.</i> ¹⁷⁰²	2012	39	Carboplatin/paclitaxel	59	9.6
Kitagawa <i>et al.</i> ^{1660,1661}	2015	123	Carboplatin/paclitaxel	62.6	17.5
Hisamatsu <i>et al.</i> ¹⁷⁰⁵	2012	61	Carboplatin/paclitaxel	60.7	14
Nagao <i>et al.</i> ¹⁶⁸⁴	2005	17	Carboplatin/docetaxel	76	nr
Tewari <i>et al.</i> ^{1662,1663}	2014	111	Topotecan/paclitaxel	27	12.7
Look <i>et al.</i> ¹⁷⁰⁰	1996	45	5-Fluorouracil/leucovorin	9	nr
Look <i>et al.</i> ¹⁷⁰¹	1998	34	Isotretinoin/ interferon alfa	3	3.9

nr not reported

Table 45. Response rates and survival according to triplet combination chemotherapy administered in patients with advanced, persistent, or recurrent cervical cancer

Author ^{reference}	Year	N	Drugs	Response rate (%)	Survival (months)
Bloss <i>et al.</i> ¹⁶⁴⁰	2002	141	Cisplatin/ifosfamide/bleomycin	31.2	8.4
Ramm <i>et al.</i> ¹⁶⁸⁹	1992	20	Cisplatin/ifosfamide/bleomycin	15	9
Buxton <i>et al.</i> ¹⁶⁹⁰	1989	49	Cisplatin/ifosfamide/bleomycin	69	10.2
Murad <i>et al.</i> ¹⁶⁹¹	1994	36	Carboplatin/ifosfamide/bleomycin	60	11
Fanning <i>et al.</i> ¹⁶⁹²	1995	30	Cisplatin/ifosfamide/5-Fluorouracil	53	12
Choi <i>et al.</i> ¹⁶⁴⁶	2006	45	Cisplatin/ifosfamide/paclitaxel	47	19
Dimopoulos <i>et al.</i> ¹⁶⁴⁷	2002	57	Cisplatin/ifosfamide/paclitaxel	46	18.6
Zanetta <i>et al.</i> ¹⁶⁴⁹	1999	45	Cisplatin/ifosfamide/paclitaxel	67	nr
Serkies <i>et al.</i> ¹⁶⁹³	2006	44	Cisplatin/ifosfamide/mitomycin-C	34	10
Tewari <i>et al.</i> ^{1662,1663}	2014	115	Cisplatin/paclitaxel/bevacizumab	50	17.5
Hainsworth <i>et al.</i> ¹⁶⁹⁴	2001	60	Carboplatin/paclitaxel/5-Fluorouracil	65	nr
Symonds <i>et al.</i> ¹⁶⁶⁴	2015	34	Carboplatin/paclitaxel/cediranib	64	13.6
Kurtz <i>et al.</i> ¹⁶⁹⁹	2009	19	Cisplatin/topotecan/cetuximab	32	7.3
Tewari <i>et al.</i> ^{1662,1663}	2014	112	Topotecan/paclitaxel/bevacizumab	47	16.2
Hsiao <i>et al.</i> ¹⁶⁹⁶	2008	21	Cisplatin/5-Fluorouracil/leucovorin	25	10.5

nr not reported

15 Follow-up

15.1 Summary of available scientific evidence

15.1.1 Timing and location of recurrence

As part of a systematic review published by Elit *et al.*¹⁷²⁵, 62% to 89% of cervical cancer recurrences were detected within 2 years of primary treatment. In year three, the proportion rose to 75% to 85% of cervical cancer recurrences detected, and by year five, 89% to 99% of recurrent disease had been detected by that time (Table 46). It should be noted that no subgroup analyses by stage is available. The location of recurrence was reported in 15¹⁷²⁶⁻¹⁷⁴⁰ of the 17 included studies¹⁷²⁶⁻¹⁷⁴². Overall, 15% to 61% of patient had recurrences that were distant or detected at multiple sites and 14% to 57% of patients had a central recurrence.

LoE 1-

15.1.2 Follow-up strategy

Most studies included in the systematic review published by Elit *et al.*¹⁷²⁵, followed similar intervals: follow-up visits every 3 to 4 months within the first 2 years, every 6 months for the next 3 years, and then annually thereafter or until year 10 or discharge at the discretion of the treating physician (Table 47). Scheduled follow-up visits ranged from a low of nine visits over a 5-year period to a high of potentially 28 visits over a 5-year period. No discernable pattern emerged from the included studies for the most appropriate follow-up strategy for patients with cervical cancer who are clinically disease free after receiving primary treatment. All but one¹⁷⁴² of the included studies reported scheduled follow-up beyond year 5, but in the majority of studies the termination of specialized follow-up was not clearly reported. Two included studies^{1739,1740} reported that scheduled follow-up visits extended to year 10 after primary treatment.

LoE 1-

Two other systematic reviews^{1743,1744} were also identified:

- The first one¹⁷⁴³ aimed to evaluate notably the benefits and harms of different follow-up protocols for women who have completed primary treatment for cervical cancer
- The second one¹⁷⁴⁴ aimed to evaluate the effectiveness of patient-reported outcome measures as an alternative to routine follow-up of women after treatment for gynaecological cancers.

The authors did not find studies meeting their inclusion criteria. Therefore no data were analyzed.

15.1.3 Physical exam

All seventeen trials¹⁷²⁶⁻¹⁷⁴² included in the systematic review published by Elit *et al.*¹⁷²⁵, reported that a physical exam (with or without patient histories) was performed at each follow-up visit (Table 48). Physical exam, with patient history, led to a sizable proportion of recurrences being detected in patients who were asymptomatic at follow-up. Upon exclusion of one study in which only two patients had an asymptomatic recurrence, asymptomatic recurrent disease was detected using physical exam in 29-71% of patients (median detection rate: 52%).

LoE 1-

15.1.4 Vaginal vault cytology

Vaginal vault cytology were the second most common follow-up surveillance method reported in the studies included in the systematic review published by Elit *et al.*¹⁷²⁵ (thirteen^{1726-1728,1730-1732,1734,1735,1737-1741} of the seventeen included studies¹⁷²⁶⁻¹⁷⁴²). The detection rates of asymptomatic recurrent disease with vaginal vault cytology (0-17%, median: 6%) were

LoE 1-

considerably lower than those with physical exams (Table 48). It should be noted that the accuracy of the cervico-vaginal cytology may be compromised by anatomical and tissue changes from the radiation in post-radiated patients.

Gupta *et al.*¹⁷⁴⁵ assessed the utility of cervico-vaginal/vault cytology in the follow-up of women treated for cervical cancer and benign gynaecological conditions. Confirmatory biopsies were conducted for smears that were indicative of malignancy or were inconclusive. In 1,972 women who had previously been treated for gynaecological malignancies, 140 recurrences were detected. In all cases in which a biopsy was conducted based on a smear malignancy, the diagnosis was confirmed (specificity: 100%). However, a confirmatory biopsy was conducted in 72% of positive smears. It should be noted that sensitivity and false-negative rates could not be calculated because negative smears were not followed up with biopsy. Of the 140 women who tested positive for recurrence with cytology, 65.7% presented with advanced disease, most within 2 years (92.1%) of initial treatment. In nearly 24% of cases, cytology testing was the method of detection.

LoE 2-

As part of an evaluation of the utility of liquid-based cytology in detecting recurrent cervical cancer, Rimel *et al.*¹⁷⁴⁶ documented cancer recurrence in 15.8% of the women in their study population, with 8.1% being detected by Pap test. When stratified notably by stage and compared with patients treated using radiation therapy, patients treated with surgery were less likely to have abnormal results (OR = 0.41 (95% CI = 0.29-0.59), $p < 0.001$). In this study, Pap surveillance appeared to have led to salvage for recurrence in 0.3% of patients. It should be noted that no data on recurrences detected by other methods were provided.

Another study¹⁷⁴⁷ not included in the systematic review mentioned above was identified and found a very low yield with continued cytology surveillance among women who had completed 5 years of post-treatment surveillance without recurrence. No cases of cancer were diagnosed in the study population.

Of the 4,376 vaginal smears reviewed by Injumba *et al.*¹⁷⁴⁸, 5 (0.1%) showed abnormal cytology but only 1 had malignant cells and tumour recurrence. In this study, the sensitivity and specificity of vaginal vault cytology for detection of recurrence were 4.3% and 99.3%, respectively.

The results of the other identified studies¹⁷⁴⁹⁻¹⁷⁵³ are limited notably due to the very small number of patients evaluated.

LoE 3

15.1.5 HPV DNA testing

Despite the increasing interest in the clinical uses of HPV testing, only two follow-up studies^{1754,1755} of patients conservatively treated for FIGO stage IA have been identified. In the first one¹⁷⁵⁴, HPV was detected in 87% of the initial diagnostic specimens. HPV testing showed a sensitivity of 100% for recurrent disease. In the second one¹⁷⁵⁵, the value of HPV testing for residual disease and recurrence detection was higher than of cytology and colposcopy. HPV testing showed 100% sensitivity. In this study Hybrid Capture 2 test was more useful for residual disease and recurrence detection than PCR, showed higher specificity (96% versus 79.2%). It should be noted that this second study assessed the performance of HPV DNA testing in follow-up after treatment of high-grade cervical lesions, adenocarcinoma in situ, and microinvasive carcinoma and no subgroup analysis taking into account specifically microinvasive carcinoma is available.

LoE 3

A systematic review¹⁷⁵⁶ assessing the performance of HPV DNA testing in follow-up after treatment of microinvasive carcinoma was identified but is not described because it contains

LoE 1-

no additional studies beyond those already described above.

As part of another systematic review¹⁷⁵⁷ (fifteen studies¹⁷⁵⁸⁻¹⁷⁷²) investigating notably the potential correlation of HPV LN infection and cancer recurrence, was identified. The authors reported discordant results affected by the bias linked to the different techniques used and the non-homogeneous and comparable cohort of patients investigated. Large part of included reports^{1759,1761,1764-1767,1770-1772} noticed that the presence of HPV DNA in LNs increase the risk of recurrences and reduce the OS. Some authors^{1759,1761,1764-1767,1770-1772} confirmed the role of HPV LNs positivity in worsening the oncological prognosis demonstrating that both disease recurrence and OS resulted negatively affected by viral LNs spread (both in case of negative or positive histology).

Singh *et al.*¹⁷⁷³ suggested that in post-radiotherapy cervical cancer patients, high viral load in exfoliated cells and HPV DNA in plasma samples could be used to identified patients at increased risk for disease recurrence and progression. The recurrence of the disease was significantly associated with the presence of HPV in the exfoliated cell ($p = 0.01$) and plasma ($p = 0.007$) as well as high viral load in the exfoliated cell ($p = 0.0002$). The HPV prevalence in exfoliated cell and their high viral load had very high sensitivity (100%) in detecting recurrence, but their specificities were low (29% and 37%, respectively). Plasma samples have higher specificity (93%) than sensitivity (57%).

LoE 3

Song *et al.*¹⁷⁷⁴ reported higher sensitivity and specificity at 3 months ater radiotherapy than at 1 month after radiotherapy, possibly as a result of the presence of cellular debris after radiotherapy. A patient's HPV status at 24 months was significantly associated with local relapse after radiotherapy.

LoE 2-

Pornthanakasem *et al.*¹⁷⁷⁵ have reported that the presence of plasma HPV DNA after complete treatment was an indicator to develop recurrence or to have distant metastasis. Fifty per cent of plasma HPV DNA positive patients but none of the other patients with HPV associated cancers had distant metastasis at the time of blood analysis (RR = 15.67 (95% CI = 5.24-46.83), $p < 0.001$). The amount of plama HPV DNA from metastatic patients was three times more than other patients without metastases. The later cases had tendency to develop recurrence distant metastases within one year after complete treatment when compared with other HPV associated cervical cancer patietns with the same stage but without the presence of plasma HPV DNA.

LoE 3

Another identified study¹⁷⁷⁶ found that high-risk HPV status was predictive of 3-year survival rate and disease recurrence ($p < 0.05$). Pelvic recurrence ($p = 0.018$), but not distant metastasis ($p = 0.232$), was influenced by high-risk HPV status. The authors also found that high-risk HPV had a significant higher sensitivity (71.43% versus 62.86%, $p = 0.036$) and specificity (94.20% versus 78.26%, $p = 0.028$) thanh cervical or vaginal vault cytology with respect to predicting recurrence. It should be noted that rates of abnormal cytology were found higher among those with positive high-risk HPV compared to those with negative high-risk HPV (87.88% versus 16.43%, $p < 0.05$). Regarding the correlation between high-risk HPV testing and prognosis, Yu *et al.*¹⁷⁷⁷ studied the role of high-risk HPV testing in predicting cervical cancer recurrence and noticed that of patients whose disease recurred, 42% of patients had tested positive for high-risk HPV during their surveillance period, compared to 11% for whom disease did not recur ($p = 0.002$). On mutivariate logistic regression, high-risk HPV status remained significantly predictive of disease recurrence (OR = 12.3 (95% CI = 1.5-99.6), $p = 0.02$). In all cases, persistence of high-risk HPV preceded the diagnosis of recurrence by a range of 0 to 11 months with a mean of 2.8 months. The authors also found that while cervicovaginal cytology had limited specificity (5.7% (95% CI = 2.4-11.6)), the combination of cytology with high-risk HPV

LoE 2-

testing increased the specificity of testing (89.3% (95% CI = 82.3-94.2).

Badaracco *et al.*¹⁷⁷⁸ suggested that the HPV DNA persistence may represent an indicator of risk of recurrence. Sixty per cent of patients for whom HPV DNA persisted, recurred whereas two-thirds of patients for whom HPV DNA cleared had no recurrence of disease. **LoE 3**

15.1.6 Serum biomarkers

SCC-Ag: a multivariate analysis, performed by Hoogendam *et al.*¹⁷⁷⁹ indicated that elevated serum level of SCC-Ag was associated with increased odd of experiencing a disease recurrence in all histological types (OR = 1.140 (95% CI = 1.051-1.235)). The adjusted OR specific to the subgroup with only squamous cell carcinoma cases was highly similar (OR = 1.150 (95% CI) 1.058-1.251)). As part of another multivariate analysis, performed by Shimura *et al.*¹⁷⁸⁰, an elevated serum SCC-Ag level was also an independent prognostic factor for poor post-recurrence survival. In this study, serum SCC-Ag levels were elevated in 75% of patients when recurrence was diagnosed. Bonfrer *et al.*¹⁷⁸¹ and Yen *et al.*¹⁷⁸² observed that an elevated post-treatment serum SCC-Ag level was also associated with a poor survival rate. However, Juang *et al.*¹⁷⁸³ and Molina *et al.*¹⁷⁸⁴ observed that SCC-Ag level was not a significant predictor of survival outcome. **LoE 2-**

Oh *et al.*¹⁷⁸⁵ reported that the first indicator of relapse was abnormal serum SCC-Ag level in 40% of patients. Adding SCC-Ag measurement to the basic follow-up protocol improved the sensitivity for detecting recurrence (88.7% versus 49.1%, $p < 0.001$). In the study published by Pras *et al.*¹⁷⁸⁶, elevated SCC-Ag post-treatment indicated residual tumour in 92% of patients. At recurrence, 70% of patients developing recurrent disease during follow-up had a rise of SCC-Ag. Nineteen of 25 patients (76%) with a local recurrence only as the first sign of recurrent disease had elevated pretreatment SCC-Ag levels. Of 22/25 patients post-treatment SCC-Ag data were available: 17/22 (77%) had elevated SCC-Ag during follow-up. A raised SCC-Ag was observed before the clinical manifestation of recurrence in 43% of cases whereas in 15% of cases, the clinical recurrence preceded the SCC-Ag rise. Comparably, Forni *et al.*¹⁷⁸⁷ published a 79% sensitivity for detection of recurrences (histological distribution unknown) with all of these cases showing SCC-Ag elevation prior to clinical symptoms by a mean lead time of 5 months. Equally in line with the data mentioned above, Yoon *et al.*¹⁷⁸⁸ reported a sensitivity and specificity of 61% and 98% for the detection of 18 recurrences in their population, composed of all histological tumour types. Eleven recurrence case showed elevated SCC-Ag serum levels with a median of 2 months before clinical manifestation.

Duk *et al.*¹⁷⁸⁹ present also consistent findings with those previously reported. After treatment, the sensitivity was 79% and the specificity was 91%. During follow-up, the sensitivity of the assay was 85.5% in patients with recurrent disease. Bolli *et al.*¹⁷⁹⁰ observed that in patients with recurrence, 81% had elevated values. SCC-Ag predicted recurrence an average of 6.9 months prior to detection of clinically evident disease. In another identified study¹⁷⁹¹, the authors showed that 90.0% of the patients whose disease recurred or progressed, had a significant increase of this marker compared to 13.9% of patients without evidence of disease.

Only 27% of patients with nonsquamous carcinoma of the cervix enrolled in the report published by Rose *et al.*¹⁷⁹² had elevated SCC-Ag levels. SCC-Ag levels were elevated in 50% of patients with recurrent disease.

The small study published by Meier *et al.*¹⁷⁹³ presents also consistent findings with those previously reported. Roijer *et al.*¹⁷⁹⁴ studied whether any of the SCC-Ag isoforms (SCC-Ag1 and SCC-Ag2) would provide additional and more specific/sensitive clinical information than SCC-Ag. Rising levels of SCC-Ag1 and SCC-Ag2 were seen in patients with recurrence or progressive **LoE 3**

disease. The rise in SCC-Ag2 was usually more prominent than in SCC-Ag1. However, SCC-Ag2 did not show improved tumour specificity as compared with SCC-Ag1 or total SCC-Ag.

In the ten other identified studies^{1736,1795-1803}, increasing serum SCC-Ag preceded the clinical diagnosis of relapse in 46-92% of the cases, with a mean lead time ranging from 2 to 7.8 months. Dodd *et al.*¹⁸⁰¹ found elevated SCC-Ag levels before the clinical evidence of recurrence in 50% of patients and at the time of recurrence in 25% of patients with fatal squamous cell cervical cancer. In the study published by Esajas *et al.*¹⁷³⁶, recurrent disease occurred in 16% of patients and was preceded or accompanied by serum SCC-Ag elevation 26 times (sensitivity, 74%). Increasing serum SCC-Ag was the first indicator of relapse in 14% of these patients. In 12% of the patients without recurrences, serum SCC-Ag values became falsely elevated. The repeat sample after 6 weeks showed a normal SCC-Ag in 7 out of 10 cases. Raised SCC levels were detected in 72.7% of patients with locoregional failures, 80% of patients with distant failures and 67% of patients with both locoregional and distant failures. Although the SCC-Ag level just at the end of radiation therapy was not correlated with local control, Abe *et al.*¹⁷⁹⁸ observed that re-elevation of the SCC-Ag was highly associated with early relapse.

LoE 2-

CYFRA 21-1: eleven^{1779,1781,1784,1786,1797,1804-1809} of twelve^{1779,1781,1784,1786,1797,1804-1810} identified studies reported that CYFRA 21-1 was a less sensitive serum marker than SCC-Ag for detecting squamous cell cervical cancer and recognizing tumour progression or recurrence, as well as the absence of a relationship of CYFRA 21-1 with histological type. Moreover, the addition of CYFRA 21-1 did not significantly increase the sensitivity of SCC-Ag.

LoE 2-

CA 125: seven^{1779,1796,1811-1815} of the eight identified studies^{1779,1796,1801,1811-1815} suggested that rising serum CA 125 during follow-up may be coincident with or precede the clinical diagnosis or recurrent cervical cancer. In the study published by Duk *et al.*¹⁸¹¹, rising CA 125 levels were measured in all patients with abdominal recurrence. Leminen *et al.*¹⁸¹² reported that serum CA 125 levels increased in 71% of the patients with progressive disease. Borrás *et al.*¹⁸¹⁵ detected all cases with recurrence or progression by elevation of CA 125. This biomarker showed an intermediate diagnostic accuracy with an AUC of 0.730 (95% CI = 0.642-0.818) in the study published by Hoogendam *et al.*¹⁷⁷⁹.

LoE 2-

Other biomarkers: fifteen studies^{1779,1781,1783,1784,1793,1798,1800-1802,1807,1812,1813,1815-1817} investigating the potential usefulness of other biomarkers (hsCRP, CA 15-3, CA 19-9, CA 125, CEA, CYFRA 21-1, IL-6, TNF- α , VEGF, IAP, TPA, TATI, and CIC) aimed at identifying recurrence in cervical cancer patients, were also identified.

LoE 2-

As part of the multivariate analysis performed by Hoogendam *et al.*¹⁷⁷⁹, elevated serum level of hsCRP was associated with increased odd of experiencing a disease recurrence in all histological types (OR = 1.027 (95% CI = 1.013-1.040)). The adjusted OR specific to the subgroup with only squamous cell carcinoma cases was highly similar (OR = 1.025 (95% CI = 1.010-1.039)). The diagnostic accuracy of hsCRP and SCC-Ag combined was 0.87 (95% CI = 0.805-0.935). Seven other biomarkers tested in the same study (CA 15-3, CA 125, CEA, CYFRA 21-1, IL-6, TNF- α and VEGF) did not add significantly to the ability to predict recurrence.

In a small series¹⁸¹⁷, the median time to progression was 5 months in patients with pretreatment serum VEGF > 244 pg/ml compared to 19 months in those with lower antigen levels ($p = 0.003$), and this serum marker retained a prognostic relevance at multivariate analysis.

LoE 3

Juang *et al.*¹⁷⁸³ built a multivariate Cox model by forward and backward selection with survival as the dependent variable including TPA, CEA, and SCC-Ag markers as covariates. In this model,

LoE 2-

TPA was the only significant predictor of survival outcome (HR = 22.3 (95% CI = 2.19-226.3), p = 0.031). A report published by Gaarenstroom *et al.*¹⁸⁰⁷ indicated that the clinical performance of post-treatment SCC-Ag levels in predicting complete remission versus the presence of tumour during follow-up was better than TPA. For squamous cell carcinoma of the cervix, SCC-Ag was also better tumour marker than TPA in the study published by Ngan *et al.*¹⁸⁰². In this study, the addition of TPA to SCC-Ag in serial monitoring increased the sensitivity of detection of recurrence but decreased its specificity.

Bonfrer *et al.*¹⁷⁸¹ observed also that SCC-Ag appeared to be a better parameter than TPA in predicting the presence of tumour during follow-up and survival of patients with cervical cancer. Dodd *et al.*¹⁸⁰¹ reported that the data for CIC, CA125, and CEA were not individually useful as a marker. Furthermore, combining the data from all analytes to give a panel of potential markers did not improve the prognosis already evident with SCC-Ag alone.

LoE 3

As part of a multivariate analysis, Molina *et al.*¹⁷⁸⁴ observed that CEA was not a significant predictor of survival outcome. Pectasides *et al.*¹⁸⁰⁰ indicated that patients who has a renewed progression after a complete remission with normal marker levels, showed an increase in SCC-Ag in 95% and CEA in 25%. TATI did not vary in these patients. In patients whose disease did not respond to treatment, a change in serum marker levels cannot be evidenced with the available numbers.

LoE 2-

CEA levels increased in 36% of the patients with progressive disease, serum TATI levels in 46%, and urine TATI levels in 20% of the patients in the study published by Leminen *et al.*¹⁸¹². In all patients with regressive disease, the tumour markers levels decreased or stayed unchanged. Among patients with recurrent adenocarcinoma investigated by Tabata *et al.*¹⁸¹³, the positive rates were 62% for CA 19-9 and 29% for CEA. There were 71% of cases positive for CA 19-9 and/or CEA. In patients with recurrent adenosquamous carcinoma, the corresponding positive rates were 46% (CA 19-9) and 64% (CEA), with 100% positive for CA 19-9, CEA, and/or SCC-Ag.

LoE 3

Abe *et al.*¹⁷⁹⁸ suggested that follow-up of patients by periodical serum examination for CA 19-9 biomarker may be useful for the early detection of tumour relapse. Borrás *et al.*¹⁸¹⁵ reported a specificity during follow-up of 92% for CEA and 92.6% for CA 19-9. Furthermore, CA 19-9 and/or CEA detected all metastases.

LoE 2-

One study¹⁸¹⁶ investigating the potential usefulness of IAP in the follow-up of cervical cancer was identified. As for the monitoring of the disease, raised serum IAP was measured in all patients with recurrent cervical cancer compared with 17% of the patients who were free of recurrence.

15.1.7 Imaging

CT and/or MRI: as part of a meta-analysis, Meads *et al.*¹⁸¹⁸ evaluated notably the diagnostic accuracy of CT scan and MRI as surveillance in women with suspected recurrent or persistent cervical cancer and in asymptomatic women. Among the seven included studies¹⁸¹⁹⁻¹⁸²⁵, four¹⁸¹⁹⁻¹⁸²² evaluated CT, two^{1823,1824} evaluated MRI, and one¹⁸²⁵ evaluated both MRI and CT.

LoE 1-

The sensitivity and specificity for detection of cervical cancer recurrence with CT ranged between 78% and 93% and 50% and 100%, respectively. The summary estimate of the sensitivity of CT for detection of recurrence based on the bivariate hierarchical model was 89.64% (95% CI = 81.59-94.41) and specificity was 76% (95% CI = 43.68-92.82). The authors could not performed meta-analysis for MRI test accuracy due to clinical heterogeneity. The sensitivity and specificity of MRI in pelvic recurrence varied between 82 and 100% and

between 78% and 100%, respectively. It should be noted that (1) most included studies¹⁸²⁰⁻¹⁸²⁵ were published in 2000 or earlier and most did not use standard imaging methods, and (2) no subgroup analyses taking into account specifically asymptomatic or symptomatic women, is available.

A health technology assessment¹⁸²⁶ report published by the same team was identified but is not described because it contains no additional studies beyond those already captured by their meta-analysis¹⁸¹⁸ mentioned above.

As part of a systematic review, Elit *et al.*¹⁷²⁵ evaluated accuracy of several follow-up tests, including notably CT (four studies^{1738-1740,1742}) and MRI (three studies^{1735,1738,1740}), for detecting asymptomatic recurrences among patients with cervical cancer. Asymptomatic recurrent disease was detected using CT in 0-100% and MRI in 0-9% of patients. Of note, there were only two patients with asymptomatic recurrence in the study¹⁷⁴² where 100% of recurrence was detected using CT, and upon exclusion of this study¹⁷⁴² the range of recurrent disease detection with CT was 0-34% (Table 48).

PET(-CT): among the nine studies^{217,226,1819,1827-1832} included in the meta-analysis published by Meads *et al.*¹⁸¹⁸, the sensitivities and specificities of detection of local and distant recurrence combined with PET-CT ranged between 83 and 100% and between 50 and 100%, respectively. For distant recurrence alone, the sensitivity of PET-CT was 86% and the specificity was 100%. The overall estimated of sensitivity was 94.8% (95% CI = 91.2-96.9), and the specificity, 86.9% (95% CI = 82.2-90.5). A sensitivity analysis omitting one study²¹⁷ that reported accuracy for distant recurrence only did not affect accuracy estimates to any significant degree (sensitivity = 95.0% (95% CI = 91.4-97.2), specificity = 86.7% (95% CI = 81.9-90.4)). It should be noted that (1) eight^{217,226,1819,1828-1832} of nine included studies^{217,226,1819,1827-1832} in the analysis included suspected and/or symptomatic patients and (2) no subgroup analyses taking into account specifically this population is available.

LoE 1-

Only three^{226,1819,1831} of the nine included studies provided results for both standard imaging alone and standard imaging with the addition of whole body PET-CT with the same reference standard of histology or clinical evidence of disease. The addition of PET-CT resulted systematically in improving sensitivity. However, there was no difference in specificity between the two imaging strategies. It should be noted that the numbers of women imaged in all three studies^{226,1819,1831} were small.

The minimum important elicited increase in accuracy of the addition of PET-CT to CT and/or MRI considered necessary to warrant the introduction of PET-CT as a routine investigation in this sample of clinical experts was similar for asymptomatic women (a mean 8.7% reduction in false positives and 6.3% reduction in false negatives) and symptomatic women (a mean 7.7% reduction in false positives and 6.4% reduction in false negatives).

Here again, the identified health technology assessment¹⁸²⁶ report published by the same team is not described because it contains no additional studies beyond those already captured by their meta-analysis¹⁸¹⁸ mentioned above.

A meta-analysis¹⁸³³ comparing the overall value of PET and PET-CT in diagnosing recurrent cervical cancer (eighteen studies^{204,217,225,226,1782,1819,1820,1828-1830,1832,1834-1840}) was also identified. No statistical differences between PET and PET-CT in terms of its pooled sensitivity (91% (95% CI = 87-94) versus 94% (95% CI = 89-97), $p > 0.05$) or pooled specificity (92% (95% CI = 91-94) versus 84% (95% CI = 74-91), $p > 0.05$) were observed. These results are consistent with the results of another identified meta-analysis¹⁸⁴¹ reporting pooled sensitivity and specificity of PET stand alone for diagnosing recurrent cervical cancer of 91% and 92%,

respectively, compared with 94% and 84% for PET-CT. This meta-analysis showed also that the pooled sensitivity and specificity of PET and PET-CT to detect distant metastasis in recurrent cervical cancer were 87% (95% CI = 80-92) and 97% (95% CI = 96-98), respectively. The pooled sensitivity and specificity for local regional recurrence were 82% (95% CI = 72-90) and 98% (95% CI = 96-99), respectively.

In one study¹⁸²⁸ included in the meta-analyses mentioned above, PET-CT accurately detects lung metastasis, local recurrence, LN metastasis, and even peritoneal dissemination that may be missed by PET alone. The sensitivity and specificity were 92% and 92.6%, respectively while for PET, the corresponding figures were 80.0% and 77.8%, respectively.

LoE 2-

As part of a small study published by Lai *et al.*²²⁵, the sensitivity of PET was greater than that of CT-MRI in terms of overall lesion detection (91% versus 67%, $p = 0.001$), and the difference was even greater for detection of metastatic lesions (92% versus 60%, $p = 0.0003$). It should be noted that the difference in terms of sensitivity for detection of recurrent/persistent local tumours did not reach statistical significance maybe due to the small number of patients enrolled in the study (90% versus 84%, $p = 0.631$).

LoE 3

Thirteen studies^{219,1842-1853} not included in the meta-analyses mentioned above were also identified. Yen *et al.*¹⁸⁴² compared the diagnostic value of PET and CT-MRI in documented or suspected recurrence after primary treatment. Of the final diagnoses, there was additional benefit from PET over CT-MRI in 73.8%, with PET correcting false-negatives on CT-MRI in 74.2% and correcting false-positives on CT-MRI in 25.8%. Among lesions confirmed by PET, 75.4% were extrapelvic.

LoE 2-

In the study published by Brooks *et al.*¹⁸⁴³, PET findings indicative of recurrence (confirmed by tissue biopsy) were mentioned in 84% of symptomatic patients at the time of surveillance. Tumour recurrence detected by PET was described in 12% of asymptomatic patients. All recurrences were confirmed by biopsy or radiologic progression. Eighty percent of asymptomatic recurrences detected by PET were isolated to either the cervix, pelvic, or para-aortic nodes. There were 38 patients whose first surveillance PET scan was negative for recurrent disease who subsequently underwent a second surveillance PET study. The median time from the first surveillance PET to the second was 6.5 months. All of the patients with symptoms had evidence of tumour recurrence by PET. There were 28 asymptomatic patients of whom 24 had negative PET findings and 4 had evidence of recurrent tumour. Three of the four patients with asymptomatic recurrences had isolated sites disease recurrence.

A study¹⁸⁴⁴ investigating the detection of relapse with PET scan in patients treated with curative intent chemoradiotherapy, was also identified. After complete metabolic response, only 1.6% of patients relapsed without symptoms and were detected through physical examination. Patients with a partial metabolic response had a HR for distant failure 36 times (95% CI = 7-191) the HR of patients with a complete metabolic response ($p < 0.0001$). Patients with a partial metabolic response had a HR for nodal failure that was 51 times (95% CI = 3-846) the rate of patients with a complete metabolic response ($p = 0.0061$). A multivariate analysis performed by Schwarz *et al.*¹⁸⁴⁵, demonstrated that the HR for risk of recurrence based on the post-therapy metabolic response showing progressive disease was 32.57 (95% CI = 10.22-103.82). The HR for a partial metabolic response on the 3-month post-therapy PET was 6.30 (95% CI = 2.73-14.56, $p < 0.001$). The same team¹⁸⁴⁶ found that a majority of failures within complete metabolic response patients were distant (85%). Of failures within the partial metabolic response patients, 58% of them were isolated local failures, and 42% were distant. A Cox proportional hazards model of survival outcome, performed by Grigsby *et al.*¹⁸⁴⁷, indicated that any abnormal post-therapy FDG uptake (persistent or new) was the most significant

prognostic factor for developing metastatic disease and death from cervical cancer when compared with pretreatment and treatment-related prognostic factors ($p < 0.0001$).

Another identified study¹⁸⁴⁸ evaluated the clinical impact of PET as a post-therapy surveillance of cervical cancer especially in asymptomatic patients who reached complete response after primary treatment. The PET scan detected 96.1% of patients with recurrent disease. The sensitivity and specificity of PET scan in assessment of recurrence were 96.1% and 84.4%, respectively. PET scan detected recurrent lesions in 85% of asymptomatic patients.

The results of the other identified studies^{219,1849-1853} are limited notably due to the very small number of patients evaluated. **LoE 3**

Chest radiography: Elit *et al.*¹⁷²⁵ mentioned that the detection of asymptomatic recurrences with chest x-rays was effective in a sizable proportion of asymptomatic patients tested. Based on data from six studies^{1728,1730,1732,1734,1735,1738}, chest x-ray detected asymptomatic recurrent disease in 19-47% of patients (**Table 48**). **LoE 1-**

Of 817 patients with carcinoma of the uterine cervix that were followed-up by Imachi *et al.*¹⁸⁵⁴, 50 (6.1%) developed pulmonary metastases. Of the patients in whom lung metastases were detected, 41.7% had no symptoms. Ninety-six per cent was diagnosed within 2 years from the initiation of treatment. All the patients had abnormal shadows in chest x-rays. **LoE 2-**

US: US was not generally employed as a surveillance tool in the seventeen studies¹⁷²⁶⁻¹⁷⁴² included in the systematic review published by Elit *et al.*¹⁷²⁵ (**Table 48**), nor was it effective where it was used as a part of routine follow-up. US detected only 4 of the 179 asymptomatic recurrences observed (2%, three studies^{1734,1738,1740}). **LoE 1-**

Intravenous pyelography: the three studies^{1726,1728,1732} included in the systematic review published by Elit *et al.*¹⁷²⁵, did not reported any asymptomatic recurrences with the routine use of intravenous pyelography (**Table 48**). **LoE 1-**

15.1.8 Hormonal replacement therapy

Ploch *et al.*¹⁸⁵⁵ studied the use of HRT in cervical cancer survivors. All patients enrolled were younger than 45 years of age and had FIGO stage I/II disease treated with surgery or radiotherapy. After treatment, no significant difference in DFS or OS at 5 years was noted between patients treated with HRT and controls. HRT resulted in significantly lower radiotherapy-related complications rates in those patients who required radiotherapy (17% versus 45%, $p \leq 0.01$). **LoE 2-**

Lacey *et al.*¹⁸⁵⁶ reported that women with adenocarcinoma given unopposed oestrogen HRT had a significant increased risk of recurrence (OR = 2.7 (95% CI = 1.1-6.8)). It should be noted that this association lost its statistical significance in case of combined oestrogen and progesteron HRT and/or when analysis was restricted to the HPV positive controls. It should also be noted that no such association was reported for women with squamous cell carcinoma. Menopausal status was not associated with adenocarcinoma or squamous cell carcinomas and did not modify the other associations.

After multivariate analysis, a longer duration of follow-up was significantly associated an increased likelihood of receiving counseling or a prescription for HRT (OR = 1.011 (95% CI = 1.001-1.020), $p = 0.0252$) in a study published more recently by Rauh *et al.*¹⁸⁵⁷. Patients with recurrent disease showed a non significant trend towards reduced odds of being counseled and/or prescribed HRT (OR = 0.450 (95% CI = 0.193-1.048), $p = 0.0643$).

15.2 Previous initiatives

Eleven previous initiatives^{419,421-426,529,531,1858,1859} presenting guidelines for follow-up were identified.

15.3 Development group comments

There is no evidence for most appropriate follow-up strategy. The risk of recurrence and disease- and treatment-related morbidity is individual, and depends on prognostic factors, treatment modality and patients' characteristics. Follow-up schemes for cervical cancer patients may therefore be individualized taken these aspects into account. The start off for further follow-up should be the treatment evaluation, with documentation of tumor response as well as disease- and treatment related morbidity. Since the majority of recurrences appear within 2-3 years after primary treatment, follow-up should be more intense within this period. With the exception of follow-up after fertility-sparing surgery, recurrence-free patients rarely need to be followed more than 5 years after primary treatment, unless treatment-related long-term or late side effect exists. Prospective studies addressing new follow-up strategies are warranted.

Evidence suggest that patient-reported outcome measures are important to supplement physician-reported adverse events, improving the precision of capturing symptomatic adverse events concerning e.g. frequency, severity and interference with daily activities. The effectiveness of patient-reported outcome as an alternative to routine follow-up however needs to be explored in prospective trials.

Follow-up visits should be conducted or coordinated by a physician experienced in the surveillance of gynecological cancer patients. The vaginal vault cytology has low positive predictive value to detect recurrence post chemoradiotherapy and post-surgery and is therefore not routinely recommended. Instead of use of vaginal cytology, HPV testing may be useful in identification of vaginal cancer precursors and tumor recurrence, but the robust evidence is still missing. The clinical relevance of tumor markers, such as SCC-Ag is controversial. Although the SCC-Ag may precede clinical diagnosis of recurrence in 46-92% of cases (median lead time of 2-8 months)¹⁸⁶⁰ there is no strong evidence that earlier detection of recurrence is associated with better survival in recurrent cervical cancer. Tumour markers, such as SCC-Ag, are therefore not recommended in a routine follow-up. Likewise imaging and laboratory tests are not routinely advocated in asymptomatic patients. Recurrences should be proven by biopsy before treatment planning.

15.4 Guidelines

15.4.1 General recommendations



Primary objectives of follow-up for patients with cervical cancer should include the following:

- 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, for example, 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 (eg, Common Terminology Criteria for Adverse Events)
- Prevention and management of cancer- and treatment-related adverse effects, for example, sexual dysfunction (eg, counseling, vaginal lubricants, local estrogen)



In case of the appearance of treatment-related symptoms, a referral to a dedicated specialist (eg, gastroenterologist, urologist/gynecologist) 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, lifestyle 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 adverse 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 5 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 suggestive of 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 tumor 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 tumor 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.

15.4.2 Follow-up after fertility sparing treatment



All women remain at risk of tumor 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 (eg, gynecologic oncologist, colposcopy expert).

C

Follow-up intervals should be 3 to 4 months for the first 2 years postoperatively, and then 6 to 12 months up to 5 years. Thereafter the patient may return to population-based screening. The duration of follow-up, however, may be individualized depending on the risk of recurrence or persistence of treatment-related complications.

C

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 to 5 years as long as follow-up is indicated.

15.4.3 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.

15.4.4 Follow-up after definitive chemoradiotherapy

✓

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

✓

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

B

For re-evaluation purposes, the optimal diagnostic workup 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 because vaginal stenosis and dryness may occur. Vaginal dilation should be offered, as well as vaginal lubricants and local estrogen.

Table 46. Original studies presenting data on location and timing of recurrence for patients with cervical cancer after receiving primary treatment

Author ^{reference}	Year	N	Recurrent disease			Location of recurrence			Timing of recurrence				
			Total	Sympt.	Asympt.	Central	Sidewall	Distant/multiple sites	2 years*	3 years*	5 years*	Sympt.**	Asympt.**
Krebs <i>et al.</i> ¹⁷²⁶	1982	312	327	164	163	187	31	109	nr	nr	nr	36	24
Muram <i>et al.</i> ¹⁷²⁷	1982	323	47	nr	nr	40	27	29	78%	nr	98%	19-24	-
Larson <i>et al.</i> ¹⁷²⁸	1988	249	27	17	10	6	10	11	89%	nr	96%	14	11
Rintala <i>et al.</i> ¹⁷²⁹	1989	89	44	nr	nr	17	-	27	nr	nr	nr	7	-
Soisson <i>et al.</i> ¹⁷³⁰	1990	203	31	22	9	13	-	18	71%	87%	97%	15	-
Look <i>et al.</i> ¹⁷³¹	1990	96	21	14	7	3	9	9	81%	nr	nr	11	10
Tinga <i>et al.</i> ¹⁷³²	1992	367	71	55	16	17	15	39	nr	nr	nr	12	12
Gerdin <i>et al.</i> ¹⁷³³	1994	167	19	16	3	5	8	6	74%	nr	nr	15	-
Ansink <i>et al.</i> ¹⁷⁴¹	1996	674	112	92	20	nr	nr	nr	62%	75%	nr	25	-
Samlal <i>et al.</i> ¹⁷³⁴	1998	271	27	18	9	5	9	13	nr	77%	nr	14	-
Bodurka-Bevers <i>et al.</i> ¹⁷³⁵	2000	993	133	114	19	37	21	75	nr	nr	nr	17	16
Esajas <i>et al.</i> ¹⁷³⁶	2001	225	35	16	19	22	-	13	nr	nr	nr	11	-
Duyn <i>et al.</i> ¹⁷³⁷	2002	277	47	41	6	16	7	24	nr	nr	nr	18	-
Lim <i>et al.</i> ¹⁷⁴²	2004	291	53	45	2	nr	nr	nr	63%	77%	98%	18	-
Morice <i>et al.</i> ¹⁷³⁸	2004	583	45	38	7	25	13	7	64%	78%	89%	16	13
Sartori <i>et al.</i> ¹⁷³⁹	2007	63	63	41	22	36	-	27	nr	87%	nr	28	23
Zola <i>et al.</i> ¹⁷⁴⁰	2007	327	327	164	163	187	31	109	nr	nr	nr	36	24

* recurrences diagnosed yearly after primary treatment (%), ** median timing to recurrence (months), Asympt. asymptomatic, nr not reported, Sympt. symptomatic

Table 47. Original studies presenting data on follow-up strategy for patients with cervical cancer who are clinically disease free after receiving primary treatment

Author ^{reference}	Year	N	Year	Year	Year	Year	Year	Total (years 1 to 5)	Year
			1	2	3	4	5		6+
Krebs <i>et al.</i> ¹⁷²⁶	1982	312	12	3-4	3-4	3-4	3-4	24-28	2
Muram <i>et al.</i> ¹⁷²⁷	1982	323	nr	nr	nr	nr	nr	nr	nr
Larson <i>et al.</i> ¹⁷²⁸	1988	249	4	3	2	2	2	13	1
Rintala <i>et al.</i> ¹⁷²⁹	1989	89	4	4	2	2	2	14	2
Soisson <i>et al.</i> ¹⁷³⁰	1990	203	4	3	2	2	2	13	1
Look <i>et al.</i> ¹⁷³¹	1990	96	5	4	2	2	2	15	1
Tinga <i>et al.</i> ¹⁷³²	1992	367	4	3	2	2	2	13	1
Gerdin <i>et al.</i> ¹⁷³³	1994	167	4	3	2	2	2	13	1
Ansink <i>et al.</i> ¹⁷⁴¹	1996	674	4	2	1	1	1	9	1
Samlal <i>et al.</i> ¹⁷³⁴	1998	271	4	2	2	1	1	10	1
Bodurka-Bevers <i>et al.</i> ¹⁷³⁵	2000	993	4	3	3	2	2	14	1
Esajas <i>et al.</i> ¹⁷³⁶	2001	225	6	4	3	2	2	17	2
Duyn <i>et al.</i> ¹⁷³⁷	2002	277	4	3	2	2	2	13	1
Lim <i>et al.</i> ¹⁷⁴²	2004	291	4	2	1	1	1	9	0
Morice <i>et al.</i> ¹⁷³⁸	2004	583	4	3	2	1	1	11	1
Sartori <i>et al.</i> ¹⁷³⁹	2007	63	4	3	2	2	2	13	1
Zola <i>et al.</i> ¹⁷⁴⁰	2007	327	3-4	3-4	2	2	2	12-14	1

nr not reported

Table 48. Original studies included in the systematic review published by Elit *et al.*¹⁷²⁵, presenting data on the detection of asymptomatic recurrences by type of follow-up test

Author ^{reference}	Year	N	Disease recurrence		Physical	Vaginal vault	CT	MRI	Chest x-ray	US	Intravenous pyelography
			All	Asymptomatic	exam	cytology					
Krebs <i>et al.</i> ¹⁷²⁶	1982	312	40	10	nr	nr	-	-	-	-	nr
Muram <i>et al.</i> ¹⁷²⁷	1982	323	47	nr	nr	3	-	-	-	-	-
Larson <i>et al.</i> ¹⁷²⁸	1988	249	27	10	7	1	-	-	-	-	0
Rintala <i>et al.</i> ¹⁷²⁹	1989	44	-	nr	-	-	-	-	-	-	-
Soisson <i>et al.</i> ¹⁷³⁰	1990	203	31	9	nr	nr	-	-	2	-	-
Look <i>et al.</i> ¹⁷³¹	1990	96	21	7	5	0	-	-	-	-	-
Tinga <i>et al.</i> ¹⁷³²	1992	367	71	16	12	1	-	-	3	-	0
Gerdin <i>et al.</i> ¹⁷³³	1994	167	19	3	2	-	-	-	-	-	-
Ansink <i>et al.</i> ¹⁷⁴¹	1996	674	112	29	nr	nr	-	-	-	-	-
Samlal <i>et al.</i> ¹⁷³⁴	1998	271	27	9	4	1	-	-	3	0	-
Bodurka-Bevers <i>et al.</i> ¹⁷³⁵	2000	993	133	19	8	0	0	0	9	-	-
Esajas <i>et al.</i> ¹⁷³⁶	2001	225	35	19	nr	-	-	-	-	-	-
Duyn <i>et al.</i> ¹⁷³⁷	2002	277	47	6	4	1	-	-	-	-	-
Lim <i>et al.</i> ¹⁷⁴²	2004	291	53	2	0	-	2	-	-	2	-
Morice <i>et al.</i> ¹⁷³⁸	2004	583	45	7	2	1	2	0	2	0	-
Sartori <i>et al.</i> ¹⁷³⁹	2007	63	63	22	9	0	10	-	-	-	-
Zola <i>et al.</i> ¹⁷⁴⁰	2007	327	327	163	85	5	55	15	-	4	-

CT computed tomography, MRI magnetic resonance imaging, nr not reported, US ultrasonography

16 Cervical cancer in pregnancy

16.1 Summary of available scientific evidence

16.1.1 Imaging

MRI: two small studies^{1861,1862} evaluating the possible usefulness of MRI (without injection of intravenous contrast agent) for the management of patients with cervical cancer during pregnancy were identified. In the first one¹⁸⁶¹, the six enrolled subjects underwent MRI at the time of first referral. Five patients underwent a second MRI examination before surgery. The final histopathological staging and the final MRI staging agreed in five cases. In one case, MRI suggested parametrial infiltration which was not confirmed in the surgical specimen, and the tumour volume suggested by MRI markedly exceeded the volume measured after the excision.

LoE 3

In the second identified study, Balleyguier *et al.*¹⁸⁶² assessed the role of MRI in decision making regarding treatments options for twelve patients with uterine cervical cancer during pregnancy. The mean term of pregnancy at the time of the diagnosis was the early second trimester (9 to 28 weeks). In the five patients with localized disease discovered on the Pap smear during the first trimester of pregnancy, MRI was normal (N = 4) or detected a small lesion (FIGO stage IB1, N = 1), and pregnancies were allowed to continue. In the seven patients with invasive disease revealed later, during the second or third trimester, MRI detected a lesion in every case, and positive LNs were depicted in 2 cases. The physical examination revealed four cases of parametrial extension (MRI, N = 4) and two cases of vaginal extension (MRI, N = 1). Suspected bladder extension (MRI, N = 1) was confirmed by cystoscopy. MRI examination of cervical cancers during pregnancy helped the authors to decide upon adequate treatment in all cases and modified management in two cases (17%).

PET-CT: two studies^{1863,1864} assessing the fetal radiation exposure resulting from PET procedures performed in pregnant patients with cervical cancer were identified.

LoE 3

The first one¹⁸⁶³ enrolling 5 pregnant patients with malignancies including 2 patients with cervical cancer. All patients underwent PET studies with a reduced FDG dose (except for one patient who had a negative pregnancy test immediately before the FDG PET procedure but was confirmed to be pregnant a few weeks later), including vigorous hydration and diuresis to minimize radiation exposure to the fetus. Six PET studies were analyzed. The PET scans were obtained in early pregnancy (N = 1), the second trimester (N = 2), and the third trimester (N = 3). In the patient who underwent PET early during pregnancy, the fetus was not clearly visualized, and only diffusely increased FDG activity was noted in the uterine region. In all other patients, the fetus was clearly delineated with FDG uptake. The fetal dose exposure from FDG PET studies was estimated to range from 1.1 to 2.43 mGy for various trimesters in pregnancy (except for the patient in the early stage of pregnancy, in whom activity in the whole uterus was considered, and the fetal dose was estimated to be 9.04 mGy). All patients delivered healthy infants with no visible abnormalities at term.

The second identified study¹⁸⁶⁴ enrolled six pregnant patients including one patient with cervical cancer. Three patients were scanned during the first trimester (one with PET and 2 with PET-CT), two patients were scanned during the second trimester with PET-MRI, and one was scanned during the third trimester with PET. The fetus was clearly visible on the PET images from all patients except for one patient, for whom the whole uterus was used for dosimetric calculation. The two fetuses imaged with PET-MRI were visible in fine detail on the MRI. Therefore, fetal contours could be delineated precisely. The fetal absorbed doses from FDG injection were consistent with those published by Takalkar *et al.*¹⁸⁶³, ranging from approximately 1.4 to 5.1 mGy, according to the activity administered, with the highest values

generally being found in early pregnancy. The placenta concentrated 0.27% of the injected activity of FDG.

16.1.2 Laparoscopic lymph node staging

Feasibility and safety of laparoscopic pelvic (\pm para-aortic) lymphadenectomy during pregnancy were assessed in a few pregnant patients¹⁸⁶⁵⁻¹⁸⁷² with cervical cancer.

LoE 3

Eighteen patients with cervical cancer who underwent laparoscopic pelvic lymphadenectomy during pregnancy (6 to 23 weeks of gestation) were analyzed by Favero *et al.*¹⁸⁶⁵. All laparoscopic procedures were successfully completed without surgery-associated mortality, morbidity, or conversion to laparotomy. There were no complications for either mother or child related to the general anesthesia. Except for three patients, all women were diagnosed and operated in the second trimester of gestation. The three patients with LN involvement received immediate cancer treatment. One patient decided to interrupt the gestation before delivery despite negative LNs. Fourteen patients reached fetal maturity (32 to 36 weeks of gestation) and gave birth to healthy babies by cesarean section. All patients were alive without evidence of disease at a mean follow-up time of 38 months.

Vercellino *et al.*¹⁸⁶⁶ described successful laparoscopic pelvic lymphadenectomies performed in 32 pregnant women with cervical cancer (mean gestational week = 17.5 weeks). No maternal and neonatal complications related to anesthesia or directly to the surgical procedure arose. Of the 32 patients, 4 had LN metastases (FIGO stage IB1: N = 3, FIGO stage IIA: N = 1). They all interrupted the pregnancy. All children born through cesarean delivery at a mean 34 gestational weeks were well and showed normal clinical neurological development.

Alouini *et al.*¹⁸⁶⁷ reported successful procedures for the eight patients undergoing laparoscopic pelvic (\pm para-aortic) lymphadenectomy during pregnancy (12 to 32 weeks of gestation), without maternal or fetal complications, or conversion. Here again, no complications for either mother or child related to the general anesthesia were also described. The three patients with LN involvement died from recurrence of the disease. Seven patients out of eight reached fetal maturity (28 to 36 weeks of gestation) and gave birth by cesarean section to healthy babies.

All women presented in the identified case reports¹⁸⁶⁸⁻¹⁸⁷² were also treated successfully during pregnancy (10 to 22 weeks of gestation). The authors did not report any complications connected with the laparoscopic procedure.

16.1.3 Sentinel node detection

In 2006, Silva *et al.*¹⁸⁷³ have reported the sole case of SN detection by technetium-labelled radiocolloid lymphoscintigraphy in a pregnant woman with cervical cancer (14 weeks' gestation, FIGO stage IB2). Two unilateral positive SNs were detected during radical surgery, which included complete pelvic lymphadenectomy and radical hysterectomy with the fetus in situ (14 weeks' gestation). The patient evolved well postoperatively without complications and was submitted to adjuvant treatment. She remains without evidence of disease at 30 months of follow-up.

LoE 3

More recently, Papadia *et al.*¹⁸⁷⁴ presented cases of two pregnant patients with early-stage cervical cancer who have undergone ICG sentinel LN mapping followed by laparoscopic sentinel LN biopsy, pelvic lymphadenectomy, and cervical conisation. Sentinel LNs were identified in both hemipelvises in both patients. In the final pathologic analysis, both sentinel LNs and non-sentinel LNs were negative for metastatic disease. No adverse events from ICG injection were recorded.

16.1.4 Delayed treatment

Twenty-seven studies^{1861,1865,1867,1868,1875-1897} presenting maternal outcome data in patients managed with delay before definitive treatment of the cervical tumour post-partum were identified (Table 49). Ninety-nine per cent of described patients had FIGO stage I-II disease, and most had very early-stage disease (FIGO stage IA and small FIGO stage IB1), for which the risk of clinical significant disease progression was small. It should be noted that data on treatment delay during pregnancy for patients with advanced-stage disease are very limited.

LoE 3

Treatment of the identified patients with FIGO stages I-II was delayed for between 3 and 56 weeks. Of the 100 patients for whom the outcome is known, only 4 died of the disease. Eighteen studies^{1861,1865,1867,1868,1875,1879,1883-1892,1894,1896} described reports of delays in treatment exceeding 6 weeks in patients with FIGO stages I-II. Of the 70 patients for whom the outcome is known, only 2 (2.9%) died of the disease. It should be noted that 16 (23%) of these cases were diagnosed in first trimester.

16.1.5 Neoadjuvant chemotherapy

To date, less than 60 cases^{562,1205,1898-1924} of cervical cancer in pregnancy that have been treated with NACT, were identified. The stage at diagnosis during pregnancy was early (FIGO stages I and II) in 96% of women. The most commonly used drug was cisplatin administered either as monotherapy^{562,1898,1899,1903-1906,1909,1910,1919,1921,1924} or combined with vincristine^{1900,1904,1908,1916,1920,1922,1923}, paclitaxel^{1901,1902,1904,1911,1912,1918}, adriamycin¹⁹¹³, etoposide¹⁹¹⁴, bleomycin¹⁹¹⁷, vincristine + bleomycin¹²⁰⁵, or etoposide + dactinomycin + cyclophosphamide¹⁹¹⁵ (Table 50). The vast majority of the patients responded to chemotherapy, which prolonged the pregnancies. Fetal well-being was not compromised in any of the cases reported.

LoE 3

Two systematic reviews^{1925,1926} were identified but are not described because they contain no additional studies beyond those already described above.

16.1.6 Radical hysterectomy

In the small study published by Bigelow *et al.*¹⁹²⁷, complication rates in pregnant women undergoing radical hysterectomy were similar to those outside of pregnancy. Time to treatment was significantly longer for pregnant women compared to nonpregnant patients (20.8 weeks versus 7.9 weeks, $p = 0.0014$) but there was no survival difference between groups. Women who underwent gravid radical hysterectomy had significantly higher estimated blood loss than those who had a radical hysterectomy in the postpartum period (2033 ml versus 425 ml, $p = 0.0064$), but operative characteristics were otherwise similar. None of the pregnant women who died delayed treatment due to pregnancy. Oncologic outcomes were similar between pregnant patients and nonpregnant control subjects.

LoE 3

As part of another small study¹⁸⁸⁶ enrolling thirteen patients treated with radical hysterectomy and bilateral PLND with the fetus in situ and eight others with cesarean delivery followed by radical hysterectomy and bilateral PLND, no perioperative deaths occurred. After documentation of maturity, seven healthy infants were delivered with no major morbidity. Twenty patients (95%) were alive and free of disease with a mean follow-up of 40 months. Except for the increased blood loss in conjunction with cesarean section, Monk *et al.*¹⁸⁸⁶ reported that the outcome of radical hysterectomy with the fetus in situ or after cesarean delivery did not differ significantly from that of radical hysterectomy in the nonpregnant state.

A study¹⁸⁹³ evaluating the morbidity of radical hysterectomy and PLND or simple hysterectomy for patients with cervical cancer treated during pregnancy was also identified. No differences in operative morbidity and major complication rate between pregnant and nonpregnant

patients were described.

Results of the other identified studies^{1872,1875,1877,1928-1930} are limited notably by (1) the very small number of patients evaluated, (2) the inclusion of patients as much as 18 months' postpartum, and/or (2) the absence of details regarding the surgical management.

16.1.7 Abdominal radical trachelectomy

In 2006, Ungar *et al.*¹⁹³¹ first published the use of abdominal radical trachelectomy in five pregnant patients with cervical cancer between 7 and 18 weeks' gestation. All the patients were in FIGO stage IB1. Three of the cases resulted in miscarriage after surgery. Four case reports^{858,1932-1934} describing this procedure were also identified (Table 51).

LoE 3

16.1.8 Radical vaginal trachelectomy

In 2008, van de Nieuwenhof *et al.*¹⁹³⁵ reported the first radical vaginal trachelectomy performed in a pregnant patient with cervical cancer. To date, eight identified reports^{1867,1870,1935-1940} described fifteen cervical cancer cases managed with vaginal radical trachelectomy during pregnancy. At the time of delivery, the gestational age ranged between 26 and 37 weeks (Table 51).

LoE 3

16.1.9 Simple trachelectomy

Two case reports^{1869,1941} presenting pregnant patients treated by a simple trachelectomy were identified. In the first published case¹⁸⁶⁹, simple trachelectomy and cerclage were performed in the 22nd week of pregnancy. Adjuvant chemotherapy with three cycles of cisplatin was performed after surgery. Delivery was performed by cesarean section followed by radical hysterectomy in the 32nd week of pregnancy. The newborn developed normally and showed no chemotherapically related side effects. Patient had no surgery related complications. No relapse of cancer has been diagnosed during the following 16 months.

LoE 3

The second case¹⁹⁴¹ was a patient treated by a simple trachelectomy and cerclage during 24th week of pregnancy. The woman gave birth to a healthy baby at the end of her pregnancy. Definitive treatment was completed three months after giving birth. After 17 months of monitoring, the patient showed no signs of recurrence.

16.1.10 Radiotherapy

Among the 26 pregnant patients with cervical carcinoma managed primarily with radiation therapy in the study published by Sood *et al.*¹⁸⁸¹, three patients were diagnosed in the first trimester, 6 in the second, and 17 in the third. All patients in the second trimester underwent hysterotomy prior to radiation, and in all cases the infant died. Among the 15 patients for whom there was not a planned delay in treatment, 2 infants born at 27 and 29 weeks died of complications related to prematurity. All other infants were 34 weeks at birth and had no significant morbidity or mortality. All the patients diagnosed during the first trimester were treated with radiation with the fetus in situ, and all had spontaneous abortions 20-24 days after the start of radiation (mean dose: 34 Gy). The authors reported no statistically significant differences in recurrence rates or survival between the pregnant group and the controls. Short term toxicity was comparable in pregnant and nonpregnant patients and easily controlled. Long term complications were more common in controls but the difference was not statistically significant.

LoE 3

It should be noted that their observations of patients irradiated in the first trimester of pregnancy were consistent with two previous reports^{1883,1942}. Another previous study reported that in the second trimester, fetal issues appear to be less sensitive to radiation, and spontaneous abortion is more delayed and occurs less reliably¹⁸⁷⁵. It should be noted that the

results of these previous reports^{1875,1883,1942} and those of the other previous identified studies^{1876,1877,1928,1943,1944} evaluating the radiotherapeutic management of cervical carcinoma diagnosed during pregnancy are limited notably by (1) the very small number of patients evaluated, (2) the inclusion of patients treated up to several months postpartum, and/or (2) the heterogeneity of radiotherapy protocols used.

16.1.11 Chemoradiotherapy

Very few cases^{1945,1946} of cervical cancer in pregnant patients treated with chemoradiation have been identified. The first published article¹⁹⁴⁵ focused on the modalities of uterine evacuation and not on the impact on the outcomes of two patients (patients were followed up only 12 months after the end of treatment). In this report, women diagnosed with FIGO stage IB2 cervical cancer at approximately 15 weeks gestation, underwent radiotherapy with radiosensitizing chemotherapy. After intrauterine fetal demise was detected, both women underwent induction with misoprostol. Results included one complete abortion and one incomplete abortion without complications or delays in treatment.

LoE 3

In the second report¹⁹⁴⁶, two patients were treated using chemoradiation therapy with fetus in utero for advanced-stage squamous cervical carcinoma diagnosed during the first trimester of pregnancy. The first patient with a FIGO stage IVA disease diagnosed at 12 weeks of gestation recurred 20 months after the end of the treatment and died of the disease. The second patient had a FIGO stage IIB disease diagnosed at 12 weeks of gestation and was treated by chemoradiation therapy followed by completion surgery (radical hysterectomy and para-aortic lymphadenectomy) due to the presence of a suspicious residual disease. This patient was alive and free of disease 24 months after surgery. In this report, the uterine evacuation occurred spontaneously in one case and was performed surgically in the other case.

16.1.12 Mode of delivery

As part of multivariate analysis, Sood *et al.*¹⁹⁴⁷ reported that vaginal delivery was the most significant predictor of recurrence (OR = 6.91 (95% CI = 1.45-32.8)), followed by high stage (OR = 4.66 (95% CI = 1.05-20.8)).

LoE 2-

Survival after vaginal delivery appeared to be worse than after a cesarean section in two studies^{1948,1949}, but it should be noted that (1) the p value was not specified and (2) seven other identified studies^{1883,1884,1892,1894,1928,1944,1950} did not report a significant difference in survival between vaginal delivery and abdominal delivery. Several case reports^{1943,1951-1954} have described tumour implantation in episiotomy sites with a poor prognosis. Only one identified report¹⁹⁵⁵ described a recurrence where the cesarean section had been performed. It should be noted that two cases^{1956,1957} of placental metastasis of cervical cancer have been published.

LoE 3

16.2 Previous initiatives

Eight previous initiatives presenting guidelines^{423,424,426,529,531,1958-1960} on the management of cervical cancer in pregnancy were identified.

16.3 Development group comments

Today due to improved prenatal care, majority of cervical cancers coincidental diagnosed in pregnancy are detected in early stages. In the last century, oncologic therapy has predominantly focussed on women's outcome and radical hysterectomy (following cesarean section or primary with fetus in situ) was first recommendation independent from week of pregnancy. Given the limited number of studies and case reports even today there is a low level of evidence for following recommendations.

Nearly all women with histological proven lymph node metastases of cervical cancer in pregnancy recur or die post partum. Therefore and due to limited validity of imaging systems in pregnancy, surgical lymph node staging predominantly done by minimal-invasive approach can be safely performed. In pregnancies later than 24 weeks of gestation (fetal viability) lymph node dissection is not indicated.

Conisation in pregnancy for diagnostic or therapeutic purposes can be associated with considerable bleeding and higher rates for non in sano resection of CIN III and invasive cancer. Vaginal, total laparoscopic or abdominal trachelectomy are challenging procedures in pregnancy. Especially abdominal radical trachelectomy can induce second trimester miscarriages or accompanied by live-threatening bleeding.

Radical hysterectomy in graviditate following cesarean section or with fetus in situ is feasible without increased intra- or postoperative morbidity and does not worsen oncologic outcome. Primary chemoradiotherapy in early pregnancy induces spontaneous abortion and use of misoprostol can simplify uterine evacuation. Depending on tumor stage and gestational age at diagnosis delay of oncologic therapy between 3-29 weeks does seem to have no negative effect on maternal outcome.

Available data are inconsistent with respect to best regimen and maximal number of NACT cycles. In accordance to other gynecologic tumor entities in pregnancy different neoadjuvant combination schemata empirical do not cause permanent development delay of fetus/children. However, potential risks and benefits of cumulative chemotherapy have to be balanced with possible problems of fetal prematurity. MRT can be used to monitor effect of NACT in pregnant patients with proven cervical cancer.

There are conflicting data with respect to mode of delivery. Occurrence of episiotomy scar recurrence can be associated with negative oncologic outcome. Until more valid data available, cesarean section should be preferred mode of delivery.

16.4 Guidelines

- ✓ Every patient diagnosed with CCIP must be counseled by a multidisciplinary team. This team should consist of experts in the fields of gynecologic 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 patient's intention, tumor 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 gynecologic oncology centers associated with a highest level perinatal center with expertise in all aspects of oncologic therapy in pregnancy and intensive medical care of premature neonates. Because of the low incidence of CCIP, centralization 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. Because of limited experience and inherent radioactivity PET-CT (PET-MRI) should be indicated only under very selected circumstances.
- ✓ Tumor involvement of suspicious nodes should be verified histologically because of its prognostic significance and the impact on the management up to 24th week of gestation (fetal viability), preferably by minimally invasive approach.

D

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

- Adapted surgery including removal of the tumor: conization, 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 weeks of gestation) and beginning of cancer-specific treatment immediately after delivery by cesarean section.
- Chemotherapy until fetal maturity and beginning of cancer specific treatment immediately after delivery by cesarean section. Treatment after delivery must consider application of previous chemotherapy. In patients with locally advanced stage or with residual tumor after conization that cannot be completely excised (risk of premature rupture of membranes (PROM) 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, cesarean section after the 32nd week of gestation (if possible) is the recommended mode of delivery. At the time of or following cesarean section, definitive stage-adjusted oncologic therapy has to be performed corresponding to that of nonpregnant women, taking into account therapy that has already been given during pregnancy.

Table 49. Original studies presenting maternal outcome data in patients managed with delay before definitive treatment of the cervical tumour post-partum

Author ^{reference}	Year	N	Histologic subtype	Gestational age at diagnosis (weeks)	Delay (weeks)	Follow-up (months)	Progression during delay	Status
FIGO stage I								
Prem <i>et al.</i> ¹⁸⁷⁵	1966	5	nr	20-34	11-17	34-64	nr	NED
Dudan <i>et al.</i> ¹⁸⁷⁶	1973	2	nr	nr	8-16	nr	IIA, IIIB	nr
FIGO stage IA								
Thompson <i>et al.</i> ¹⁸⁷⁷	1975	7	nr	nr	5-28	3-120	no	NED
FIGO stage IA1								
Boutselis <i>et al.</i> ¹⁸⁷⁸	1972	5	nr	8-24	nr	72-180	no	NED
Lee <i>et al.</i> ¹⁸⁷⁹	2008	4	SCC (2), ACC (1), AM (1)	11, 6, 6, 18	27, 9, 34, 18	27, 9, 34, 18	nr	NED
Lin <i>et al.</i> ¹⁸⁸⁰	2013	1	SCC	10	nr	7	nr	NED
FIGO stage IA2								
Sood <i>et al.</i> ¹⁸⁸¹	1997	2	SCC	3 rd trimester	3, 3	nr	nr	NED
Ben-Arie <i>et al.</i> ¹⁸⁸²	2004	1	SCC	15	nr	24	nr	NED
FIGO stage IB								
Lee <i>et al.</i> ¹⁸⁸³	1981	1	SCC	24	12	120	no	NED
Nisker <i>et al.</i> ¹⁸⁸⁴	1983	1	nr	2 nd trimester	24	nr	nr	DOD
Greer <i>et al.</i> ¹⁸⁸⁵	1989	1	GCC	22	6	15	nr	DOD
		4	SCC (4)	20, 21, 24, 24	17, 14, 10, 11	13, 26, 27, 35	nr	NED
Monk <i>et al.</i> ¹⁸⁸⁶	1992	3	nr	19-23	10-16	2-6	nr	NED
Duggan <i>et al.</i> ¹⁸⁸⁷	1993	5	nr	19, 15, 30, 28, 27	12, 21, 24, 19, 7	16, 34, 10, 30, 34	nr	NED
Allen <i>et al.</i> ¹⁸⁸⁸	1995	2	SCC (2)	16, 16	18, 19	69, 62	nr	NED
Sorosky <i>et al.</i> ¹⁸⁸⁹	1995	7	nr	18, 8, 16, 21, 28, 18, nr	15, 22, 29, 16, 7, 19, 40	68, 60, 43, 42, 23, 19, 13	nr	NED
Sorosky <i>et al.</i> ¹⁸⁹⁰	1996	5	nr	18, 18, 32, 16, 8	15, 15, 9, 22, 28	67, 12, 120, 52, 48	nr	NED
Van Vliet <i>et al.</i> ¹⁸⁹¹	1998	2	nr	23, 26	6, 10	16, 106	nr	NED
Germann <i>et al.</i> ¹⁸⁹²	2005	4	nr	2 nd trimester	4-16	60	nr	NED

ACC adenocarcinoma, AM adenoma malignum, DOD dead of disease, GCC glassy cell carcinoma, NED no evidence of disease, nr not reported, SCC squamous cell carcinoma

Original studies presenting maternal outcome data in patients managed with delay before definitive treatment of the cervical tumour post-partum (continued)

Author ^{reference}	Year	N	Histologic subtype	Gestational age at diagnosis (weeks)	Delay (weeks)	Follow-up (months)	Progression during delay	Status
FIGO stage IB1								
Sood <i>et al.</i> ¹⁸⁹³	1996	3	SCC	nr	3-32	12-360	no	NED
Zanetta <i>et al.</i> ¹⁸⁶¹	1998	3	ACC (3)	20,, 20, 25	18, 15, 13	49, 40, 55	no	NED
Takushi <i>et al.</i> ¹⁸⁹⁴	2002	2	SCC	18, 17	13, 15	97, 108	nr	NED
Germann <i>et al.</i> ¹⁸⁹²	2005	5	nr	1 st trimester	12-24	60	nr	NED
Traen <i>et al.</i> ¹⁸⁹⁵	2006	1	SCC	14	16	30	nr	NED
Lee <i>et al.</i> ¹⁸⁷⁹	2008	4	SCC (2), CC (1), SMC (1)	11, 14, 23, 23	25, 18, 13, 14	58, 15, 22, 12	nr	NED (4)
		1	ASqC (1)	25	6	34	nr	DOD (1)
Alouini <i>et al.</i> ¹⁸⁶⁷	2008	3	SCC (2), ACC (1)	15, 20, 2	9, 12, 15	14, 26, 84	nr	NED
Ishioka <i>et al.</i> ¹⁸⁹⁶	2009	2	SCC (2)	21, 25	6, 9	17, 120	no	NED
Gurney <i>et al.</i> ¹⁸⁹⁷	2009	1	SCC	21	nr	10	no	NED
Favero <i>et al.</i> ¹⁸⁶⁵	2010	6	SCC (5), ACC (1)	12, 14, 14, 22, 23, 23	9, 11, 13, 18, 26, 28	9, 11, 13, 18, 26, 28	nr	NED
FIGO stage IB2								
Takushi <i>et al.</i> ¹⁸⁹⁴	2002	1	SCC	26	6	84	nr	NED
Stan <i>et al.</i> ¹⁸⁶⁸	2005	1	SCC	16	20	48	no	NED
Alouini <i>et al.</i> ¹⁸⁶⁷	2008	1	SCC	25	7	62	nr	NED
		1	SCC	20	8	17	nr	DOD
Ishioka <i>et al.</i> ¹⁸⁹⁶	2009	1	SCC	11	19	111	no	NED
Favero <i>et al.</i> ¹⁸⁶⁵	2010	1	ACC	23	12	68	nr	NED
FIGO stage IIA								
Allen <i>et al.</i> ¹⁸⁸⁸	1995	1	SCC	21	56	88	nr	NED
Lee <i>et al.</i> ¹⁸⁷⁹	2008	1	SCC	20	17	75	nr	NED
FIGO stage IIB								
Ishioka <i>et al.</i> ¹⁸⁹⁶	2009	1	ACC	25	3	10	no	NED
FIGO stage IIIB								
Lee <i>et al.</i> ¹⁸⁷⁹	2008	1	SCC	32	3	104	nr	NED

ACC adenocarcinoma, ASqC adenosquamous carcinoma, CC clear cell carcinoma, DOD dead of disease, NED no evidence of disease, nr not reported, SCC squamous cell carcinoma, SMC small cell carcinoma

Table 50. Original studies presenting data in patients treated with NACT during pregnancy

Author ^{reference}	Year	N	NACT	Response	Treatment	Follow-up (months)	Status	Baby
FIGO stage IB1								
Giacalone <i>et al.</i> ¹⁸⁹⁸	1996	1	CisP	CR	CS/RH/PLND/PALND	12	NED	well
Caluwaerts <i>et al.</i> ¹⁸⁹⁹	2006	1	CisP	PR	CS/RH/PLND/PALND	10	NED	well
de Lima <i>et al.</i> ¹⁹⁰⁰	2013	1	CisP, VinC	PR	CS/RH/PLND/CT	24	NED	well
Chun <i>et al.</i> ¹⁹⁰¹	2010	1	CisP, Tax	PR	CS/RH/PLND/PALND	49	DOD	well
Kong <i>et al.</i> ¹⁹⁰²	2014	2	CisP, Tax	PR	CS/RH/PLND/CT	24, 104	NED	well
Favero <i>et al.</i> ¹⁹⁰³	2010	5	CisP	nr	nr	5, 10, 12	NED (3) nr (2)	nr
Fruscio <i>et al.</i> ¹⁹⁰⁴	2010	4	CisP	PR (3), SD (1)	CS/RH (4)	41-65	NED	well
Lanowska <i>et al.</i> ¹⁹⁰⁵	2011	7	CisP	nr	CS/RH (6) CS/RH/CT/RT (1)	1, 1, 3, 3, 7, 12, 17	NED	well
Ayhan <i>et al.</i> ¹⁹²⁴	2012	1	CisP	CR	CS/RH/PLND	36	NED	well
Hecking <i>et al.</i> ¹⁹⁰⁶	2016	1	CisP	SD	CS/RH/CT/RT	26	NED	well
FIGO stage IB2								
Lai <i>et al.</i> ¹²⁰⁵	1997	2	CisP, VinC, Bleo	SD (1), PR (1)	CS/RH (2)	52, 59	DOD	nr
Tewari <i>et al.</i> ¹⁹⁰⁸	1998	1	CisP, VinC	PR	CS/RH/PLND	24	NED	well
Karam <i>et al.</i> ¹⁹⁰⁹	2007	1	CisP	nr	CS/RH/PLND/PALND	14	NED	well
Smyth <i>et al.</i> ¹⁹⁰⁷	2010	1	Adria, Cyclo	PR	CS	nr	NED	well
Chun <i>et al.</i> ¹⁹⁰¹	2010	1	CisP, Tax	PR	CS/RH/PLND/PALND	60	NED	well
Rabaiotti <i>et al.</i> ¹⁹¹⁰	2010	1	CisP	SD	CS/RT	24	DOD	well
Li <i>et al.</i> ¹⁹¹¹	2011	2	CisP, Tax	PR (2)	CS/RT (1), CS (1)	13, 21	NED	well
Lanowska <i>et al.</i> ¹⁹⁰⁵	2011	1	CisP	Nr	CS/RH/CT/RT	1	NED	well
Islam <i>et al.</i> ⁵⁶²	2011	1	CisP	PR	CS/RH/CT/RT/PLND	36	NED	well
Fruscio <i>et al.</i> ¹⁹⁰⁴	2012	5	CisP, VinC (1) CisP (2) CisP, Tax (2)	PR (3) SD (2)	CS/RH/RT (2) CS/RH (3)	13,21, 27, 113, 153	NED (4) DOD (1)	well
Yousefi <i>et al.</i> ¹⁹¹²	2013	1	CisP, Tax	nr	CS/RH	nr	nr	well
Kong <i>et al.</i> ¹⁹⁰²	2014	1	CisP, Tax	PR	CS/RH/PLND/CT	35	NED	well
Peculis <i>et al.</i> ¹⁹¹³	2015	1	CisP, Adria	CR	CS/RH/PLND	20	NED	well
Wang <i>et al.</i> ¹⁹¹⁴	2015	1	CisP, Eto	CR	RT/BT	8	NED	nr
FIGO stage IIA								
Tewari <i>et al.</i> ¹⁹⁰⁸	1998	1	CisP, VinC	PR	CS/RH/PLND	5	DOD	well
Balderston <i>et al.</i> ¹⁹¹⁵	1998	1	CisP, Eto, Dac, Cyclo	PR	CS/CT/RT	66	NED	well
Bader <i>et al.</i> ¹⁹¹⁶	2007	1	CisP, VinC	PR	CS/RH/PLND	80	NED	well
Chun <i>et al.</i> ¹⁹⁰¹	2010	1	Carbo, Tax	PR	CS/RH/PLND/PALND	48	AWD	well
FIGO stage IIB								
Marana <i>et al.</i> ¹⁹¹⁷	2001	1	CisP, Bleo	nr	CS	13	DOD	well
Palaia <i>et al.</i> ¹⁹¹⁸	2007	1	CisP, Tax	PR	RH/PLND	10	NED	well
Boyd <i>et al.</i> ¹⁹¹⁹	2009	1	CisP	nr	RT	15	NED	well
Lanowska <i>et al.</i> ¹⁹⁰⁵	2011	1	CisP	nr	CS/RH/CT/RT	3	NED	well
da Fonseca <i>et al.</i> ¹⁹²⁰	2011	1	CisP, VinC	CR	CS/RH/PLND/PALND	12	NED	well
Dawood <i>et al.</i> ¹⁹²¹	2013	1	CisP	PD	CS/CT/RT/BT	24	DOD	well
FIGO stage IIIB								
Benhaim <i>et al.</i> ¹⁹²²	2008	1	CisP, VinC	PD	CT/RT	10	DOD	well
Seamon <i>et al.</i> ¹⁹²³	2009	1	CisP, VinC	PR	RT	48	NED	well

Adria adriamycin, AWD alive with disease, Bleo bleomycin, BT brachytherapy, Carbo carboplatin, CisP cisplatin, CR complete response, CS cesarean section, CT chemotherapy, Cyclo cyclophosphamide, Dac dactinomycin, DOD dead of disease, Eto etoposide, NACT neoadjuvant chemotherapy, NED no evidence of disease, nr not reported, PALND para-aortic lymph node dissection, PLND pelvic lymph node dissection, PR partial response, RH radical hysterectomy, RT radiation therapy, SD stable disease, Tax paclitaxel, VinC vincristine

Table 51. Original studies presenting data in patients treated with radical trachelectomy as a fertility-preserving alternative to radical hysterectomy

Author ^{reference}	Year	N	Age (years)	Pre-trachelectomy		Intraop. compl.	Post-trachelectomy diagnosis	Tumour size	Cancer recur.	Follow-up (months)	Fetal demise	Gestational age (weeks)		Cesarean section
				Type	FIGO stage							at trachelectomy	at delivery	
Abdominal radical trachelectomy														
Ungar <i>et al.</i> ¹⁹³¹	2006	5	25 (1) nr (4)	SCC (5)	IB1 (5)	none	no change	nr	none	40 (10-60)	yes (3) no (2)	7, 8, 9, 13, 18	38, 39 NA (3)	yes (2) NA (3)
Mandic <i>et al.</i> ¹⁹³⁴	2009	1	27	PC	IB1	none	no change	4 mm	none	12	no	19	36	yes
Karateke <i>et al.</i> ⁸⁵⁸	2010	1	25	SCC	IB1	none	SCC, stage IB2	5 x 5 cm	nr	nr	yes	22	22	NA
Abu-Rustum <i>et al.</i> ¹⁹³²	2010	1	37	LE-like	IB1	nr	no change	12 mm	none	12	no	15	39	yes
Enomoto <i>et al.</i> ¹⁹³³	2011	1	27	SCC	IB1	nr	SCC, pT2a1, pN0, pM0	nr	none	6	no	15	37	yes
Radical vaginal trachelectomy														
Van de Nieuwenhof <i>et al.</i> ¹⁹³⁵	2008	1	30	SCC	IB1	none	Severe cervical dysplasia	8 x 2.3 mm	none	9	no	18	36	yes
Alouini <i>et al.</i> ¹⁸⁶⁷	2008	2	28 32	SCC ACC	IB1 IB1	none	no change	20 mm 25 mm	1	132 36	yes (1) no (1)	12 12	12 30	yes (1) NA (1)
Iwami <i>et al.</i> ¹⁹³⁶	2011	1	32	ACC	IB1	none	no change	nr	none	14	no	16	34	yes
Sioutas <i>et al.</i> ¹⁸⁷⁰	2011	3	34 36 37	ASqC (1) ACC (1) SCC (1)	IB1 (2) IA2 (1)	none	SCC in situ Atypical glandular cells Mild cervical dysplasia	nr nr 3.6 mm	none	47 30 27	no (3)	13+5 13+1 12+6	37 + 4 29 + 4 37 + 2	yes (3)
Ferriaioli <i>et al.</i> ¹⁹³⁷	2012	5	29 28 26 30 30	SCC (3) ACC (2)	IB1 (3) IA2 (2)	none	no change	12 x 7 mm 10 x 4 mm 4 x 2 mm 27 x 18 mm 12 x 5 mm	1	204 240 120 nr 200	yes (2) no (3)	4 6 2 20 26	34 36 35 NA: N = 2	yes (3) NA (2)
Bravo <i>et al.</i> ¹⁹³⁸	2012	1	41	NK SCC	IB1	none	NK SCC with grade III CIN	35 x 30 x 30 mm	none	40	no	11	36	yes
Kolomainen <i>et al.</i> ¹⁹³⁹	2013	1	27	ACC	nr	none	ACC, IB2	42 mm	none	46	no	16	26	yes
Saso <i>et al.</i> ¹⁹⁴⁰	2015	1	22	SCC	IB1	none	no change	nr	none	16	no	19	36	yes

ACC adenocarcinoma, ASqC adenosquamous carcinoma, CIN cervical intra-epithelial neoplasia, Intraop. compl. Intraoperative complications, LE Lymphoepithelioma, NA not applicable, NK non-keratinizing, nr not reported, PC planocellular carcinoma, recurr. recurrence, SCC squamous cell carcinoma

17 Acronyms and abbreviations

3D 3-dimensional	CIN cervical intraepithelial neoplasia
5-FU 5-fluorouracil	CKC cold knife conisation
ACC adenocarcinoma	CoCanCPG coordination of cancer clinical practice guidelines
ACPG alberta clinical practice guidelines	COMPAQ-HPST coordination pour la mesure de la performance et l'amélioration de la qualité, hôpital, patient, sécurité, territoire
AGDH australian government department of health	CR complete response
AHRQ agency for healthcare research and quality	CRS conventional radical surgery
AM adenoma malignum	CS cesarean section
AQuAS agència de qualitat i avaluació sanitàries de Catalunya	CT computed tomography
ARH abdominal radical hysterectomy	CTV-T _{HR} high-risk clinical target volume
ASqC adenosquamous carcinoma	CTV-T _{IR} intermediate-risk clinical target volume
ASCO american society of clinical oncology	CYFRA 21-1 cytokeratin fragment 21-1
AWD alive with disease	DFS disease-free survival
BCCA british columbia cancer agency	DOD dead of disease
BMI body mass index	DSS disease-specific survival
BT brachytherapy	EBRT external beam radiotherapy
CA 125 cancer antigen 125	EORTC european organization for research and treatment of cancer
CA 15-3 cancer antigen 15-3	EORTC-CGC european organization for research and treatment of cancer-gynecological cancer group
CADTH canadian agency for drugs and technologies in health	EQD2 equi-effective dose to 2 Gy
CCIP cervical cancer in pregnancy	ESGO european society of gynaecological oncology
CCO cancer care ontario	ESMO european society of medical oncology
CCRT concurrent chemoradiotherapy	ESP european society of pathology
CEA carcinoembryonic antigen	ESTRO european society for radiotherapy and oncology
CEPO comité de l'évolution des pratiques en oncologie	FACT-Cx functional assessment of cancer therapy-cervix
CES-D epidemiologic studies depression scale	FEM fixed-effects method
CI confidence interval	
CIC circulating immune complexes	

FIGO fédération internationale de gynécologie et d'obstétrique	KCE centre fédéral d'expertise des soins de santé
FSFI female sexual functioning index	LACC locally advanced cervical cancer
FSS fertility sparing surgery	LARVH laparoscopic-assisted radical vaginal hysterectomy
FST fertility sparing treatment	LDR low-dose rate
GCC glassy cell carcinoma	LEEP loop electrosurgical excision procedure
GCIG gynecologic cancer intergroup	LH laparoscopic hysterectomy
GEC-ESTRO groupe européen de curiethérapie - european society for radiotherapy and oncology	LLETZ large loop excision of the transformation zone
GIN guidelines international network	LN lymph node
GTV-T _{res} residual gross tumor volume	LN+ positive lymph nodes
HAS haute autorité de santé	LND lymph node dissection
HDR high-dose rate	LVSI lymphovascular space involvement
H&E haematoxylin and eosin	M-H mantel- haenszel
HPV human papillomavirus	MD mean difference
HR hazard ratio	MRI magnetic resonance imaging
hsCRP high sensitivity C-reactive protein	MSAC medical services advisory committee
IAP immunosuppressive acidic protein	NA not available
ICG indocyanine green	NAB-paclitaxel nano-particule albumin bound paclitaxel
IES impact of events scale	NACT neoadjuvant chemotherapy
IGABT image guided adaptive brachytherapy	NCCN national comprehensive cancer network
IGRT image guided radiotherapy	NED no evidence of disease
IHC immunohistochemistry	NHMRC national health and medical research council
IL-6 interleukin 6	NHS national health service
IMRT intensity modulated radiotherapy	NICE national institute for health and care excellence
INAHTA international network of agencies for health technology assessment	NICU neonatal intensive care unit
INCa institut national du cancer	nr not reported
INESSS institut national d'excellence en santé et en services sociaux	NSRS nerve-sparing radical surgery
IORT intraoperative radiation therapy	NZGG new zealand guidelines group
IV inverse variance	

OH open hysterectomy	RR relative risk
OR odd ratio	RT radiation therapy
OS overall survival	SCC squamous cell carcinoma
OT ovarian transposition	SCC-Ag squamous cell carcinoma antigen
PALN para-aortic lymph node	SD stable disease
PALND para-aortic lymph node dissection	SDM standard differences in means
PDR pulsed-dose rate	SEER surveillance, epidemiology, and end results
PET positron emission tomography	SH simple hysterectomy
PET-CT positron emission tomography-computed tomography	SIGN scottish intercollegiate guidelines network
PFS progression-free survival	SLN sentinel lymph node
PLN pelvic lymph node	SMC small cell carcinoma
PLND pelvic lymph node dissection	SN sentinel node
pPROM preterm spontaneous rupture of membranes	TATI tumour-associated trypsin inhibitor
PR partial response	TNF- α tumour necrosis factor alpha
PROM premature rupture of membranes	TPA tissue polypeptide antigen
PTL preterm labour	US ultrasound
RCT randomized controlled trial	VALRH vaginal-assisted laparoscopic radical hysterectomy
REM random-effects method	VEGF vascular endothelial growth factor
RFS relapse-free survival	WG weeks gestation
RH radical hysterectomy	WMD weighted mean difference

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19 Appendices

19.1 Appendix 1 - People involved in the development of the guidelines

19.1.1 List of the international development group

Name	Specialty	Affiliation
David Cibula	Surgeon (chair)	Gynecologic Oncology Center, Department of Obstetrics and Gynecology, First Faculty of Medicine, Charles University and General University Hospital, Prague (Czech Republic)
Richard Pötter	Radiation oncologist (chair)	Medical University of Vienna, Vienna (Austria)
Maria Rosaria Raspollini	Pathologist (chair)	University Hospital, Careggi - Florence (Italy)
François Planchamp	Methodologist	Institut Bergonié, Bordeaux (France)
Elisabeth Avall-Lundqvist	Medical oncologist	Linköping University, Linköping (Sweden)
Daniela Fischerova	Radiologist	Gynecologic Oncology Center, Department of Obstetrics and Gynecology, First Faculty of Medicine, Charles University and General University Hospital, Prague (Czech Republic)
Christine Haie Meder	Radiation oncologist	Institut Gustave Roussy, Villejuif (France)
Christhardt Köhler	Surgeon	Asklepios Hambourg Altona and University of Cologne, Medical Faculty, Department of Gynecology (Germany)
Fabio Landoni	Surgeon	University of Milan Bicocca, Monza (Italy)
Sigurd Lax	Pathologist	General Hospital Graz Sued-West, Graz (Austria)
Jacob Christian Lindegaard	Radiation oncologist	Aarhus University, Aarhus (Denmark)
Umesh Mahantshetty	Radiation oncologist	Tata Memorial Hospital, Mumbai (India)
Patrice Mathevet	Surgeon	Lausanne University, Lausanne (Switzerland)
W Glenn McCluggage	Pathologist	Department of Pathology, Belfast Health And Social Care Trust, Belfast (United Kingdom)
Mary McCormack	Medical oncologist	University College Hospital London, London (United Kingdom)
Raj Naik	Surgeon	Queen Elizabeth Hospital, Gateshead (United Kingdom)
Remi Nout	Radiation oncologist	Leiden University, Leiden (Netherlands)
Sandro Pignata	Medical oncologist	Istituto Nazionale per lo Studio e la Cura dei Tumori "Fondazione G Pascale", IRCCS, Naples (Italy)
Jordi Ponce	Surgeon	University Hospital of Bellvitge (IDIBELL), Barcelona (Spain)
Denis Querleu	Surgeon	Institut Bergonié, Bordeaux (France)
Francesco Raspagliesi	Surgeon	Fondazione IRCCS Istituto Nazionale Tumori, Milan (Italy)
Alexandros Rodolakis	Surgeon	Athens University, Athens (Greece)
Karl Tamussino	Surgeon	Medical University of Graz, Graz (Austria)
Pauline Wimberger	Surgeon	Dresden University, TU Dresden, Dresden (Germany)

19.1.2 List of external panel of physicians and patients (international reviewers)

Name	Physician/Patient	Country
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Patriciu Achimas-Cadariu	Obstetric & gynaecology	Romania
Stefan Aebi	Medical oncology	Switzerland
Anastazija Aleksandrova Stanojevic	Radiation oncology	Croatia
Igor Aluloski	Gynaecology	Republic of Macedonia
Frederic Amant	Gynaecological oncology	Belgium
Anonymous	Patient	United Kingdom
Natalia Artymuk	Obstetric & gynaecology	Russia
Syuzanna Babloyan	Obstetric & gynaecology	Armenia
Janos Balega	Gynaecological oncology	United Kingdom
Anne-Sophie Bats	Gynaecological oncology	France
Ergin Bengisu	Gynaecological oncology	Turkey
Virginia Benito	Gynaecological oncology	Spain
Margarida Bernardino	Gynaecological oncology	Portugal
Tatjana Bozanovic	Gynaecological oncology	Serbia
Maria Brito	Pathology	Portugal
Kjersti Bruheim	Clinical oncology	Norway
Katharina Buser	Medical oncology	Switzerland
Angelo Cagnacci	Obstetric & gynaecology	Italy
Rita Canas Marques	Pathology	Portugal
Cyrus Chargari	Radiation oncology	France
Annamaria Cerrotta	Radiation oncology	Italy
Karen Chatland-Svane	Patient	Denmark
Nicoletta Colombo	Gynaecological oncology	Italy
Ovidiu Florin Coza	Radiation oncology	Romania
Sabrina Croce	Pathology	France
Vasileia Damaskou	Pathology	Greece
Javier de Santiago Garcia	Gynaecological oncology	Spain
Suha Deen	Pathology	United Kingdom

Name <i>(continued)</i>	Physician/Patient	Country
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François Desmons	Gynaecological oncology	France
Javier Diez Garcia	Gynaecological oncology	Spain
Johannes Dimopoulos	Radiation oncology	Greece
Geanina Dragnea	Obstetric & gynaecology	Romania
Andreas du Bois	Gynaecological oncology	Germany
Michael Eichbaum	Gynaecological oncology	Germany
Guenter Emons	Gynaecological oncology	Germany
Brynhildur Eyjolfsdottir	Gynaecological oncology	Norway
Henrik Falconer	Gynaecological oncology	Sweden
Daniela Fanni	Pathology	Italy
Afshin Fazel	Gynaecological oncology	France
Scott Fegan	Gynaecological oncology	United Kingdom
Tanja Fehm	Gynaecological oncology	Germany
Ana Felix	Pathology	Portugal
Elena Fidarova	Radiation oncology	Austria
Jose Fonseca-Moutinho	Gynaecological oncology	Portugal
Michael Friedrich	Gynaecological oncology	Germany
Raji Ganesan	Pathology	United Kingdom
Antonio Gil Moreno	Gynaecological oncology	Spain
Noreen Gleeson	Gynaecological oncology	Ireland
Frederic Goffin	Gynaecological oncology	Belgium
Marek Gogacz	Obstetric & gynaecology	Poland
François Golfier	Obstetric & gynaecology	France
Mikel Gorostidi	Gynaecological oncology	Spain
Bjorn Hagen	Gynaecological oncology	Norway
Michael Halaska	Gynaecology	Czech Republic
Herman Haller	Gynaecological oncology	Croatia
Sissi Hamnström Cole	Patient	Sweden

Name (<i>continued</i>)	Physician/Patient	Country
Annette Hasenburg	Gynaecological oncology	Germany
Steffen Hauptmann	Pathology	Netherlands
Lukas Hefler	Gynaecological oncology	Germany
Gines Hernandez Cortes	Obstetric & gynaecology	Spain
Christoph Honegger	Gynaecological oncology	Switzerland
Lars-Christian Horn	Pathology	Germany
Peter Hoskin	Medical oncology	United Kingdom
Cem Iyibozkurt	Gynaecological oncology	Turkey
Robert Jach	Gynaecological oncology	Poland
Matias Jurado	Gynaecological oncology	Spain
Ina-Maria Jurgenliemk-Schulz	Radiation oncology	Netherlands
Ioannis Kalogiannidis	Gynaecological oncology	Greece
Sean Kehoe	Gynaecological oncology	United Kingdom
Vesna Kesic	Gynaecological oncology	Serbia
Rainer Kimmig	Gynaecological oncology	Germany
Gurkan Kiran	Gynaecological oncology	Turkey
Christian Kirisits	Radiation oncology: Medical Physicist	Austria
Preben Kjolhede	Obstetric & gynaecology	Sweden
Maximilian Klar	Gynaecological oncology	Germany
Pawel Knapp	Gynaecological oncology	Poland
Jan Kotarski	Gynaecological oncology	Poland
Stefan Miladinov Kovachev	Gynaecological oncology	Bulgaria
Frederic Kridelka	Obstetric & gynaecology	Belgium
Gunnar Kristensen	Gynaecological oncology	Norway
Ali Kucukmetin	Gynaecological oncology	United Kingdom
Antonio Lagoa	Gynaecological oncology	Portugal
Luis Ignacio Lete Lasa	Gynaecological oncology	Spain
Fabrice Lécuru	Gynaecology	France
Tally Levy	Gynaecological oncology	Israel

Name (<i>continued</i>)	Physician/Patient	Country
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Kristina Loessl	Radiation oncology	Switzerland
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Tiziano Maggino	Gynaecological oncology	Italy
Aljosa Mandic	Gynaecological oncology	Serbia
Simone Marnitz	Radiation oncology	Germany
Christian Marth	Gynaecological oncology	Austria
Leon Massuger	Gynaecological oncology	Netherlands
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Xavier Matias-Guiu	Pathology	Spain
Mihai Meirovitz	Gynaecological oncology	Israel
Santosh Menon	Pathology	India
Milos Mlyncek	Gynaecological oncology	Slovakia
Rodolfo Montironi	Pathology	Italy
Bahar Muezzinoglu	Pathology	Turkey
Peter Niehoff	Radiation oncology	Germany
Zoltan Novak	Gynaecological oncology	Hungary
Ernst Oberlechner	Gynaecological oncology	Germany
Felipe Ojeda	Gynaecological oncology	Spain
Claudia Ordeanu	Radiation oncology	Romania
Theo Panoskaltsis	Gynaecological oncology	Greece
Anna Pesci	Pathology	Italy
Patrick Petignat	Gynaecological oncology	Switzerland
Primoz Petric	Radiation oncology	Qatar
Bradley Pieters	Radiation oncology	Netherlands
Radovan Pilka	Obstetric & gynaecology	Czech Republic
Eleonore Piot	Patient	France
Igor Pljesa	Gynaecology	Serbia
Robert Poka	Obstetric & gynaecology	Hungary

Name <i>(continued)</i>	Physician/Patient	Country
Mario Preti	Gynecology	Italy
Anna Protasova	Gynaecological oncology	Russia
Athanasios Protopapas	Obstetric & gynaecology	Greece
Alin Cristian Rancea	Gynaecological oncology	Romania
Isabelle Ray-Coquard	Medical oncology	France
Nicholas Reed	Radiation oncology	United Kingdom
Alexader Reinthaller	Gynaecological oncology	Austria
Jose Ernesto Moro Rodriguez	Pathology	Spain
Angeles Rovirosa	Radiation oncology	Spain
Muzaffer Sancy	Gynaecological oncology	Turkey
Antonella Savio	Pathology	Italy
Wlodzimierz Sawicki	Gynaecological oncology	Poland
Sergio Schettini	Obstetric & gynaecology	Italy
Dietmar Schmidt	Pathology	Germany
Barbara Segedin	Radiation oncology	Slovenia
Cristiana Sessa	Medical oncology	Switzerland
Paul Sevelda	Gynaecological oncology	Austria
Alejandro Soderini	Gynaecological oncology	Argentina
Erik Soegaard-Andersen	Gynaecological oncology	Denmark
Philippe Simon	Gynaecological oncology	Belgium
Tayup Simsek	Gynaecological oncology	Turkey
Naveena Singh	Pathology	United Kingdom
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Drago Sredanovic	Obstetric & gynaecology	Slovenia
Hana Stankusova	Radiation oncology	Czech Republic
Artem Stepanyan	Gynaecological oncology	Armenia
Simona Stolnicu	Pathology	Romania
Vratislav Strnad	Radiation oncology	Germany
Alina Sturdza	Radiation oncology	Austria

Name <i>(continued)</i>	Physician/Patient	Country
Jacek Sznurkowski	Gynaecological oncology	Poland
Li Tee Tan	Clinical oncology	United Kingdom
Kari Tanderup	Radiation oncology: Medical Physicist	Denmark
Alexandra Taylor	Clinical oncology	United Kingdom
Ico Toth	Patient	Hungary
Jacobus van der Velden	Gynaecological oncology	Netherlands
Rene Henricus Maria Verheijen	Gynaecological oncology	France
Elena Villafranca	Radiation oncology	Spain
Boris Vranes	Gynaecological oncology	Serbia
Jacek Wilczynski	Gynaecological oncology	Poland
Edward Wight	Epidemiology	Switzerland
Petronella Witteveen	Medical oncology	Netherlands
Gian Franco Zannoni	Pathology	Italy
Vanna Zanagnolo	Gynaecological oncology	Italy

19.2 Appendix 2 - List of evidence-based medicine websites consulted

Organism/agency	Website
ACPG	http://www.topalbertadoctors.org/home/
AGDH	http://www.health.gov.au/
AHRQ	http://www.guideline.gov/
AQuAS	http://aquas.gencat.cat/ca/
ASCO	http://www.asco.org/
BCCA	http://www.bccancer.bc.ca/default.htm
CADTH	http://www.cadth.ca/
CCO	https://www.cancercare.on.ca/
CEPO	http://www.msss.gouv.qc.ca/index.php
COMPAQ-HPST	http://www.compaqhpst.fr/fr/
CoCanCPG	http://www.cocancpg.eu/
ESMO	http://www.esmo.org/
GIN	http://www.g-i-n.net/
HAS	http://www.has-sante.fr/portail/jcms/fc_1249588/fr/accueil
INAHTA	http://www.inahta.org/
INESSS	http://www.inesss.qc.ca/
INCa	http://www.e-cancer.fr/
KCE	https://kce.fgov.be/fr
MSAC	http://www.msac.gov.au/
NCCN	http://www.nccn.org/
NHMRC	http://www.nhmrc.gov.au/
NHS	http://www.nhs.uk/Pages/HomePage.aspx
NICE	http://www.nice.org.uk/
NZGG	http://www.health.govt.nz/
SIGN	http://www.sign.ac.uk/

ACPG Alberta clinical practice guidelines, AGDH Australian government department of health, AHRQ agency for healthcare research and quality, AQuAS agència de qualitat i avaluació sanitàries de Catalunya, ASCO American society of clinical oncology, BCCA British Columbia cancer agency, CADTH Canadian agency for drugs and technologies in health, CCO cancer care Ontario, CEPO comité de l'évolution des pratiques en oncologie, CoCanCPG coordination of cancer clinical practice guidelines in Europe, COMPAQ-HPST coordination pour la mesure de la performance et l'amélioration de la qualité, hôpital, patient, sécurité, territoire, ESMO European society of medical oncology, GIN guidelines international network, HAS haute autorité de santé, INAHTA international network of agencies for health technology assessment, INCa institut national du cancer, INESSS institut national d'excellence en santé et en services sociaux, KCE centre fédéral d'expertise des soins de santé, MSAC medical services advisory committee, NCCN national comprehensive cancer network, NHMRC national health and medical research council, NHS national health service, NICE national institute for health and care excellence, NZGG New Zealand guidelines group, SIGN Scottish intercollegiate guidelines network.

19.3 Appendix 3 - Key to evidence statements and grades of recommendations¹

LEVELS OF EVIDENCE

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
1-	Meta-analyses, systematic reviews, or RCTs with a high 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
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

GRADES OF RECOMMENDATIONS

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+

GOOD PRACTICE POINTS

✓	Recommended best practice based on the clinical experience of the guideline development group
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¹ <http://www.sign.ac.uk/guidelines/fulltext/50/annexoldb.html>



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