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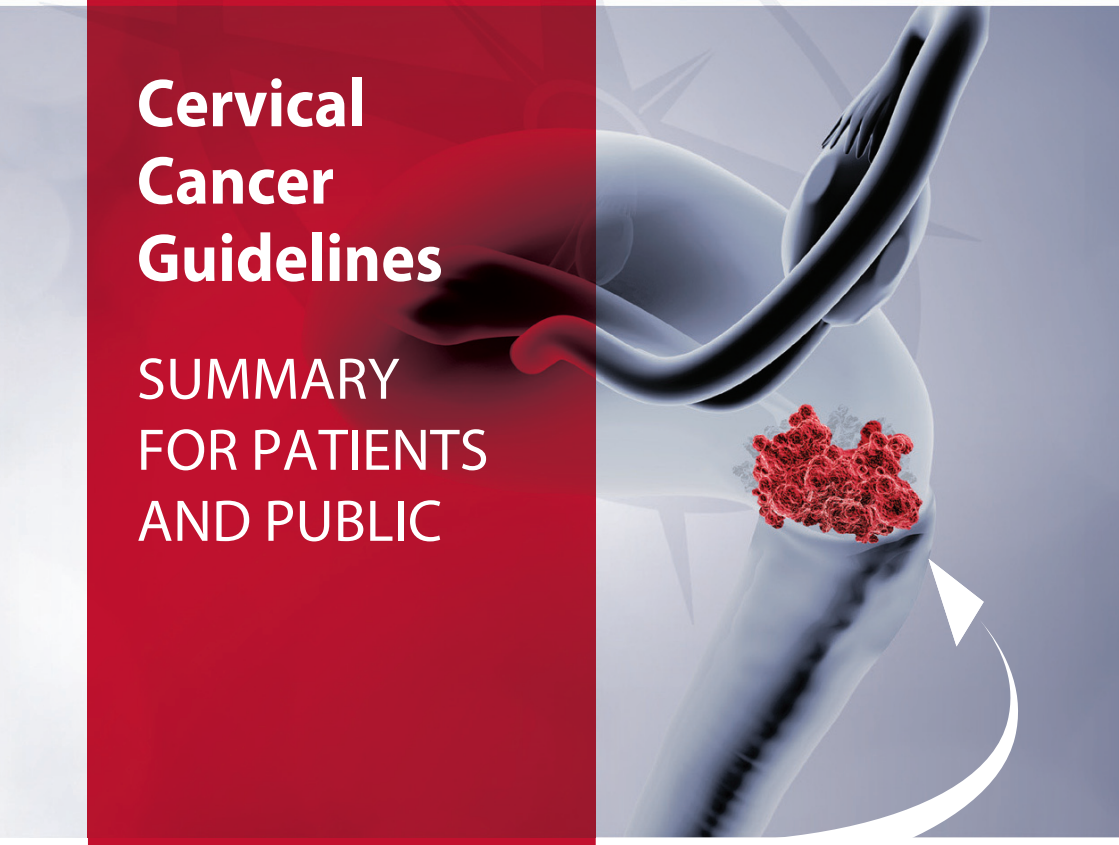
Cervical Cancer Guidelines

SUMMARY FOR PATIENTS AND PUBLIC



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The European Society of Gynaecological Oncology (ESGO) is a non-profit organization dedicated to management and prevention of gynaecological cancer. If you wish to donate, please contact adminoffice@esgo.org. Your support will be appreciated and acknowledged.

Dear patient,

This document sets out the adapted guideline for the treatment of cervical cancer. This is an up-to-date adaption for lay people (patients, but also a patient's relatives and friends) that has been modified from the European Society for Gynaecological Oncology (ESGO) professional guidelines that your medical team use when managing cervical cancer.

It may be that, despite the adaptation, the technical content and terms will be difficult to understand fully. However, our aim is to show you what a professional guideline is like. Excessive simplification, which would make things look "simple", has been avoided.

We hope that after reading this guideline you will understand why your doctors ask you certain questions, administer various tests, discuss results, change decisions, and advise you to undergo or to refuse particular medical procedures. You will also see how strong and specific these recommendations sometimes are. You will see how tremendous knowledge and experience need to come together so that your medical team can foresee all the factors, including complicated ethical and psycho-social factors, needed to avoid clinical or technical errors.

On the other hand, recommendations are not always adapted to individual cases. In addition, guidelines from other international or national learned societies are available. Whatever the guidelines, your doctor is not "obliged" to follow them, but must show knowledge of them, and must explain to you the reasoning if he or she does not strictly follow them. You will see how difficult it can be sometimes to maintain an individualised, personalised attitude while simultaneously following the approved recommendations.

Finally, modern medicine is a close collaboration between doctor and patient. We must make common decisions to fight for your health, taking into account each other's opinions, experiences, feelings, and conditions. So, this adapted version of the professional guidelines is not only simple educational material about the disease but a real tool that can improve your understanding of the very serious work you and your doctor's team are undergoing to save your life and hopefully defeat the cancer definitively.

Sincerely,

Eka Sanikidze (GE), Dina Kurdiani (GE), Murat Gultekin (TR),
Karina Dahl Steffensen (DK), Esra Urkmez (USA), Icó Tóth (HU),
Birthe Lemley (DK), Maria Papageorgiou (GR), Charo Hierro (ES),
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Despite significant advances in the screening, detection, and treatment of **pre-invasive (pre-cancerous) cervical lesions**, invasive cervical cancer is the fifth most common cancer in European women. There are large disparities in Europe and worldwide in the incidence, management, and mortality of cervical cancer.

The European Society of Gynaecological Oncology (ESGO), the European Society for Radiotherapy and Oncology (ESTRO), and the European Society of Pathology (ESP) jointly developed **clinically relevant and evidence-based** guidelines covering comprehensively cervical **cancer staging**, management, and follow-up for patients with cervical cancer.

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

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

The European Society of Gynaecological Oncology (ESGO www.esgo.org) is a non-profit organization dedicated to the treatment and prevention of gynaecologic cancers. If you wish to donate, please contact adminoffice@esgo.org. Your support will be appreciated and acknowledged.

The European Network of Gynaecological Cancer Advocacy Groups (ENGAGe) is a network of European patient advocacy groups established by ESGO in 2012, representing all gynaecological cancers, particularly ovarian, endometrial, cervical, vulvar, and rare cancers.

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1. CERVICAL CANCER STAGING

FIGO staging and TNM classification

Patients with cervical cancer should be staged according to the TNM classification. TNM is the method used to determine tumour status (T), lymph node status (N), and systemic status—metastasis (M). TNM should be based on a correlation of various modalities (integrating physical examination, imaging, and pathology) after discussion in a multidisciplinary forum.

The method used to determine tumour status (T), lymph node status (N) and systemic status (M), i.e., clinical (c), imaging (i), and/or pathological (p) should be recorded. Lymph node metastases should be classified according to the TNM classification. Clinical staging (FIGO) should also be documented. (Table 1 from the original guideline.)

Table 1. FIGO staging and TNM classification

T category[3]	FIGO stage[4]	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.

[3] Union for International Cancer Control (UICC). 8th edition of the UICC TNM classifi cation of malignant tumours (2016).

[4] Pecorelli, S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet 105, 103-104 (2009);*
Pecorelli, S., Zigliani, L. & Odicino, F. Revised FIGO staging for carcinoma of the cervix. *Int J Gynaecol Obstet 105, 107-108 (2009);* Pecorelli, S. Corrigendum to „Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet 108, 176 (2010).*

Local clinical and radiological diagnostic work-up

Pelvic examination and biopsy (removing damaged tissue from a living body to check), with or without the addition of colposcopy (a diagnostic procedure to examine the cervix, vagina, and vulva), are mandatory components for the diagnosis of cervical cancer. The mandatory initial work-up for the assessment of pelvic tumour extent and to guide treatment options is pelvic magnetic resonance imaging (MRI). Endovaginal/transrectal ultrasound is an option if performed by a properly trained sonographer. When suspicious lesions in the urinary bladder or rectum are found by MRI or ultrasound, taking material from these lesions by biopsy may be considered. Biopsy could be done via endoscopy with a special instrument. This procedure is called cystoscopy for bladder and rectoscopy for the rectum.

Another kind of imaging scan is PET-CT. It can be used for the diagnosis of ovarian, as well as fallopian tube and peritoneal, cancer.

2. MANAGEMENT OF STAGE T1a

A diagnosis of T1a cancer should be based on a conisation (surgery that removes a cone-shaped piece of cervical tissue) or excision (cutting out, removing) of tissue to be examined by an expert pathologist. Management must be based on an expert pathology review, with accurate measurement of the maximum horizontal two dimensions, depth of invasion, margin status, coexisting pathology, and reliable assessment of LVSI (lymphovascular space invasion or involvement of this area in the process). Loop or laser conisation are preferable to cold-knife conisation in women desiring fertility preservation. Maximum care should be taken to provide an intact (un-fragmented) specimen with a minimal thermal artefact. The cone specimen should be oriented for the pathologist. Surgical margins of the cone specimen should be clear of both invasive and pre-invasive (precancerous) disease (except for pre-invasive disease in the ectocervix, the vaginal portion of the cervix).

Management of stage T1a1 disease

Management of patients with stage T1a1 disease should be individualised depending on age, the desire for fertility preservation, and the presence or absence of LVSI. In case of positive margins (except for pre-invasive disease in the ectocervix), a repeat conisation should be performed to rule out more extensive invasive disease. Lymph node staging is not indicated in T1a1 LVSI-negative patients but can be considered in T1a1 LVSI-positive patients. Sentinel lymph node (the first lymph node(s) to which cancer cells are likely to

spread from a primary tumour) biopsy (without additional pelvic lymph node dissection) is an acceptable method of lymph node staging. Conisation can be considered a definitive treatment; hysterectomy does not improve the outcome. Radical surgical approaches such as radical hysterectomy (removing the uterus) or parametrectomy (a delicate operation to remove the parametrium, tissue that connects the cervix and the bladder) represent overtreatment for patients with T1a1 disease.

Management of stage T1a2 disease

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

3. MANAGEMENT OF STAGES T1b1/T2a1

General recommendation

The treatment strategy should aim to avoid the combination of radical surgery and radiotherapy due to high morbidity after combined treatment. Ovarian preservation should be offered to premenopausal patients with squamous cell carcinoma and usual-type (human papillomavirus- (HPV-) related) adenocarcinoma. Bilateral salpingectomy, the surgical removal of the fallopian tubes, should be considered.

4. FERTILITY-SPARING TREATMENT

Patients with early-stage cervical cancer who wish to get pregnant may be candidates for fertility-sparing surgery using loop excision techniques and radical trachelectomy in order to preserve the uterus. Before starting fertility-sparing treatment (FST), a consultation at a fertility centre is recommended. FST is recommended for women under 40 who want to have children. FST should be performed exclusively in gynaecological-oncological centres that have comprehensive expertise in this kind of oncologic therapy. The prognostic factors, clinical staging, and preoperative workup do not differ for patients who would like FST from those who are not considering it (see above). Every woman with a desire to spare fertility and who has histologically proven squamous cell carcinoma or usual-type (HPV-related) adenocarcinoma ≤2 cm of the largest diameter should be counselled about the possibility of FST. This consultation should encompass the risk of FST abandonment in the case of positive margins or lymph node involvement, oncologic, and obstetric risks related to this type of management. However, FST should not be recommended for rare histological subtypes of cervical cancer, including neuroendocrine carcinomas and non-HPV-related adenocarcinomas (except for adenoid basal carcinoma), which tend to exhibit aggressive behaviour. Expert sonography and/or pelvic MRI are recommended; these are imaging tests to measure remaining (after cone biopsy) cervical length and non-involved cervical length. However, no imaging system can exactly predict the extent of necessary local resection in order to reach sound margins with an adequate safety distance. Negative pelvic lymph node status is the precondition for any FST. Therefore, pelvic lymph node (sentinel lymph node) staging should always be the first step in each FST procedure. Identification of the sentinel lymph node and its ultrastaging is highly recommended since it increases staging accuracy, namely, the identification of micrometastases and small macrometastases. The involvement of suspicious lymph nodes should be confirmed by histology. An intraoperative assessment of lymph node status is highly recommended. All sentinel lymph nodes from both sides of the pelvis and any suspicious lymph nodes should be sent for frozen section. If a bilateral sentinel lymph node is not detectable, the intraoperative assessment of pelvic lymph nodes should be considered (see the management of stages T1b1/T2a1). Lymph node staging is not indicated in stage T1a1 LVSI negative.

Intraoperative placement of permanent cerclage should be performed during simple or radical trachelectomy, in which the cervix is surgically removed. FST in patients with tumours >2 cm cannot be recommended and is considered an experimental approach. In more advanced cases, different propositions for fertility preservation should be discussed. The goal of 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 a high-risk pregnancy and delivery should be performed in a perinatal centre. Following simple or radical trachelectomy, with its inherent placement of a permanent cerclage, delivery can be performed only by caesarean section. Routine hysterectomy after finishing fertility plans is not necessary.

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

For patients with tumour stage pT1a1 (regardless of LVSI status) and pT1a2 LVSI-negative with clear margins (no cancer cells at the edge of the biopsied material) in the hysterectomy specimen, no additional treatment is recommended.

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

Pelvic lymph node dissection should be performed as the first step of the surgery. An intraoperative assessment of pelvic lymph nodes may be considered. If intraoperative lymph node assessment is negative or it is not performed, radical parametrectomy with the resection of the upper vagina should be performed, preferably using 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 tumour. A complete description of the template used for radical parametrectomy should be present in the operative report.

Debulking (removing as much of a tumour as possible via surgery) of suspicious nodes may be considered.

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

In patients with stage pT1b2 and higher, involved surgical margins, or in those with residual tumour, including involved lymph node on imaging, chemo-radiotherapy is recommended and further surgery should be avoided. Debulking of suspicious pelvic lymph nodes may be considered.

5. MANAGEMENT OF LOCALLY ADVANCED CERVICAL CANCER

Stage T1b2/T2a2 and negative lymph nodes on radiological staging

Radical surgery is an alternative option, in particular in patients without negative risk factors (combinations of tumour size, LVSI, and/or depth of stromal invasion). Quality of surgery, both parametrectomy and lymph node dissection, is, however, of key importance in the management of large tumours. Intraoperative assessment of lymph node status (frozen section) is recommended as the first step. If lymph node involvement is detected intraoperatively, including macrometastases or micrometastases, further pelvic lymph node dissection and radical hysterectomy should be avoided, and patients should be referred for definitive **chemoradiotherapy** and **brachytherapy**.

Paraaortic lymph node dissection, at least up to the inferior mesenteric artery, may be considered for staging purposes. If intraoperative lymph node assessment is negative or is not done, systematic pelvic lymph node dissection should be performed.

Type C2 radical hysterectomy is recommended. In general, involvement of lymph nodes in the process defines further decision about pelvic lymph node dissection and radical hysterectomy. It should be avoided if lymph node involvement is detected intraoperatively and should be performed if lymph node assessment is negative or is not done.

Stage T1b2/T2a2 and involved lymph nodes on radiological staging

Definitive chemoradiotherapy and brachytherapy is recommended in patients with unequivocally involved pelvic lymph nodes on imaging.

Stages T2b, T3a/b, T4a

Definitive platinum-based chemoradiotherapy and brachytherapy is recommended. Debulking of suspicious pelvic lymph nodes may be considered. **Pelvic exenteration** is an option in selected cases with stage T4N0M0 disease.

6. 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.

Patients with lymph nodes above the clavicle as the only site of distant disease can be considered for chemoradiotherapy with curative intent. The treatment algorithm may include additional chemotherapy.

Adjuvant chemotherapy may be considered in cases carrying a high risk of recurrence, such as positive margins, positive lymph node, or LVSI-positive tumours.

Palliative treatment

Recommendations for palliative treatment should only be made after a thorough review of the case by a specialist multidisciplinary team and should take into account the performance status, co-morbidities, and symptoms and wishes of the patient. The palliative care specialist should be actively involved.

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.

7. FOLLOW-UP

Primary objectives of follow-up for patients with cervical cancer should include:

- Early detection of recurrent disease
- Patient education and support
- Cancer rehabilitation with the goal to prevent and reduce psychosocial, physical, social, and existential consequences of cancer and its treatment, starting at the 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 counselling should be available, e.g., psychologist, sexual therapist, physiotherapist, and dietitian.
- Assessment of long-term outcome of novel treatment strategies

Quality control of care for each visit should be composed of the following:

- Patient history (including elicitation of relevant symptoms)
- A physical examination (including a speculum examination and bimanual pelvic examination)
- Physician assessment of adverse events using validated scales (e.g., Common Terminology Criteria for Adverse Events)
- Prevention and management of cancer- and treatment-related side effects, e.g., sexual dysfunction (counselling, vaginal lubricants, dilators, local oestrogen). In case of the appearance of treatment-related symptoms, a referral to a dedicated specialist (gastroenterologist, uro/gynaecologist) should be considered. Patients should be educated about symptoms of potential recurrence and potential long-term and late effects of treatment. Patients should also be counselled on sexual health, lifestyle adaptation, nutrition, exercise, obesity, lymphoedema, and stopping smoking.

8. PRINCIPLES OF RADIOTHERAPY

Definitive management (without tumour-related surgery) consists of concomitant pelvic chemo-radiotherapy (platinum-based) and brachytherapy or pelvic External Beam Radiation Therapy (also called EBRT; refers to the delivery of tightly targeted radiation beams from outside the body) alone and brachytherapy. Overall treatment time for the definitive treatment should not exceed 7–8 weeks. Delay of treatment and/or treatment interruptions should be avoided.

EBRT is the recommended minimum as 3D conformal radiotherapy. The preferred treatment is intensity-modulated radiotherapy (IMRT), due to the more conformal dose distribution that maximises sparing of organs at risk. EBRT can be applied as concomitant chemoradiotherapy with total dose of 45–50 Gy (1.8 Gy per fraction) and single-agent radio-sensitising chemotherapy, preferably cisplatin (weekly 40mg/m^2) so that definitive radiotherapy is not compromised. If cisplatin is not applicable, alternative treatment options are fluorouracil (5FU) or carboplatin.

EBRT may also be applied without concomitant chemotherapy according to treatment selection (i.e., patients unfit for any chemotherapy). In such cases, regional hyperthermia may be considered. Tumour- and lymph node-related target volume for IMRT includes the primary cervical tumour and the adjacent tissues such as parametria, uterine corpus, upper vagina, and the pelvic lymph nodes (obturator, internal, external and common iliac, pre-sacral). In case of pelvic lymph node involvement indicating an increased risk of para-aortic lymph node spread, EBRT may include the paraaortic region up to the renal vessels (45 Gy).

In case of paraaortic lymph node involvement, target volume includes, at minimum, the region up to the renal vessels. A reduced target volume for EBRT resulting in a small pelvic field not including the common iliac nodes may be considered in low- and intermediate-risk T1b1 patients with negative lymph nodes on imaging and no LVSI.

Boost treatment for involved lymph node(s) may be applied as simultaneous integrated boost within the IMRT treatment or as a sequential boost. The total dose including the contribution from brachytherapy should be 55–60 Gy (equi-effective dose to 2 Gy per fraction (EQD2)). An alternative treatment option is surgical debulking of enlarged nodes. Image-guided radiotherapy (IGRT) is recommended for IMRT to ensure safe dose application in the tumour related targets, to account for motion uncertainties, to reduce margins, and to achieve reduced doses to organs at risk. Overall treatment time for EBRT should not exceed 5–6 weeks.

Image-guided adaptive brachytherapy (IGABT) is recommended, preferably using MRI at the time of brachytherapy. IGABT is delivered in large tumours towards the end of or after concomitant chemoradiotherapy. Repeated gynaecological examination is mandatory and alternative imaging modalities such as CT and ultrasound may be used. Intracavitary and combined intracavitary/interstitial brachytherapy should be performed under anaesthesia. The brachytherapy applicator should consist of a uterine tandem and a vaginal component (ovoids/ring/mould/combined ring/ovoid). Combined intracavitary/interstitial brachytherapy for adjusting the application further to the individual target should be considered.

The vaginal component carries holes for straight or oblique needle guidance into the parametria. In case of significant residual disease in the parametrium (as in any extracervical area, e.g., vagina, uterine corpus, adjacent organ), this should become part of the CTV-THR. The brachytherapy application should be a combined intracavitary/interstitial approach in order to achieve a sufficiently high radiation dose in the whole CTV-THR. 3D and 2D dose volume and point constraints for rectum, bladder, vagina, sigmoid, and bowel are recommended and they have to be based on the published clinical evidence. Brachytherapy should be delivered in several fractions as high dose rate (usually 3–4) or in 1–2 fractions as pulse dose rate brachytherapy.

In large tumours, brachytherapy should be delivered within 1–2 weeks towards the end of or after chemoradiotherapy. In limited size tumours, brachytherapy may start earlier, during chemoradiotherapy. For the tumour-related targets (GTV-Tres, CTV-THR, CTV-TIR), the use of external beam therapy for giving an extra dose (e.g., parametrial boost, cervix boost) is discouraged, even when using advanced EBRT technology such as stereotactic radiotherapy. The use of a midline block for boosting the parametrium is discouraged when applying advanced image-guided radiotherapy, in particular beyond 45 to 50 Gy. Care should be taken to optimize patient comfort during (fractionated) brachytherapy. Preferably this includes a multidisciplinary approach.

Adjuvant radiotherapy or chemoradiotherapy follows analogue principles for target selection and dose and fractionation as outlined for definitive treatment. The application of IMRT and IGRT is to be considered since treatment-related morbidity may be reduced. Adjuvant (additional) brachytherapy should only be considered if a well-defined limited area—accessible through a brachytherapy technique–is at high risk of local recurrence (e.g., vagina, parametrium). Such adjuvant brachytherapy should follow the major principles outlined above for image-guided brachytherapy.

3D conformal radiotherapy alone or as definitive concomitant chemoradiotherapy (platinum-based) ± paraaortic radiotherapy and/or 2D radiography-based brachytherapy is recommended if IMRT and/or IGABT are not available. In the case of 3D conformal radiotherapy and/or radiography-based brachytherapy, the recommendations for EBRT and

IGABT as outlined above in regard to target, dose, fractionation, and overall treatment time have to be respected as much as possible. A sequential lymph node boost is applied as appropriate after completion of 3D EBRT. The planning aim for brachytherapy should be based on point A. The dose to point A should be ≥75 Gy (EQD2) in limited-width adaptive CTV-THR (≤3 cm) and should aim at higher doses in large-width adaptive CTV-THR (>4 cm). In addition, the dose for the maximum width of the adaptive CTV-THR 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 have to be based on published clinical evidence.

Patient information, previous cervical cytology, histological specimens, clinical, and radiological data and colposcopic findings need to be included on the specimen request form. Details of cytology, biopsy, and surgical specimen (cone/loop specimen, trachelectomy, type of hysterectomy, presence of ovaries and fallopian tubes, presence of lymph nodes and designation of the lymph node sites, presence of vaginal cuff, and presence of parametria) need to be itemised 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 specimens should ideally be sent intact with a suture to identify the 12 o'clock position.

Small biopsy specimens should be enumerated and measured. The diameter (two dimensions) and depth of cone/loop specimens should be measured. If the specimen is complete or fragmented, it should be recorded. If more than one piece of tissue is received, every piece should be measured in three dimensions and entirely examined. Inking of the surgical margins of cone/loop specimens is optional. Dissection of cone/loop specimens should be performed in an appropriate fashion. All the pieces submitted should be in consecutive numerical order. This is important since, if tumour is present in more than one piece, it needs to be known whether these are consecutive pieces and thus a single tumour or if it represents a multifocal tumour. It is recommended to place only one piece of tissue in each cassette.

There are also techniques which allow embedding more than one piece in a cassette if they are small enough. In cases which do not comprise intact cone/loops, serial radial sectioning and placing of each slice of tissue in a single cassette should be performed. The description of the specimen (hysterectomy, trachelectomy, presence of ovaries and fallopian tubes, presence of lymph nodes and indication of the lymph node sites, presence of vaginal cuff, presence of parametria) should be recorded and checked for consistency with the description given in the specimen request form. The presence of any gross abnormality in any organ should be documented. The dimensions of the uterus for a hysterectomy specimen and the cervix for a trachelectomy specimen should be documented. The minimum and maximum length of the vaginal cuff should be documented. The size of the parametria should be documented in two dimensions (vertical and horizontal). Gross tumour involvement of the parametrium, vagina, uterine corpus, or other organs should be documented. The relationship of the cervical tumour to the vaginal and parametrial margins (and upper margin in case of a trachelectomy specimen) should be measured and appropriate sections taken to demonstrate this. Parametrial and vaginal margins should be inked.

The total parametria should be submitted for histological examination. The upper surgical margin of a trachelectomy specimen should be inked. The upper margin of a trachelectomy specimen should be sampled in its entirety in a way that demonstrates the distance of the tumour to the margin. The vaginal margin should be examined totally as radial sections if no tumour is seen grossly. When the tumour is small (or with tumours which cannot be identified macroscopically), the cervix should be separated from the corpus, opened and processed as for a cone/loop specimen. In the case of a large tumour, the hysterectomy or trachelectomy specimen should be opened on the sagittal plane (i.e., separating left and right).

The description of the cervix and measurement of any gross tumour mass should be documented. Gross tumours should be measured in three dimensions, namely two measurements of horizontal extent and the depth of invasion. The tumour site within the cervix should be documented. The cervical tumour should be sampled in order to demonstrate the maximum depth of invasion, the relationship of the tumour with the surgical borders and the extension to other organs. If visible, the site of a previous cone biopsy should be documented. At least one block per centimetre of the greatest tumour dimension for large tumours should be taken. Additional blocks, including the cervix adjacent to the tumour, should be taken in order to demonstrate precursor lesions. The whole cervix should be sampled in the case of a small tumour or where no macroscopic tumour is identified. The uterine corpus, vagina, and adnexa should be sampled according to standard protocols if not involved by tumour. If the uterine corpus and/or adnexa are grossly involved, additional blocks should be sampled. The entire vaginal margin should be blocked.

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

Pathological assessment of sentinel lymph node

Intraoperative assessment should be performed on a grossly suspicious sentinel node and may be performed on a "non-suspicious" sentinel lymph node(s), since the confirmation of tumour involvement will result in abandoning a hysterectomy or trachelectomy. For intraoperative evaluation, the sentinel lymph node(s) need to be sent to the pathology department in a container without liquid fixative. Intraoperative analysis requires gross dissection of the resected adipose tissue by the pathologist with the selection of the lymph node(s). For a lymph node with obvious gross tumour, a single section is adequate for frozen section. Frozen section may be combined with imprint cytology. Any non-suspicious sentinel node should be bisected (if small) or sliced at 2 mm thickness and entirely frozen. From each sample, histological sections should be cut and stained with H&E. After frozen section analysis, the tissue should be put into a cassette, fixed in liquid fixative, and subsequently processed and embedded in paraffin. Sentinel lymph node(s) tissue blocks should be entirely analysed by examining multiple serial sections at different levels with H&E stains.

Cytokeratin stains should be performed on all blocks. Cytokeratins are protein components whose presence marks some types of tumours. The detection of micrometastases and isolated tumour cells should be improved by immunohistochemistry with pancytokeratin antibodies (e.g., AE1/AE3). A description of the specimen(s) is submitted for histological evaluation. This includes the macroscopic description of specimen(s) (biopsy, loop/cone, trachelectomy, hysterectomy), including specimen dimensions (three dimensions), the number of tissue pieces for loop/cones, and maximum and minimum length of vaginal cuff and the parametria in two dimensions. When multifocal separate tumours are present, each should be described and measured separately and the largest used for tumour staging. Specimens from prior conisation and subsequent conisation, trachelectomy or hysterectomy should be correlated for estimation of the tumour size. This is important because different specimens may have been reported at different institutions. It should also be recognized that simply adding together the maximum tumour size in separate specimens may significantly overestimate the maximum tumour dimension.

Requirements for the pathology report

- Histological tumour type and tumour grade.
- The presence or absence of LVSI.
- Coexisting pathology (squamous intraepithelial lesion/cervical intraepithelial neoplasia, adenocarcinoma in situ, stratified mucin-producing intra-epithelial lesion).
- Minimum distance of uninvolved cervical stroma.
- Margin status (invasive and preinvasive diseases). Specify the margin(s).
- Lymph node status including sentinel lymph node status, the total number of nodes found and the number of positive lymph nodes and the presence of extranodal extension (list for all separates sites).
- Micrometastasis (greater than 0.2 mm and up to 2 mm) are reported as pN1(mi). Isolated tumour cells no greater than 0.2 mm in regional nodes should be reported as pN0 (i+).
- Pathologically confirmed distant metastases.
- Provisional pathological staging pre-tumour board/multidisciplinary team meeting (AJCC 8th edition).

9. GLOSSARY

- **Bilateral salpingectomy**—The surgical removal of the fallopian tubes.
- **Brachytherapy**—The treatment of cancer by inserting radioactive implants directly into the tissue.
- **Cancer staging**—The process of recording how much cancer a patient has in her body, including the cancer's location and if it has spread. FIGO staging and the TNM classification are two widely used systems.
- **Chemoradiotherapy (also radiochemotherapy, chemoradiation)**—A cancer treatment that combines chemotherapy and radiotherapy, either at the same time or one following the other.
- **Clinically relevant**—Results from a study that are scientifically meaningful. Clinically relevant results are considered for transfer into practice.
- **Dilator**—an instrument that dilates something; used, for example, in treating sexual dysfunction.
- **ESGO Guidelines**—ESGO's clinical guidelines are a set of criteria for medical professionals to use when diagnosing, managing, and treating gynaecological cancers. The goal of the clinical guidelines project is to standardise care for patients of these cancers. Learn more at https://www.esgo.org/explore/guidelines/.
- **Evidence-based**—Uses results from current research to form a practical approach.

- **FIGO**—The Fédération Internationale de Gynécologie et d'Obstétrique (International Federation of Gynaecology and Obstetrics), commonly known as "FIGO". Its system is widely used for cancer staging.
- **Hyperthermia (also thermal therapy, thermotherapy)**—A type of treatment for cancer that exposes tissue to heat in order to kill or damage cancer cells.
- **Image-guided surgery (IGS)**—A surgery in which the surgeon adjusts the procedure using preoperative or interoperative images.
- **Loop/LEEP**—A procedure to remove abnormal cervical cells using an electrical wire loop. LEEP stands for "Loop Electrosurgical Excision Procedure."
- **Lymphedema (also spelled lymphoedema)**—Excess fluid in soft tissue resulting from a blockage in the lymphatic system. It can occur after a lymphadenectomy, the surgical removal of lymph nodes.
- **Lymphovascular space invasion (LSVI; also lymphovascular invasion or LVI)**—When cancer invades the blood vessels, lymphatic system.
- **Macrometastases**—A relatively large metastasis.
- **Micrometastases**—a very small tumour (or simply a collection of cancer cells) that are not large enough to be detected by a scan.
- **Multidisciplinary**—Comprised of health care professionals from different disciplines, for example, oncologists, physical therapists, social workers, psychiatrists, nutritionists, etc.).
- **Parametrectomy**—A delicate operation to remove the parametrium, the tissue that connects the cervix and the bladder.
- **Pelvic exenteration (also pelvic evisceration)**—Radical surgery to remove all organs from the pelvic area, including the bladder, urethra and rectum. Patients who undergo pelvic exenteration will need urinary diversion and colostomy.
- **Pre-invasive cervical lesion**—A lesion before the cancer penetrates nearby tissues.
- **Precancerous cervical lesion**—Abnormal cells in the cervix that have the potential to develop into cancer.
- **Predictive factor**—A factor that may increase someone's risk for a particular disease; (also) a factor that may predict how well a person's cancer responds to (a specific) treatment.
- **Prognostic factor**—A factor that may indicate the chance of recovery.

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Access the full ESGO Guidelines

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