ESGO

Pocket Guidelines

PUBLISHED IN 2023

Cervical Cancer

THE EUROPEAN VOICE OF GYNAECOLOGICAL ONCOLOGY

ESGO
European Society of Gynaecological Oncology

POCKET GUIDELINES

Based on

ESGO/ESTRO/ESP Guidelines for the management of patients with cervical cancer - Update 2022 -

Cibula, D., Raspollini, M.R., … Lindegaard, J.C. (2023). ESGO/ESTRO/ESP Guidelines for the management of patients with cervical cancer - Update 2022. *International Journal of Gynecological Cancer* (in press)

The European Society of Gynaecological Oncology (ESGO) jointly with the European Society for Radiotherapy & Oncology (ESTRO) and the European Society of Pathology (ESP) published in 2018 evidence-based guidelines for the management of patients with cervical cancer. Given the large body of new evidence addressing the management of cervical cancer, the 3 sister societies jointly decided to update these evidence--based guidelines and moreover to cover new topics in order to provide comprehensive guidelines on all relevant issues of diagnosis and treatment in cervical cancer.

The updated guidelines cover comprehensively staging, management, follow-up, long-term survivorship, quality of life and palliative care. Management includes fertility sparing treatment, early and locally advanced cervical cancer, invasive cervical cancer diagnosed on a simple hysterectomy specimen, cervical cancer in pregnancy, rare tumours, recurrent and metastatic diseases.

The guidelines were developed using a five-step process as defined by the ESGO Guideline Committee:



The objective of these ESGO/ESTRO/ESP Guidelines is to improve the quality of care for women with cervical cancer across Europe and worldwide. They are intended for use by all health professionals who are involved in the management of patients with cervical cancer, across all allied disciplines.

These guidelines 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.

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 2017 and March 2022 was carried out.

The guidelines were adopted if they were supported by sufficient high level of scientific evidence and/or when a large consensus among experts was obtained. An adapted version of the "Infectious Diseases Society of America-United States Public Health Service Grading System" was used to define the level of evidence and grade of recommendation for each of the recommendations:

LEVELS OF EVIDENCE

I Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well conducted, randomised trials without heterogeneity

II Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity)

III Prospective cohort studies

IV Retrospective cohort studies or case-control studies

V Studies without a control group, case reports, and/or expert opinions

GRADES OF RECOMMENDATIONS

A Strong evidence for efficacy with a substantial clinical benefit, strongly recommended

B Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended

C Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs…), optional

D Moderate evidence against efficacy or for adverse outcome, generally not recommended

E Strong evidence against efficacy or for adverse outcome, never recommended

ESGO would like to thank 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 (see below). ESGO is also very grateful to the 155 international external reviewers for their participation (list available on the ESGO website).

NAME	SPECIALTY	AFFILIATION
David Cibula	Gynecologic oncologist (chair)	First Faculty of Medicine, Charles University and General University Hospital in Prague, Prague (Czech Republic)
Jacob Christian Lindegaard	Radiation oncologist (chair)	Aarhus University Hospital, Aarhus (Denmark)
Maria Rosaria Raspollini	Pathologist (chair)	University Hospital Careggi, Florence (Italy)
François Planchamp	Methodologist	Institut Bergonié, Bordeaux (France)
Carlos Centeno	Radiation oncologist (palliative medicine)	Clínica Universidad de Navarra, Pamplona (Navarra) (Spain)
Cyrus Chargari	Radiation oncologist	Institut Gustave Roussy, Villejuif (France)
Ana Felix	Pathologist	Instituto Portugues de Oncologia de Lisboa, NOVA Medical School, Universidade Nova de Lisboa (Portugal)
Daniela Fischerova	Gynecologic oncologist	First Faculty of Medicine, Charles University and General University Hospital in Prague, Prague (Czech Republic);
Daniela Jahn-Kuch	Palliative care speciallist	Medical University of Graz, Graz (Austria);
Florence Joly	Medical oncologist	Centre François Baclesse, Caen (France)
Christhardt Kohler	Gynecologic oncologist	Asklepios Clinic Hamburg Altona and Asklepios Comprehensive Tumor Center, Hamburg (Germany)
Sigurd Lax	Pathologist	Hospital Graz II, Graz and School of Medicine, Johannes Kepler University, Linz (Austria)
Domenica Lorusso	Gynecologic oncologist	Fondazione Policlinico Universitario A.Gemelli IRCCS, Rome (Italy) Catholic University of Sacred Heart, Rome (Italy)
Umesh Mahantshetty	Radiation oncologist	Homi Bhabha Cancer Hospital & Research Centre, Visakhapatnam (India)
Patrice Mathevet	Gynecologic oncologist	CHUV (University Hospital), Lausanne (Switzerland)
Raj Naik	Gynecologic oncologist	Northern Gynaecological Oncology Centre, Gateshead (United Kingdom)
Remi Nout	Radiation oncologist	Erasmus MC Cancer Institute, University Medical Center, Rotterdam (Netherlands)
Ana Oaknin	Medical oncologist	Vall d´Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d´Hebron, Valld´Hebron Barcelona Hospital Campus, Barcelona (Spain)
Fedro Peccatori	Medical oncologist	European Institute of Oncology IRCCS Milan (Italy)
Jan Persson	Gynecologic oncologist	Skåne University Hospital, Lund, Lund University, Faculty of Medicine, Clinical Sciences, Lund (Sweden)
Denis Querleu	Gynecologic oncologist	Fondazione Policlinico Universitario A.Gemelli IRCCS, Rome (Italy) University Hospital, Strasbourg (France)
Sandra Rubio	Medical oncologist	Clínica Universidad de Navarra, Pamplona (Navarra) (Spain)
Maximilian Paul Schmid	Radiation oncologist	Medical University of Vienna, Vienna (Austria)
Artem Stepanyan	Gynecologic oncologist	Nairi Medical Center, Yerevan (Armenia)
Valentyn Svintsitskyi	Gynecologic oncologist	National Cancer Institute, Kiev (Ukraine)
Karl Tamussino	Gynecologic oncologist	Medical University of Graz, Graz (Austria)
Ignacio Zapardiel	Gynecologic oncologist	La Paz University Hospital, Madrid (Spain)

TABLE OF CONTENTS

General recommendations 8

Staging 8

Management of T1a disease 9

Management of T1b1, T1b2, and T2a1 tumours 10

Fertility-sparing treatment 12

Invasive cervical cancer diagnosed on a simple hysterectomy specimen 14

Management of locally advanced cervical cancer (T1b3-T4a) 16

Recurrent/Metastatic disease 17

Follow-up during and after treatment/long-term survivorship 19

Quality of life and palliative care 21

Cervical cancer in pregnancy 22

Rare tumours 23

General recommendations

B	Centralization of care in specialized centres and referral network is encouraged.
A	Treatment planning should be made on a multidisciplinary basis (generally at a tumour board meeting as defined in the ESGO quality indicators) and based on the comprehensive and precise knowledge of prognostic and predictive factors for oncological outcome, side effects, and quality of life.
A	Patients should be carefully counselled on the suggested treatment plan and potential alternatives, including risks and benefits of all options.
A	Treatment should be undertaken by a dedicated team of specialists in the diagnosis and management of cervical cancers.
B	Enrolment of patients with cervical cancer in clinical trials is encouraged.

Staging

TNM classification and FIGO staging

A	Patients with cervical cancer should be staged according to the TNM classification. FIGO staging should also be documented.
A	Systematic documentation and integration of the results from clinical examination, pathology and imaging including multidisciplinary team discussions of disparate findings is recommended.
A	The method used to determine tumour status (T), lymph node (LN) status (N), and systemic status (M) should be noted (clinical, imaging, pathological).
A	LN metastases should be classified according to the TNM classification.

Prognostic factors

A

Systematic documentation of the following major tumour-related prognostic factors is recommended:

- TNM and FIGO stage, including a maximum tumour size, detailed description of extracervical tumour extension (including uterine corpus involvement) and nodal involvement (e.g. total number, location, size, and metabolic activity).
- Pathological tumour type including HPV status.
- Depth of cervical stromal invasion and a minimum thickness of uninvolved cervical stroma
- Margin status (ectocervical, endocervical, radial/deep stromal and vaginal cuff)
- Presence or absence of lymphovascular space involvement (LVSI).
- Presence or absence of distant metastases.

Local clinical and radiological diagnostic work-up

A	Pelvic examination and biopsy ± colposcopy are mandatory to diagnose cervical cancer.
A	Pelvic magnetic resonance imaging (MRI) is mandatory for initial assessment of pelvic tumour extent and to guide treatment options (optional for T1a tumour with free margins after conization). Endovaginal/transrectal ultrasonography is an option if performed by a properly trained sonographer.
D	Cystoscopy or rectoscopy are not routinely recommended.

Nodal/Distant diagnostic work-up

A	In early stages managed primarily by surgery, surgical/pathological staging of pelvic lymph node (PLN) is the standard criterion to assess the prognosis and to guide treatment (except for T1a1 and T1a2 without LVSI).
B	In locally advanced cervical cancer (T1b3 and higher (except T2a1) or in early--stage disease with suspicious LN on imaging), positron emission tomography--computed tomography (PET-CT), or chest/abdomen computed tomography (CT scan) (if PET-CT is not available) is recommended for assessment of nodal and distant disease.
B	PET-CT is recommended before chemoradiotherapy (CTRT) with curative intent.
C	Paraaortic LN dissection (PALND), at least up to inferior mesenteric artery, may be considered in locally advanced cervical cancer with negative paraaortic LN on imaging for staging purposes.
B	Equivocal extrauterine disease should be considered for biopsy to avoid inappropriate treatment.

Management of T1a disease

Diagnostic of T1a disease

B	Diagnosis of T1a cancer should be based on a conization (or excision) specimen examined by an expert pathologist with accurate measurement of depth of invasion, margin status, coexisting pathology, and reliable assessment of LVSI.
B	Loop or laser conization is preferable to cold-knife conization in women wanting to preserve fertility. Care should be taken to provide an intact (unfragmented) specimen with minimal thermal artifact. The cone specimen should be oriented for the pathologist.
B	Surgical margins of the cone specimen should be clear of both invasive and preinvasive disease (except for low-grade intraepithelial lesion).

Management of T1a1 disease

B	Management of patients with T1a1 disease should be individualized depending on age, desire for fertility preservation, histological type, and presence or absence of LVSI.
B	In case of positive margins (except for low-grade intraepithelial lesion 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. Sentinel lymph node (SLN) biopsy (without additional PLN dissection (PLND)) is recommended in this situation.
C	Conization can be considered a definitive treatment as hysterectomy does not improve the outcome.
D	Radical surgical approaches such as radical hysterectomy, trachelectomy or parametrectomy represent overtreatment and should not be performed for patients with T1a1 disease.
B	Patients with T1a1 adenocarcinoma who have completed childbearing should be offered SH.

Management of T1a2 disease

B	Conization (with clear margins) alone or SH is an adequate treatment for patients with T1a2 disease.
D	Parametrial resection is not indicated.
B	SLN biopsy (without additional PLND) can be considered in LVSI-negative patients but should be performed in LVSI-positive patients.
B	Patients with T1a2 adenocarcinoma who have completed childbearing should be offered SH.

Management of T1b1, T1b2, and T2a1 tumours

General recommendations

A	Treatment strategy should aim for to the avoidance of combining radical surgery and radiotherapy because of the highest morbidity induced by the combined treatment.

Negative LN on radiological staging - Surgical treatment

A	Radical surgery by a gynaecological oncologist is the preferred treatment modality. Laparotomy is the standard approach for all procedures which include radical parametrectomy.
C	Minimally invasive approach may be considered only in low risk tumours (<2 cm and free margins after conization), in high-volume centres experienced in performing radical hysterectomy with minimally invasive surgery, which meet the ESGO quality criteria for surgery, if patient agrees after comprehensive discussion about current evidence.
A	LN assessment should be performed as the first step of surgical management.
B	Minimally invasive surgery is an acceptable approach for LN staging.
A	SLN biopsy before pelvic lymphadenectomy should be performed. Indocyanine green is the preferred technique.

B	A combination of blue dye with radiocolloid is an alternative technique.
A	Intra-operative assessment of LN status (evaluated by frozen section) is recommended. Sentinel nodes from both sides of the pelvis and/or any suspicious LN should be sent for intra-operative assessment.
A	If any LN involvement is detected intraoperatively, further PLND and radical hysterectomy should be avoided. Patients should be referred for definitive CTRT.
C	PALND at least up to inferior mesenteric artery may be considered for staging purposes.
A	After SLN biopsy, if SLN are negative on frozen section, a systematic pelvic lymphadenectomy should be performed as the standard LN staging.
B	If SLN is negative bilaterally in the pelvic level I area (below iliac bifurcation) LN dissection can be limited to level I.
A	If SLN is not detected on either side, LN dissection should include on that particular pelvic side the removal of lymphatic tissue from all traditional regions including obturator fossa, external iliac regions, common iliac regions, and presacral region.
A	After frozen section, all SLN should be processed according to pathological protocol for ultrastaging.
A	The type of radical hysterectomy (extent of parametrial resection, type A-C2) should be based on the presence of prognostic risk factors identified preoperatively such as tumour size, maximum stromal invasion, and LVSI, which 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.
A	Ovarian preservation should be discussed with women in reproductive age with squamous cell carcinoma, can be considered in HPV-associated adenocarcinoma and is not recommended for HPV-independent adenocarcinomas. Opportunistic bilateral salpingectomy should be performed if ovaries are preserved. Ovarian transposition should be discussed upfront with the patient and individualized according to risk balance.
A	If a combination of risk factors is known at diagnosis, which would require an adjuvant treatment, definitive CTRT and brachytherapy (BT) should be considered without previous radical pelvic surgery.

Negative LN on radiological staging - Alternative treatment options

B	Definitive CTRT and image-guided brachytherapy (IGBT) represent an alternative treatment option.
D	Neoadjuvant chemotherapy (NACT) or CTRT followed by surgery are not recommended.

Adjuvant treatment after radical surgery

A	Adjuvant radiotherapy should be considered in the intermediate risk group (combination of risk factors at final pathology such as tumour size, LVSI, and depth of stromal invasion).
B	When in intermediate risk group patients an adequate type of radical hysterectomy has been performed, observation is an alternative option, especially in teams experienced in this approach.
A	Adjuvant CTRT is indicated in the high-risk group: • metastatic involvement of PLN (macrometastases pN1 or micrometastases pN1(mi)) on final pathologic assessment • positive surgical margins (vagina/parametria/paracervix) • parametrial involvement.
B	Additional BT boost as part of adjuvant CTRT can be considered in cases with vaginal and/or parametrial positive disease.
C	Adjuvant treatment may be considered also if only isolated tumour cells are detected in SLN, although its prognostic impact remains uncertain.

Fertility-sparing treatment

B	Fertility sparing therapy is an oncologically valid alternative to radical hysterectomy for young patients with cervical cancer <2 cm (squamous cell carcinoma and HPV-related adenocarcinoma) who are seeking for parenthood. Before initiating fertility sparing therapy, consultation at an onco-fertility centre and discussion in a multidisciplinary tumour board is recommended.
A	Counselling of eligible patients should encompass the oncologic and obstetric risks related to this type of management as well as the risk of fertility sparing therapy abandonment if there are positive resection margins or LN involvement.
A	Fertility-sparing treatment should be performed exclusively in gynaecological--oncological centres with comprehensive expertise in all types of these surgical procedures.
D	Fertility-sparing treatment should not be recommended for uncommon and rare histological types/subtypes of cervical cancer with aggressive behavior including neuroendocrine carcinomas, HPV-independent adenocarcinomas and carcinosarcomas.
A	For patients who consider fertility sparing therapy, prognostic factors, clinical staging, and preoperative work-up do not differ from those not considering fertility sparing therapy (see above). Pelvic MRI and/or expert sonography are mandatory imaging tests to measure the non-involved cervical length (upper tumour free margin) and the remaining (after cone biopsy) cervical length.

A	Negative PLN status is the precondition for any fertility sparing therapy. Therefore, PLN staging (SLN) should always be the first step in each fertility-sparing therapy procedure. Identification of SLN and its ultrastaging is highly recommended. Any intraoperative suspicious LN (apart from SLN) should also be removed. If SLN cannot be detected on either pelvic side, a systematic pelvic lymphadenectomy should be performed on that side. Intraoperative assessment of LN status is highly recommended. All SLN from both sides of the pelvis and any suspicious LN should be sent for frozen section. LN staging is not indicated in T1a1 LVSI negative.
B	In case of intraoperatively proven PLN involvement, fertility-sparing surgery should be abandoned and patients should be referred for CTRT and BT.
C	PALND, at least up to inferior mesenteric artery, may be considered for staging purposes.
D	Ovarian transposition cannot be recommended in N1 status.
A	The specific goal of fertility-sparing surgery must be resection of invasive tumour with adequate free margins and preservation of the upper part of the cervix.
C	Intraoperative frozen section is a feasible way of assessing the upper resection margin.
B	LN staging follows the principles of management of early stages.
B	Fertility sparing procedures comprises conization, simple trachelectomy, radical (vaginal) trachelectomy, abdominal radical trachelectomy.
B	Conization and simple trachelectomy are adequate fertility sparing procedures in patients with T1a1 and T1a2 tumours, regardless of LVSI status.
B	Conization or simple trachelectomy are adequate fertility sparing procedures for T1b1, LVSI negative tumours. Radical trachelectomy is still an option.
B	Radical trachelectomy (type B) should be performed in patients with cervical cancer T1b1, LVSI-positive. In patients without deep stromal involvement and with a high probability of adequate endocervical tumour free margins, simple trachelectomy can be considered.
B	Intraoperative placement of permanent cerclage should be performed during simple or radical trachelectomy.
B	Fertility sparing therapy for patients with tumours greater than 2 cm is significantly associated with a higher risk of recurrence and can be not considered as a standard treatment. The risk of recurrence must be comprehensively discussed with the patient. NACT followed by radical vaginal trachelectomy and abdominal radical trachelectomy or cone has been described for fertility sparing treatment in patients with tumours >2 cm. PLN staging should be performed before starting NACT to confirm tumour free LN. The optimal number of chemotherapy cycles, chemotherapy regimen as well as extent of cervical resection following NACT, are still a matter of debate.

B	In more advanced cases, various fertility preservation proposals such as ovarian transposition, oocyte-, embryo- or ovarian tissue preservation and egg donation should be discussed with the patient. The aim of the fertility preservation should be to offer the most efficient approach in accordance with the legal country-specific regulations, while not increasing the oncological risk.
B	Any pregnancy following fertility sparing therapy should be considered as a high-risk pregnancy. Following simple or radical trachelectomy with placement of a permanent cerclage, delivery can only be performed by cesarean section.
C	Although evidence is limited, several antenatal management tools can be considered following fertility sparing therapy including screening and treatment of asymptomatic bacteriuria, screening for cervical incompetence and progressive cervical shortening by transvaginal ultrasonography, fetal fibronectin testing, screening (and treatment) for asymptomatic vaginal infection, vaginal progesterone application, total cervical closure according to Saling and cervical cerclage, if not placed during trachelectomy.
D	Routine hysterectomy after completion of childbearing is not mandatory.

Invasive cervical cancer diagnosed on a simple hysterectomy specimen

General recommendations

B	Management of disease found after SH should be based on expert pathology review and discussed in a multidisciplinary tumour board. In general, management of occult disease follows the principles of the standard management, and is based on pathologic findings, and clinical staging. Treatment strategy should aim for the avoidance of combining further surgery and radiotherapy because of the highest morbidity after combined treatment.
B	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 the standard management.
B	When surgical staging of nodal disease is indicated (see below for details), it can be considered either as an isolated (preferentially laparoscopic) procedure or as the first step of surgical management in radiologic node negative patients. Surgical staging of nodal disease can also be considered to assess inconclusive nodes at imaging. SLN biopsy cannot be performed in the absence of the uterus. Any suspicious LN should be sent for the intraoperative assessment (frozen section).
C	PALND, at least up to inferior mesenteric artery, may be considered for staging purposes in patients with positive pelvic nodes at imaging, or at frozen section.

Management of patients with T1a1 and T1a2 disease

B	In patients with T1a1 tumour regardless of LVSI status and T1a2 tumour LVSI negative with clear margins in the hysterectomy specimen, no additional treatment is recommended.
B	Surgical LN assessment can be considered in T1a1 tumours with LVSI and it should be performed in T1a2 LVSI positive cases.

Management of patients with T1b1 disease, with clear margins and without residual tumour

B	In patients with T1b1 tumour with clear margins and absence of residual tumour on imaging (including non-suspicious LN), surgical LN staging is recommended. In case of histological evidence of PLN involvement, definitive CTRT is recommended and PALND, at least up to inferior mesenteric artery, may be considered for staging purposes.
B	In pathologically node negative patients with T1b1 disease, potential disease in the parametria should be addressed. Parametrectomy and upper vaginectomy could be considered.
C	Radiotherapy can be considered as an alternative modality to surgical treatment, considering the risk-benefit of repeat surgery.

Management of patients with ≥T1b2 disease, involved surgical margins and/or residual tumour (including LN)

B	For patients with free surgical margins and in absence of residual tumour on imaging (including non-suspicious LN), (chemo)radiotherapy is recommended as a treatment that avoids further surgical management.
B	Radical surgery (pelvic lymphadenectomy, parametrectomy and resection of the upper vagina) is an option in selected patients without expected indication for adjuvant (chemo) radiotherapy. If surgery has been performed, indications for adjuvant (chemo)radiotherapy follow the general recommendations.
B	If there is residual tumour on imaging (including suspicious LN), or involved surgical margins, CTRT with or without BT is the treatment of choice.
C	PALND, at least up to inferior mesenteric artery, may be considered for staging purposes in patients with positive pelvic nodes and negative paraaortic LN on imaging.



Management of locally advanced cervical cancer (T1b3-T4a)

A

Definitive radiotherapy should include concomitant chemotherapy whenever possible.

B

IGBT is an essential component of definitive radiotherapy and should not be replaced with an external boost (photon or proton). If BT is not available, patients should be referred to a centre where this can be done.

B

General recommendations for prescription of CTRT and IGBT are as follows:

- 3D imaging (preferentially both MRI and (PET-)CT) with the patient in the treatment position should be used for target contouring.
- It is recommended to deliver external beam radiotherapy (EBRT) with a dose of 45 Gy/25 fractions or 46 Gy/23 fractions by use of intensity-modulated or volumetric arc technique.
- Additional dose of radiation should be applied to pathological LN on imaging, preferentially using a simultaneous integrated boost (60 Gy EQD2, combined EBRT and estimated dose from IGBT).
- Concomitant weekly cisplatin is standard. However, weekly carboplatin or hyperthermia can be considered as an alternative option for patients not suitable for cisplatin.
- Image-guided adaptive brachytherapy (IGABT) (preferentially MRI) including access to intracavitary/interstitial techniques are needed to obtain a sufficiently high dose to ensure a high rate of local control in advanced cases with poor response to initial CTRT. This is especially important for non-squamous histology.
- Boosting of the primary tumour and/or the parametria by use of EBRT should be avoided.
- The overall treatment time including both CTRT and IGBT should aim to not exceed 7 weeks.

C

PALND (at least up to inferior mesenteric artery) may be used to assess the need for elective para-aortic EBRT in patients with negative para-aortic lymph nodes (PALN) and positive PLN on imaging.

B

If PALND is not performed, risk assessment for microscopic para-aortic nodal involvement and the indication for elective para-aortic irradiation can be based on the number of level 1 positive nodes (external iliac, interiliac, internal iliac) on imaging (e.g. >2 positive nodes). However, elective para-aortic radiation should always be applied in patients which on imaging have even one positive node on imaging at level 2 (common iliac) and above. The groins should also be included in the elective target for patients with tumour involvement of the lower third of the vagina.

D

Surgical removal of large pathological pelvic and/or para-aortic nodes before definitive CTRT is not routinely recommended.

D

NACT in patients who otherwise are candidates for upfront definitive CTRT and IGBT is not recommended outside of clinical trials.

D

Adjuvant chemotherapy following definitive CTRT and IGBT does not improve survival and enhances toxicity and should not be used outside clinical trials.

E

Adjuvant/completion hysterectomy after definitive CTRT and IGBT should not be performed since it does not improve survival and is associated with both increased perioperative and late morbidities.

B

Patients with a persistent tumour 3-6 months after definitive CTRT and BT and without evidence of regional or metastatic disease should be referred to specialized centres for evaluating the necessity and the possibility of performing salvage surgery (see management of recurrent disease and follow-up chapters).

Role of surgery in T1b3 and T2a2 (LN negative) tumours

B	There is limited evidence to guide the choice between surgical treatment versus CTRT with IGBT in LN negative patients with T1b3 and T2a2 tumours. Histology, tumour size, completeness of the cervical rim, uterine corpus invasion, magnitude of vaginal invasion, age, comorbidity, menopausal status, body mass index, haemoglobin and experience with type C radical hysterectomy are some of the factors to consider.
B	For surgery, avoidance of the combination of radical surgery and postoperative external radiotherapy requires acceptance for modifications of the traditional selection criteria (tumour size, degree of invasion, LVSI) for adjuvant treatment.
A	The patient should be discussed in a multidisciplinary basis and should be counselled for the advantages and disadvantages of both treatment options (surgery versus radiotherapy) in relation to the individual presence of prognostic factors.
A	Given the limited number of patients with T1b3 and T2a2 (<10%) tumours, referral to highly specialized centres for treatment is recommended.
A	Type C radical hysterectomy is recommended. LN staging should follow the same principles as in T1b1-2 tumours.
E	NACT followed by radical surgery should not be performed outside clinical trials.

Recurrent/Metastatic disease

General recommendations

A	Treatment of recurrent disease requires centralization and involvement of a broad multidisciplinary team including gynaecological oncologist, radiation oncologist, radiologist, pathologist, medical oncologist, urologist, and plastic surgeon. A structured program for multidisciplinary diagnostic work-up, treatment, and follow-up must be present in centres responsible for the treatment.
B	Participation in clinical trials is encouraged.
B	Early involvement of palliative care specialist is encouraged.
A	Patient should be carefully counselled regarding treatment options, risks and consequences.

Diagnostic work-up

B	The aim of the diagnostic work-up is to determine the extent of the locoregional and/or metastatic disease.
B	The recurrence should be confirmed by histological examination if feasible.
D	Patients with multiple nodal/distant metastases (i.e. not oligometastatic disease) or multifocal local disease with extensive pelvic wall involvement could not be considered as candidates for radical treatment.
B	Patients with oligometastatic or oligorecurrent disease should be considered for radical and potentially curative treatment options.
A	The prognostic factors should be carefully evaluated and balanced in relation to the major morbidity caused by the treatment.

Locoregional recurrent disease - Central pelvic recurrence after primary surgery

A	Definitive CTRT combined with IGABT is the treatment of choice in radiotherapy naïve patients.
D	The use of boost by external beam techniques to replace IGBT is not recommended.
C	Small superficial lesions (ie, <5 mm thickness) in the vagina may be treated by IGBT using a vaginal cylinder, ovoids, or mold, whereas other lesions usually require combined intracavitary-interstitial techniques.

Locoregional recurrent disease - Pelvic sidewall recurrence after primary surgery

A	Definitive CTRT is the preferred option in radiotherapy naïve patients.
B	When radical radiotherapy is not feasible, extended pelvic surgery can be considered. Surgery must aim to a complete tumour resection (R = 0) also with the help of special techniques (laterally extended endopelvic resection (LEER), out of box procedures), if required.
B	Combined operative-radiotherapy procedures using intra-operative radiotherapy or IGBT are an option if free surgical margins are not achievable.

Locoregional recurrent disease - Central pelvic or pelvic sidewall recurrence after radiotherapy

B	Pelvic exenteration is recommended for central pelvic recurrence where there is no involvement of the pelvic sidewall, extrapelvic nodes or peritoneal disease.
C	Reirradiation with IGABT for central recurrences could be considered in selected patients taking into account volume of the disease, or time from the primary radiotherapy and total dose administered initially. This must be performed only in specialized centres.
B	In patients with pelvic sidewall involvement, extended pelvic surgery can be considered in specialized centres. Surgery must aim to a complete tumour resection (R = 0) also with the help of special techniques (LEER, out of box procedures), if required.
B	Patients who are not candidates for extensive surgery should be treated with systemic chemotherapy. Additional treatment can be considered depending of the response.

Oligometastatic recurrences

C	Localized para-aortic, mediastinal, and/or peri-clavicular recurrences out of previously irradiated fields may be treated by radical EBRT with or without chemotherapy.
C	The therapeutic effect of nodal resection/debulking is unclear and should, if possible, be followed by radiotherapy.
B	The management of "oligo" organ metastases (lung, liver, etc.) should be discussed in a multidisciplinary setting including the team involved in the treatment of the organ-affected metastasis. Treatment options are represented by local resection, thermal ablation, interventional BT, or stereotactic ablative radiotherapy according to the size and localization.

Distant recurrent and metastatic disease

A	Patients with recurrent/metastatic disease should have a full clinical-diagnostic evaluation to assess the extent of disease and the most appropriate treatment modality including best supportive care.
A	Platinum-based chemotherapy ± bevacizumab is recommended for chemo-naïve, medically fit patients with recurrent/metastatic disease. Carboplatin/paclitaxel and cisplatin/paclitaxel are the preferred regimens.
A	The addition of bevacizumab to platinum-based chemotherapy is recommended when the risk of significant gastrointestinal/genitourinary toxicities has been carefully assessed and discussed with the patient.
A	The addition of pembrolizumab to platinum-based chemotherapy ± bevacizumab is recommended in patients with PD-L1 positive tumours, assessed as combined positive score (CPS) of 1 or more.
A	Patients who progressed after first-line platinum-based chemotherapy should be offered treatment with the anti PD-1 agent, cemiplimab, regardless of PDL-1 tumour status as long as they had not previously received immunotherapy.
C	Patients with distant metastatic disease at diagnosis, who have responded to systemic chemotherapy, could be considered for additional radical pelvic radiotherapy (including IGBT in selected cases). Those with residual oligometastatic disease after systemic treatment could also be considered for additional regional treatment (surgery, thermal ablation, radiotherapy) to involved sites.
A	Inclusion of patients with recurrent/metastatic disease in clinical trials is strongly recommended.

Follow-up during and after treatment/long-term survivorship

General recommendations

A	Patients should be informed and educated at the time of diagnosis and throughout follow-up about signs/symptoms of recurrence and informed about possible side effects (by physicians, nurses, brochures, videos, etc.).
A	A network of health care providers including all care providers should be involved in the care of survivors (e.g. primary care physicians, gynaecologists, psychologists, sexologists, physiotherapists, dieticians, social workers) for the follow-up.
A	Follow-up strategy should be individualised in terms of intensity, duration and procedures, taking into account individual risk assessment.
B	Available prognostic models, such as the Annual Risk Recurrence Calculator available on the ESGO web site can be used to tailor surveillance strategy in an individual patient.
A	Follow-up should be centralised/coordinated in a centre specialized in the treatment and follow-up of gynaecological cancer patients.
B	Follow-up is designed to monitor disease response, to detect recurrence and to screen for subsequent primary tumours.
A	Regular and systematic monitoring of side effects and quality of life should be performed to improve the quality of care.

A

Prevention and early detection of immediate and persistent symptoms and side effects of the different cancer treatments and the individual patient supportive care needs should be identified and established at diagnosis and monitored throughout the follow-up.

A

All side effects should be identified and treated if possible, namely physical and psychosocial.

B

The development of an individual survivorship monitoring and care plan is recommended.

B

Recommendations for healthy life style should include smoking cessation, regular exercise, healthy diet and weight management.

B

Clinical trials should address long-term cancer survivorship and should include patient related outcomes.

B

Quality control of care should be established.

A

Each visit should be composed of the following:

- Patient history (including identification of relevant symptoms and side effects)
- Physical examination (including a speculum and bimanual pelvic examination)
- Imaging and laboratory tests should be performed only based on risk of recurrence, symptoms or findings suggestive of recurrence and/or side effects.
- Regular review of an ongoing survivorship plan that can be shared with other health care providers.

A
A
A
D
A

Oncological follow-up

- Patients should be educated about symptoms and signs of potential recurrence.
- Appropriate imaging test (MRI, ultrasound for pelvic assessment, CT scan or PET-CT for systemic assessment) should be used in symptomatic women.
- In case of suspected tumour persistence, recurrence or second primary cancer, histological verification is strongly recommended.
- Vaginal vault cytology is not recommended.
- After fertility sparing treatment, follow-up should include HPV testing (at 6-12 and 24 months).

B
A
B
B
C
B

Monitoring of quality of life and side effects

- Quality of life and side effects should be regularly assessed at least by the physicians/clinical care nurses and if possible by patients (using patient related outcomes). Patient self-reporting of side effects should be encouraged during and after treatment with the same frequency as medical visits.
- Checklist of potential main side effects should be included in the patient survivorship monitoring and care plan (e.g. sexual dysfunction, lymphedema, menopausal symptoms and osteoporosis, genito-urinary and gastrointestinal disorders, chronic pain, fatigue).
- After CTRT and BT, patients should be counselled about sexual rehabilitation measures including the use of vaginal dilators. Topical estrogens are indicated.
- Hormone replacement therapy is indicated to cervical cancer survivors with premature menopause and should be consistent with standard menopausal recommendation.
- Physical and lifestyle changes may also help.
- Bone status should be assessed regularly in patients with early menopause.

Follow-up after definitive CTRT and BT

A	Follow-up should be performed/coordinated by a physician experienced with follow-up care after radiotherapy and BT including monitoring of early, and late treatment-related side effects.
B	The same imaging method used at the start of treatment should be used to assess tumour response.
D	Routine biopsy to assess complete remission should not be performed.
D	Cytology is not recommended in detecting disease recurrence after radiotherapy.
B	Imaging (pelvic MRI ± CT scan or PET-CT) should be performed not earlier than 3 months after the end of treatment.
B	In patients with uncertain complete remission at 3 months post radiotherapy, the assessment should be repeated after additional 2-3 months with biopsy if indicated.

Quality of life and palliative care

General recommendations

A	Early palliative care, integrated with oncological treatments, should be offered by the clinical team to all the patients diagnosed with advanced cervical cancer for managing symptoms and improving quality of life. A multidisciplinary approach must be included in the care plan with discussion and planning for specific treatment of these symptoms.

Pain

A B	Opioids are the main analgesics for the treatment of moderate to severe cancer-related pain; the first option is oral morphine. But other opioids and alternative routes (transdermic, subcutaneous) can be required in specific situations (i.e., intestinal obstruction, problems with swallowing, renal failure).
B	Cancer-related neuropathic pain should be treated with a combination of opioids and carefully dosed adjuvants (gabapentin, pregabalin, duloxetine, and tricyclic antidepressants) if opioids alone do not provide sufficient pain relief.
B	Severe pelvic cancer pain unresponsive to an opioid regimen can benefit from other procedures like plexus block or spinal analgesia techniques.
B	Palliative EBRT (if feasible) is effective for painful pelvic progression and bone metastasis.

Renal failure

C	Urinary derivation by ureteral stent or percutaneous nephrostomy could be considered to treat renal failure caused by tumoural obstruction. There are no clear guidelines to predict which patients will benefit from these procedures in terms of survival and quality of life, and its indication should be carefully discussed.

Malignant intestinal obstruction

B	Medical management of malignant intestinal obstruction consists of antisecretory, corticosteroids, and antiemetic drugs. A nasogastric tube is recommended if vomiting and discomfort persist in spite of medical management. Surgical procedures can be considered in selected patients.

Vaginal bleeding and discharges

B

In the case of vaginal bleeding, vaginal packing, interventional radiology (selective embolization) or palliative radiotherapy (if feasible) are recommended. There is not enough evidence to prefer one over the others. In the case of massive refractory bleeding, palliative sedation can be considered. Malodorous vaginal discharge can be improved with vaginal washing and the use of a vaginal metronidazole tablets.

Psychosocial suffering

A

In patients with cervical advanced cancer, a multidisciplinary approach of physicians, nurses, psychologists, social workers, and community health workers is needed to manage psychosocial and spiritual suffering associated with social stigma deriving from genital disease, malodorous vaginal discharge, etc.

Cervical cancer in pregnancy

General recommendations

A

Every patient diagnosed with cervical cancer in pregnancy must be counselled by a multidisciplinary team. This team should consist of experts in the fields of gynaecological oncology, neonatology, obstetrics, pathology, anesthesiology, radiation oncology, medical oncology, psycho-oncology, and, spiritual and ethical counseling. National or international tumour board counseling may be considered.

A

Given the large spectrum of therapeutic options, the multidisciplinary team should recommend a treatment plan according to the patient's intention, tumour stage, and gestational age of pregnancy at the time of cancer diagnosis. The primary aims of the recommended treatment plan are the oncological safety of the pregnant woman as well as the fetal survival without additional morbidity.

A

Treatment of patients with cervical cancer in pregnancy should be exclusively done in gynaecological oncology centres associated with a highest level perinatal centre with expertise in all aspects of oncologic therapy in pregnancy and intensive medical care of premature neonates.

Clinical and imaging diagnosis

A

Clinical examination and histological verification of cervical cancer are mandatory.

C

Pathological confirmation may be obtained by colposcopy oriented biopsy or small cone (appropriate only during the first trimester of pregnancy, endocervical curettage is contraindicated).

A

Preferred imaging modalities for clinical staging in patients with cervical cancer in pregnancy include pelvic MRI or expert ultrasound as part of the primary work-up. Gadolinium-based contrast agents should be avoided.

B

The use of whole-body diffusion-weighted imaging MRI can reliably obviate the need for gadolinium contrast and radiation for nodal and distant staging during pregnancy. If not available, chest CT scan with abdominal shielding is an alternative. PET-CT should be avoided during pregnancy.

Oncological management

A Tumour involvement of suspicious nodes should be histologically confirmed because of its prognostic significance and the impact on the management up to 24 weeks of gestation (fetal viability).

C Minimally invasive approach could be considered before 14-16 weeks of gestation; however, the sentinel node biopsy concept using indocyanine green is still experimental.

B Several treatment modalities are available and should be discussed with the patient taking into account the tumour stage, gestational week of pregnancy and patient´s preferences:

- Delay of oncological treatment until fetal maturity (if possible >34 weeks of gestation) and initiate cancer-specific treatment immediately after delivery by cesarean section. This option might be considered if the term or fetal maturity is approaching.
- Conization or simple trachelectomy in order to completely remove the tumour, obtain free margins and perform nodal staging if needed, with the intention to preserve the pregnancy.
- Radical surgery or definitive CTRT according to the disease stage as recommended outside pregnancy, if the woman decides not to preserve the pregnancy. Pregnancy termination is recommended before any treatment after the first trimester, and fetus evacuation before CTRT, if possible.
- Chemotherapy until term of pregnancy (37 weeks of gestation) and initiation of definitive cancer-specific treatment immediately after delivery by cesarean section. At least a two-week interval between chemotherapy and surgery is recommended. In patients with locally advanced disease or residual tumour after surgical procedure that cannot be completely removed (risk of premature rupture of amniotic membranes and/or cervical insufficiency), chemotherapy based on cisplatin or carboplatin can be considered starting after 14 weeks of pregnancy. Combination with taxanes is an option. Bevacizumab and checkpoint inhibitors are contraindicated.
- Before starting each cycle of chemotherapy, an assessment of treatment response should be made by clinical examination and transvaginal or transrectal ultrasound. If no response is achieved after 2 cycles of chemotherapy during pregnancy, treatment strategy should be re-evaluated.

Pregnancy management

B Spontaneous delivery appears to have negative prognostic impact in patients with cervical cancer in pregnancy. Thus, cesarean section is the recommended mode of delivery.

A At the time of cesarean section, definitive cancer specific treatment should be performed corresponding to that of non-pregnant women, taking into account the treatment that has already been given during pregnancy.

Rare tumours

A Histopathological diagnosis of rare cervical tumours needs confirmation (second opinion) by expert pathologist.

A Treatment and care of rare cervical tumours needs to be centralized at referral centres and discussed in a multidisciplinary tumour board.

NOTES

NOTES

Access full ESGO Guidelines: www.esgo.org/explore/guidelines

© 2023 European Society of Gynaecological Oncology

All rights reserved. No part of this book can be reprinted, reproduced, transmitted or utilized in any form by any electronic, mechanical, or other means, now known or hereafter invented, including photocopying, microfilming, and recording, or any information storage or retrieval system, without written permissions of ESGO. Reasonable efforts have been made to publish reliable data and information, but the authors and publisher cannot assume responsibility for the validity of all materials or for the consequences of their use, and the ultimate responsibility rests with the prescribing physician

ESGO Office
7, Rue François-Versonnex
1211 Geneva 6, Switzerland
Email: adminoffice@esgo.org
www.esgo.org

© 2023 European Society of Gynaecological Oncology