Gynaecology CRG

Cervix Cancer Guidelines

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Cervical Cancer Guidelines

Lancashire and South Cumbria (L&SC) Cancer Network

These guidelines outline the management of women with an established diagnosis of cervix cancer. They should be used to guide treatment for women diagnosed with cervix cancer in the Lancashire and South Cumbria Cancer Alliance footprint.

1. Staging

The established staging system for cervix cancer was revised by the International Federation of Gynaecology and Obstetrics (FIGO) in 2018. Electronic cancer datasets (eg Somerset Cancer Register (SCR)) and the National Cancer Registration and Analysis Service take time to respond to these changes and will continue to use the previous staging format (FIGO 2014) until the end of 2019 (see appendix). It is good practice to record TNM staging in addition to FIGO staging through the L&SC cancer registration system (SCR).

International Federation of Gynaecology and Obstetrics (FIGO) staging of cancer of the cervix uteri (2018)

Stage	Description
I	The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm*
IA1	Measured stromal invasion <3 mm in depth
IA2	Measured stromal invasion ≥3 mm and <5 mm in depth
IB	Invasive carcinoma with measured deepest invasion ≥5 mm (greater than Stage IA), lesion limited to the cervix uteri¶
IB1	Invasive carcinoma ≥5 mm depth of stromal invasion, and <2 cm in greatest dimension
IB2	Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
IB3	Invasive carcinoma ≥4 cm in greatest dimension
II	The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
IIA	Involvement limited to the upper two-thirds of the vagina without parametrial involvement

IIA1	Invasive carcinoma <4 cm in greatest dimension
IIA2	Invasive carcinoma ≥4 cm in greatest dimension
IIB	With parametrial involvement but not up to the pelvic wall
III	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or para-aortic lymph nodes[Δ]
IIIA	The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney (unless known to be due to another cause)
IIIC	Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumor size and extent (with r and p notations)[Δ]
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lymph node metastasis
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. (A bullous edema, as such, does not permit a case to be allotted to Stage IV.)
IVA	Spread to adjacent pelvic organs
IVB	Spread to distant organs

When in doubt, the lower staging should be assigned.

A Imaging and pathology can be used, where available, to supplement clinical findings with respect to tumor size and extent, in all stages.

B The involvement of vascular/lymphatic spaces does not change the staging. The lateral extent of the lesion is no longer considered.

C Adding notation of r (imaging) and p (pathology) to indicate the findings that are used to allocate the case to Stage IIIC. Example: If imaging indicates pelvic lymph node metastasis, the stage allocation would be Stage IIIC1r, and if confirmed by pathologic findings, it would be Stage IIIC1p. The type of imaging modality or pathology technique used should always be documented.

2. Clinical and radiological diagnostic work-up

1- Pelvic examination and biopsy or screening detected cancer
2- Magnetic resonance imaging (MRI) pelvis and abdomen for stage T1a2 and beyond.
3- Positron emission tomography-computed tomography (PET-CT) for assessment of nodal and distant disease for any patient for radical radiotherapy.
4- Examination under anaesthesia (EUA) and insertion of radiopaque markers at the lower border of tumour, if it extends below the upper 1/3 of vagina.
5- HIV testing (for HPV associated cervix cancer).

The management algorithms below are for squamous carcinomas, adenocarcinomas or adenosquamous carcinomas (Human Papilloma Virus associated disease).

3. Fertility-sparing surgery (FST)

- 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.
- Negative pelvic lymph node status is the precondition for any FST. Therefore pelvic lymph node staging should always be the first step in each FST procedure. The involvement of suspicious lymph nodes should be confirmed by histology (ideally intraoperative frozen section). Lymph node staging is not indicated in stage T1a1 LVSI negative.
- In case of intraoperatively proven lymph node involvement, fertility sparing surgery should be abandoned and the patient referred to definitive chemoradiotherapy.
- The specific aim of fertility sparing surgery must be the resection of invasive tumour with adequate free margins and preservation of upper part of the cervix.
- Intraoperative placement of permanent cerclage should be performed during simple or radical trachelectomy.
- FST in patients with tumours > 20mm cannot be recommended.
- Any pregnancy following FST should be considered as a high risk pregnancy. Following simple or radical trachelectomy with its inherent placement of a permanent cerclage delivery can be performed only by caesarean section.
- Routine hysterectomy after completion of family is not necessary.

4. Management of stage T1a Disease:

4.1. Diagnosis of T1a cancer should be based on a LLETZ specimen examined by an expert gynaecologist 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.

4.2. Maximum care should be taken to provide an intact (unfragmented) specimen with minimal thermal artefact. The cone specimen should be oriented for the pathologist.

4.3. Surgical margins of the cone specimen should be clear of both invasive and preinvasive disease.

Treatment of stage T1a

Stage	LVSI	Fertility sparing	Non-fertility sparing
T1a1	-ve	• LLETZ with clear margins	• LLETZ with clear margins
	+ve	• LLETZ with clear margins +/- Sentinel LN mapping • Simple trachelectomy +/- Sentinel LN mapping	• LLETZ with clear margins +/- Sentinel LN mapping and biopsy
T1a2	-ve	• LLETZ with clear margins + sentinel LN mapping • simple tracheletomy + sentinel LN mapping	• Simple hysterectomy + sentinel LN mapping
	+ve	• LLETZ with clear margins + pelvic LN dissection • Simple tracheletomy + pelvic LN dissection	• Simple hysterectomy + pelvic LN dissection

5. Management of stage T1b1 and T2a1:

- Treatment strategy should aim for the avoidance of combining radical surgery and radiotherapy due to the highest morbidity after combined treatment.
- Radical hysterectomy and pelvic lymphadenectomy by a gynaecological oncologist is the preferred treatment modality. The surgical approach will be determined by the dimension of the tumour. Recently published randomised evidence demonstrates improved oncological outcomes (PFS and OS) for procedures performed as open surgery. This risk seems particularly apparent for tumours >20mm. The approach to surgery should be discussed with the patient with reference to BGCS Position Statement on Surgery in Early Stage Cervical Cancer – Lay Summary (May 2019). Open surgery is recommended for tumours >20mm in dimension.
- Ovarian preservation should be offered to premenopausal patients with squamous cell carcinoma and usual-type (human papillomavirus (HPV)-related) adenocarcinoma. Bilateral salpingectomy should be performed.
- In patients with unequivocally involved pelvic lymph nodes on imaging, definitive chemoradiotherapy is recommended
- If lymph node involvement is detected intraoperatively, further pelvic lymph node dissection and radical hysterectomy should be avoided. Patients should be referred for definitive chemoradiotherapy. Thus suggest that LN dissection should be the first operative step.
- If a combination of risk factors is known at diagnosis, which would require an adjuvant treatment, definitive radio chemotherapy and brachytherapy can be considered without previous radical pelvic surgery. Pelvic lymph node dissection should be avoided.
- Definitive radiotherapy including brachytherapy represents effective alternative treatment in case of unfavourable prognostic and predictive factors for oncological and morbidity outcomes.

Treatment of stage T1b1 and T2a1

Stage	Fertility sparing surgery	Non-fertility sparing surgery
T1b1 (<500mm^3)	• Simple trachelectomy + pelvic LN dissection • LLETZ + pelvic LN dissection	• Simple hysterectomy + pelvic LN dissection
T1b1 (>500mm^3)	• Radical trachelectomy + pelvic LN dissection	• Radical hysterectomy + pelvic LN dissection
T1b2	n/a	• Radical hysterectomy + pelvic LN dissection
T1b3	n/a	• Chemoradiotherapy
T2a1	n/a	• Radical hysterectomy + pelvic LN dissection

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

Querleu-Morrow Classification of radical hysterectomy

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 mobilised)	Minimal excision	Minimal excision
Type B1	At the ureter (at the level of the ureteral bed–ureter mobilised 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

6. Post-operative (chemo)radiotherapy

6.1. Adjuvant chemoradiotherapy if:

- Any LN positive
- Positive surgical margins
- Parametrial involvement

6.2. Adjuvant Radiotherapy if:

- Close margins defined as <5mm lateral
- Guidance from surgeon to individualised patient care for close posterior peritoneal margin (<5mm) and or close anterior anatomical margin (<3mm)
- And also

SEDLIS CRITERIA FOR EXTERNAL PELVIC RADIATION AFTER RADICAL HYSTERECTOMY IN NODE-NEGATIVE, MARGIN-NEGATIVE, PARAMETRIA-NEGATIVE CASES[1-4]

LVSI	Stromal Invasion	Tumor Size (cm) (Determined by clinical palpation)
+	Deep 1/3	Any
+	Middle 1/3	≥2
+	Superficial 1/3	≥5
-	Middle or Deep 1/3	≥4

LVSI: Lymphovascular space invasion

Post op incidental cervical carcinoma:

Clinically occult cervical cancer diagnosed after simple hysterectomy:

- Prior to making further management decisions, optimal imaging to evaluate the local and regional (nodal) disease status is necessary. Optimal imaging follows the same recommendations as that for non-occult disease.
- In general, management of occult disease follows the same principles as that of non-occult disease. Treatment strategy should aim for the avoidance of combining radical surgery and radiotherapy due to the highest morbidity after combined treatment.

Stage	Additional treatment
T1a1, regardless of LVSI T1a2, LVSI -ve, clear margins (≥5mm)	None required
T1a2 clear margins (≥5mm), LVSI+ve T1b1 or T2a1, clear margins (≥5mm)	• Pelvic LN dissection (if adequate central clearance with ≥5mm margin) OR • Radiotherapy, if no residual disease on imaging • Chemoradiotherapy, if residual disease on imaging
T1b2 and higher, involved surgical margins, residual tumour, involved LN on imaging	Chemoradiotherapy

More Advanced Disease not suitable for primary surgery on tumour or patient factors:

stage	treatment	notes
1B1, 2A1,1B2, 2A2-IVB	Chemoradiotherapy and brachytherapy MRI needed at week 5 of external Bram radiotherapy to guide brachytherapy	1] external beam boost radiotherapy is not as good as brachytherapy for primary central disease 2] see Rosemere Cancer Centre 'treatment of cervical cancer protocol' that specifies treatment duration under 56 days (ideally <50 days), external beam boost to involved LNs, 5 weekly cisplatin treatments with external beam radiotherapy, EBRT with bladder moderately full protocol 3] surgical debulking of involved lymph nodes or ovaries pre or post chemo-radiotherapy allowed 4]PA node sampling for staging purposes is not routinely performed 5]Involved PSW disease to be taken to 60Gy with combination of External Beam radiotherapy and Brachytherapy unless surgical debulking pre / post radiotherapy. 6A] Neoadjuvant chemotherapy allowed if a) LN +ve or b) bulky tumour or c) to reduce risk of fistula. Usually with weekly carboplatin AUC2 paclitaxel 80mg/m2 for 6 weeks. 6B] For PAN positive disease up to 4 cycles of 3 weekly treatment (12 weeks of weekly carboplatin paclitaxel) may be used pre definitive therapy.

Cervical cancer in pregnancy:

- 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, anaesthesiology, radiation oncology, medical oncology, psycho-oncology and, if requested, theology or ethics.
- Primary aims of recommended treatment plan are oncological safety of the pregnant woman as well as survival without additional morbidity of the fetus.
- Besides clinical examination and histologic verification of invasive cervical cancer preferred imaging modalities for clinical staging include MRI or expert ultrasound. Due to limited experience and inherent radioactivity, PET-CT should only be indicated under very selected circumstances.
- Depending on tumour stage and gestational week of pregnancy, options have to be discussed with the patient including risks and benefits of individual approaches:
  1- Adapted surgery including removal of the tumour: conisation, trachelectomy and lymph node staging at early stages of the disease with the intent to preserve the pregnancy.
  2- Radical surgery or definitive chemoradiation as recommended for the stage of the disease without preservation of the pregnancy, with or without previous pregnancy termination.
  3- Delay of oncological treatment until foetal maturity (if possible >32 week of gestation) and beginning of cancer specific treatment immediately after delivery by caesarean section.
  4- Chemotherapy until fetal maturity (platinum based chemotherapy starting the earliest at 14 weeks gestation) and beginning of cancer specific treatment immediately after delivery by caesarean section. Treatment after delivery must consider application of previous chemotherapy. In patients with locally advanced stage or with residual tumour after conisation that cannot be completely excised (risk of premature rupture of membranes and/or cervical insufficiency) platinum-based chemotherapy can be considered starting earliest at 14 weeks of gestation.
- Spontaneous delivery seems to have negative prognostic impact. Thus, caesarean section after 32th week of gestation (if possible) is the recommended mode of delivery. At the time of or following caesarean section definitive stage adjusted oncologic therapy has to be performed corresponding to that of non-pregnant women taking into account therapy which has already been given during pregnancy.
- Consider Cabergoline to prevent lactation in women receiving chemotherapy. (1mg po to be taken on the first day postpartum or 250mcg every 12hrs for 2 days for established lactation).

Small Cell Neuroendocrine carcinoma of the cervix

This is a rare disease affecting 2% of invasive carcinomas. This section covers small cell and large cell neuroendocrine carcinomas which are treated similarly. It does not cover carcinoid tumours.

Small cell and large cell neuroendocrine carcinomas:

- Have high frequency of lymph nodal and haematogenous metastases
- May show paraneoplastic syndromes
- Biopsy is required for diagnosis
- Staging with CT chest abdomen and pelvis.
- Neuraxis imaging only for relevant symptoms / signs.
- Outcome:
    - 30% 5 year survival with limited stage disease
    - Unlikely to survive over 2 years with more extensive disease
- Follow up: 3 monthly year 1, 4 monthly year 2, 6 monthly year 3, annual years 4 and 5
- CT imaging at post completion of therapy, 6 months, 12 months and 24 months.

Therapy (assuming patient is fit for interventions below):

- *Localised operable disease (stage IB1-IIA, <4cm size, no parametrial disease, no nodal or distant metastases):*
  1] Radical surgery (non-fertility sparing) followed by adjuvant platinum etoposide chemotherapy (+/- radiotherapy dependent on operative-histology)
  Or
  2] Chemoradiotherapy (option 1 i.e. surgery is favoured)

- *Locoregional unresectable but not metastatic disease:*
  Chemoradiotherapy using platinum etoposide (minimum 4 cycles) and ideally radiotherapy to start no later than cycle 3.

- *Metastatic Disease:*
  Palliative chemotherapy and or radiotherapy using regimens similar to small cell lung cancer. Platinum etoposide favoured as initial chemotherapy regimen.

- *Prophylactic cranial irradiation:*
  This is NOT generally recommended.

- *Relapsed Disease:*
  Treat along lines of small cell lung cancer

Follow-up for common malignancies:

1- 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. 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
•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, life-style adaptation, nutrition, exercise, obesity and cessation of smoking.
•Prescription of hormonal replacement treatment to cervical cancer survivors with premature menopause is advocated, and should be according to regular menopausal recommendation.

2- Each visit should be composed of the following:

• Patient history
• Physical examination (including a speculum examination)
• Physician assessment of adverse events
• Prevention and management of cancer- and treatment-related side effects e.g. sexual dysfunction (e.g. counselling, vaginal lubricants, local oestrogen)
• Imaging and laboratory tests should be performed based on symptoms or findings suspicious for recurrence or morbidity.
•In case of the appearance of treatment-related symptoms, a referral to a dedicated specialist (e.g. gastroenterologist, urogynaecologist) should be considered.

3- Imaging tests:

•Surveillance imaging after fertility sparing surgery should have MRI scan at 6 months
•Surveillance imaging after chemoradiation performed at 6 and 24 months
•PET in general only needed for salvage curative therapy (surgery or radiotherapy).
•Pathologic confirmation of any persistent or recurrent tumour should be considered. In case of clinically or radiologically suspicious disease, a negative biopsy may not be conclusive.

4- Follow up schedule:

•Women who underwent LLETZ for stage T1a, should have cervical cytology be taken six and 12 months after treatment, followed by annual cytology for the next nine years before return to routine recall to 65 years.
•Women who underwent fertility-sparing surgery clinic follow up six monthly to 3 years.
•Women who underwent radical surgery with no adverse prognostic factors, need to be seen in 6, 12, 18 and 24 months.
•Women who received primary or adjuvant (chemo-)radiotherapy, are followed up for 4 years (3 monthly to 6 months, 6 monthly to year 3, annually to year 4).

Relapsed disease:

A. Potentially curative
   - Pelvic relapse post radiotherapy—assess for radical surgery. Laterally extended endopelvic resection for disease close to / at pelvic side wall for highly selected patients.
   - Pelvic relapse post-surgery—salvage chemoradiotherapy and brachytherapy
   - Pelvic and or Retroperitoneal LN relapse---salvage chemoradiotherapy +/- brachytherapy or surgery or trimodality therapy (of surgery, chemotherapy, radiotherapy)
   - Supraclavicular fossa as isolated relapse or other site of oligometastasis (eg mediastinum)—definitive chemoradiotherapy, often with additional chemotherapy. Stereotactic irradiation can be considered for suitable situations.
   - Reirradiation (eg image guided brachytherapy for central recurrence) if patient refuses exenteration may be considered subject to patient consent of risks, ideally with agreement of second oncologist.
   - Referral to other MDTs or supraregional centres may be appropriate for SABR, RFA, brachytherapy, surgery or trials.

B. Non curative situations

   These patients can be sensitive to chemotherapy

   1.First line—platinum taxane +/- bevacizumab

   2.Second Line:
      - Long chemo free interval—rechallenge
      - Platinum topotecan

   3.Trials

   4.Palliative radiotherapy

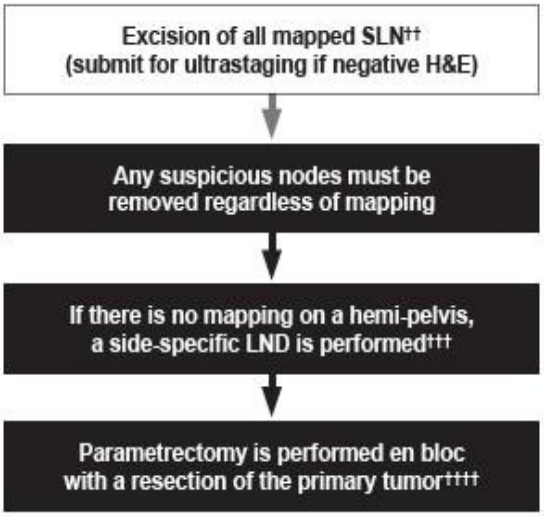
   5.Supportive / Palliative Care

Appendix 1:

PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED

The key to a successful SLN mapping is adherence to the SLN algorithm, which requires the performance of a side-specific nodal dissection in cases of failed mapping and removal of any suspicious or grossly enlarged nodes regardless of mapping (Figure 3).

Figure 3: Surgical/SLN Mapping Algorithm for Early-Stage Cervical Cancer†



H&E: Hematoxylin and eosin staining
LND: Lymphadenectomy
SLN: Sentinel lymph node

Appendix 2: Old FIGO 2014 staging

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 classification of malignant tumours (2016).

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