ESGO GUİDELİNES FOR CERVİCAL CANCER

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- These guidelines exclude the management of neuroendocrine carcinoma, sarcomas, and other rare histologic sub-types

Staging

- TNM classification
- Clinical staging (FIGO) should also be documented

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).
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).

TABLE 1 FIGO staging of cancer of the cervix uteri (2018).

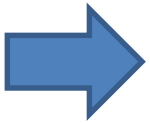
Stage	Description
I	The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm[a]
IA1	Measured stromal invasion <3 mm in depth
IA2	Measured stromal invasion ≥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[b]
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 nonfunctioning kidney and/or involves pelvic and/or para-aortic lymph nodes[c]
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 nonfunctioning 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)[c]
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

Local clinical and radiological diagnostic work-up

- Pelvic examination and biopsy +/- colposcopy are mandatory components to diagnose cervical cancer
- Pelvic MRI
- Endovaginal/transrectal ultrasound is an option
- Cystoscopy or rectoscopy

Nodal/distant diagnostic work-up

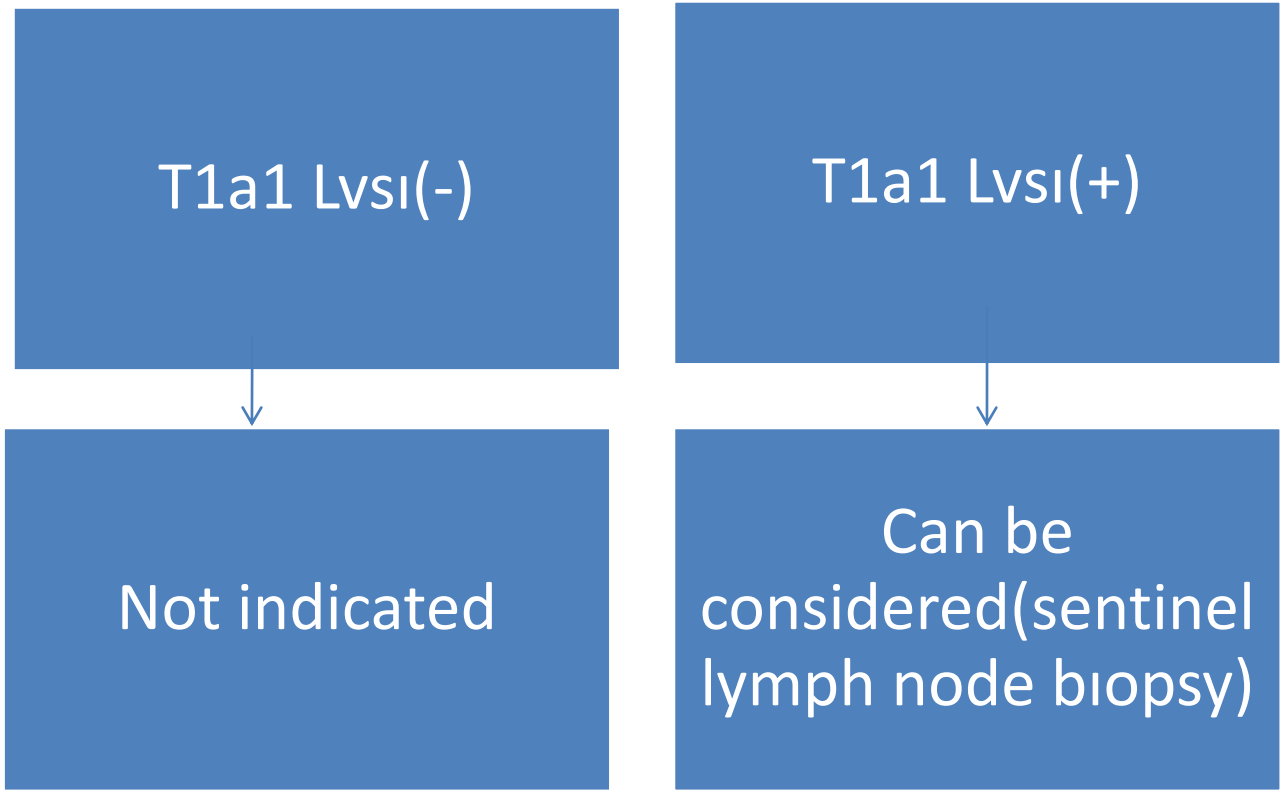
- In early stage (T1a, T1b1, T2a1), surgical/pathological staging of pelvic lymph nodes
- In locally advanced cervical cancer (T1b2 and higher except T2a1) or in early stage disease with suspicious lymph nodes on imaging, PET-CT or Torax/abdomen CT
- PET-CT is the preferred option, before chemoradiotherapy with curative intent

- Paraaortic lymph node dissection, locally advanced (negative paraaortic lymph nodes on imaging)
- Equivocal extrauterine disease  biopsy

Management of stage T1a1

- Diagnosis → conisation specimen
- In case of positive margins (except for preinvasive disease in ectocervix), a repeat conisation should be performed to rule out more extensive invasive disease.

Lymp node staging



- Conisation can be considered a definitive treatment as hysterectomy does not improve the outcome (evidence c)
- Radical hysterectomy or parametectomy overtreatment (evidence c)

Management of stage T1a2 disease

Conisation or simple hysterectomy

Lymp node staging

Lvsı(-)

Can be considered

Lvsı(+) Should be performed(sentinel)

Routine completion of hysterectomy is not recommended after conservative management

Management of stages T1b1/T2a1(≤4cm)

- avoidance of combining radical surgery and radiotherapy

Negative lymph nodes on radiological staging

- Radical surgery
- Minimal invasive approach is favored.
- Systematic pelvic lymphadenectomy (Sentinel)
- Intraoperative assessment of lymph node status (frozen section)
- Lymph node (+); avoid further surgery- refer chemoradiotherapy

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

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

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

Table 3. Querleu-Morrow classification[5]

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

Alternative treatment optionts

Definitive radiotherapy

- Unfavorable prognostic and predictive factors
- For high risk and intermediate risk, preoperative brachytherapy followed by surgery (Type A) is used in a limited number of centres.
- Neoadjuvant chemotherapy followed by surgery is not recommended (evidence c)

Positive pelvic lymph nodes on radiological staging

- Definitive chemoradiotherapy
- Paraaortic lymph node dissection
- Debulking of suspicious pelvic lymph nodes may be considered.

Adjuvant treatment

- in the presence of combination of risk factors tumour size, LVSI, and depth of stromal invasion.
- When in these situations an adequate type of radical hysterectomy has been performed observation is an alternative option

- metastatic involvement of pelvic lymph nodes, chemoradiotherapy;
- positive surgical margins (vagina/parametria) chemoradiotherapy(+/- brachytherapy)
- parametrial involvement chemoradiotherapy

FERTILITY-SPARING TREATMENT

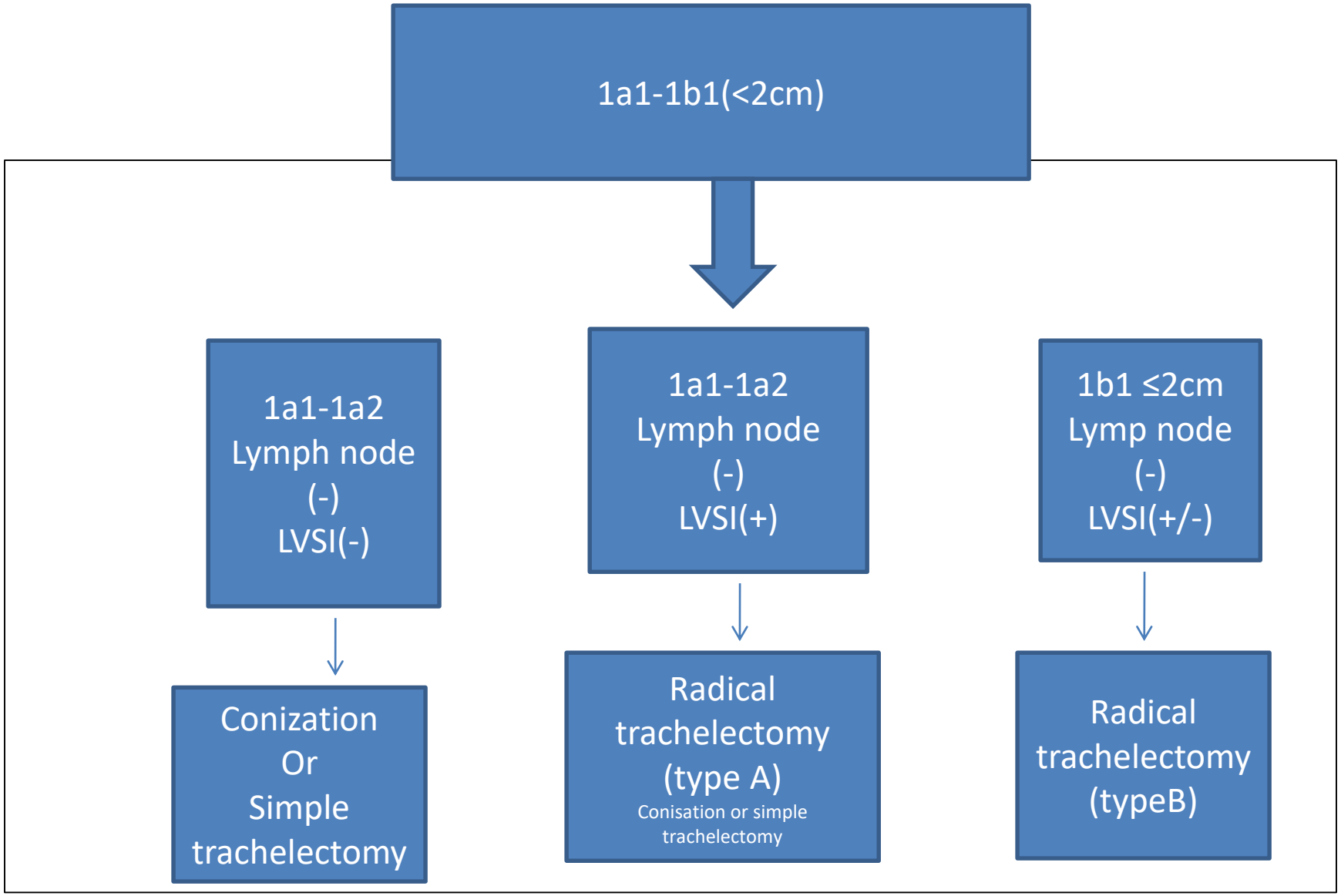
- squamous cell carcinoma or usual-type (HPV-related) adenocarcinoma
- ≤ 2 cm of the largest diameter

- pelvic lymph node (sentinel lymph node) staging: first step
- Identification of sentinel lymph node and its ultrastaging is highly recommended

- Frozen section  lymph node

- 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
- Intraoperative frozen section is a reliable way of assessing the upper resection margin in trachelectomy specimen


1a1-1b1(<2cm)
1a1-1a2
Lymph node
(-)
LVSI(-)
Conization
Or
Simple
trachelectomy
1a1-1a2
Lymph node
(-)
LVSI(+)
Radical
trachelectomy
(type A)
Conisation or simple
trachelectomy
1b1 ≤2cm
Lymp node
(-)
LVSI(+/-)
Radical
trachelectomy
(typeB)

- İntraoperative permanent cerclage during simple or radical trachelectomy
- caesarean section
- Routine hysterectomy after finishing fertility plans is not necessary

CLINICALLY OCCULT CERVICAL CANCER DIAGNOSED AFTER SIMPLE HYSTERECTOMY

- expert pathology review
- multidisciplinary tumour board.
- optimal imaging; the local and regional (nodal) disease status
- same principles as that of non-occult disease

pT1a1, LVSI ± and pT1a2 LVSI-negative, with clear margins

pT1a1, LVSI ± and pT1a2 LVSI(-), clear margins

- no additional treatment is recommended

pT1a2 LVSI(+) or pT1b1 or pT2a1, clear margins

- potential disease in the parametria and lymph nodes has to be addressed
- Radiotherapy or chemoradiotherapy → avoid further surgery
- In absence of residual tumour on imaging (including suspicious lymph nodes) radiotherapy alone
- In case of residual tumour on imaging chemoradiotherapy is recommended (evidence D)
- Paraaortic lymph node dissection
- Debulking of suspicious pelvic lymph nodes may be considered

- Radical surgery is an option in patients without lymph node involvement on imaging and in the absence of an upfront indication for adjuvant radiotherapy(evidence d)
- Pelvic lymph node dissection : first step of
- Intraoperative assessment of pelvic lymph nodes may be considered.
- Radical parametrectomy; preferably using minimal invasive techniques.

pT1b2 and higher or involved surgical margins or residual tumour including involved lymph node on imaging

- chemoradiotherapy is recommended
- Paraaortic lymph node dissection may be considered
- Debulking of suspicious pelvic lymph nodes may be considered.

MANAGEMENT OF LOCALLY ADVANCED CERVICAL CANCER

Stage T1b2/T2a2 and negative lymph nodes on radiological staging

- Definitive platinum-based chemoradiotherapy and brachytherapy is the preferred treatment (evidence A)
- Paraaortic lymph node dissection

- Radical surgery ; alternative option (without negative risk)
- Type C2
- Neoadjuvant chemotherapy followed by radical surgery is a controversial alternative.

Stage T1b2/T2a2 and involved lymph nodes on radiological staging

- Definitive chemoradiotherapy and brachytherapy
- An additional radiation boost to the involved lymph nodes should be applied (evidence c)
- Paraaortic lymph node dissection
- Debulking of suspicious pelvic lymph nodes may be considered.

Stages T2b, T3a/b, T4a

- Definitive platinum based chemoradiotherapy and brachytherapy
- An additional radiation boost to the involved lymph nodes (evidence c)
- Paraaortic lymph node dissection
- Debulking of suspicious pelvic lymph nodes may be considered.
- Pelvic exenteration is an option in selected cases with stage T4N0M0 disease

DISTANT METASTATIC DISEASE AT PRESENTATION

- combination chemotherapy Carboplatin/paclitaxel or cisplatin/paclitaxel in the first line treatment
- Addition of Bevacizumab; with good performance status

- Patients with limited distant metastatic disease , confined to the paraaortic lymph node, definitive extended field chemoradiotherapy including brachytherapy.
- Treatment algorithm may also include surgical debulking of enlarged lymph node and additional chemotherapy (evidence D)
- supraclavicular lymph node as only site of distant disease ; chemoradiotherapy

Recurrent disease

- exclude distant metastases and locoregional tumour extension beyond curative treatment
- The recurrence should be confirmed by histological examination.

Central pelvic recurrence after primary surgery

- Definitive chemoradiotherapy combined with image guided adaptive brachytherapy

Pelvic sidewall recurrence after primary surgery

- Definitive chemoradiotherapy
- Extended pelvic surgery ; does not invade extensively into the pelvic side wall
- intraoperative radiotherapy or brachytherapy; free surgical margins are not achievable

Central pelvic or pelvic sidewall recurrence after radiotherapy or chemoradiotherapy

- Pelvic exenteration is recommended for central pelvic recurrence where there is no involvement of the pelvic side-wall and extra-pelvic nodes.
- Laterally extended endopelvic resection may be considered for a recurrence that extends close to or involves the pelvic side-wall.
- Reirradiation with image guided adaptive brachytherapy(central reccurence). (unfit for or refusing exenteration surgery)

Nodal and oligo-metastatic recurrences

- Localised para-aortic, mediastinal and/or peri-clavicular recurrences above previously irradiated fields may be treated by radical external beam radiotherapy (EBRT) if possible in combination with concomitant chemotherapy.
- The therapeutic effect of nodal resection/debulking is unclear and should if possible always be followed by radiotherapy

- isolated organ metastases; local resection, radiofrequency ablation, interventional brachytherapy or stereotactic ablative radiotherapy

Palliative treatment

- Palliative taxane/ platinum combination chemotherapy with /without bevacizumab is the preferred option
- There is currently no standard second line chemotherapy

- In patients with disseminated disease at presentation, radiotherapy (usually a fractionated course) should be considered for effective palliation.
- Palliative radiotherapy to control bleeding, discharge and pain
- For spinal cord compression neuro-surgical intervention or radiotherapy
- diversion stoma and / or stenting

FOLLOW-UP

- follow-up intervals of 3 to 4 months for the first 2 years, and then 6 to 12 months up to five years are recommended.

- Imaging and laboratory tests; symptoms or findings suspicious for recurrence or morbidity.
- MRI , CT, PET-CT

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

Follow-up after fertility-sparing treatment

- Follow-up intervals should be 3 to 4 months for the first 2 years postoperatively, and then 6 to 12 months up to five years.
- Follow-up should include HPV testing (with or without cytology).
- Colposcopy + HPV testing is an option.
- high-risk HPV testing at 6, 12 and 24 months
  If HPV testing is negative, then every 3-5 years (evidence c)