COLLEGE OF ONCOLOGY

National Clinical Practice Guidelines

Cervical Cancer

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Cervical Cancer Guidelines Expert Panel

Prof. dr. Ignace Vergote
Coordinator, University Hospital Leuven
Field of expertise: gynaecology

Prof. dr. Claire Bourgain
Universitair Ziekenhuis Brussel
Field of expertise: pathology

Prof. dr. Jacques De Grève
Universitair Ziekenhuis Brussel
Field of expertise: medical oncology

Prof. dr. Frédéric Kridelka
Centre Hospitalier Universitaire de Liège
Field of expertise: gynaecology

Prof. dr. Pierre Scalliet
Cliniques Universitaires Saint-Luc
Field of expertise: radiotherapy

Prof. dr. Philippe Simon
ULB Hôpital Erasme Bruxelles
Field of expertise: gynaecology

Prof. dr. Sigrid Stroobants
University Hospital Antwerp
Field of expertise: nuclear medicine

Prof. dr. Peter Van Dam
St Augustinus GZA Antwerp
Field of expertise: gynaecology

Prof. dr. Erik Van Limbergen
University Hospital Leuven
Field of expertise: radiotherapy

Prof. dr. Geert Villeirs
University Hospital Ghent
Field of expertise: radiology

Dr. Yolba Smit
Integraal Kankercentrum Nederland

Dr. Daphne Stemkens
Integraal Kankercentrum Nederland

Dr. Robays Jo
Belgian Health Care Knowledge Centre

Dr. Sabine Stordeur
Belgian Health Care Knowledge Centre

Dr. Joan Vlayen
Belgian Health Care Knowledge Centre

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External reviewers and validators

External Reviewers	Invited professional associations
Dr. Gino Pelgrims [1,2]	Belgian Society of Medical Oncology
Prof. dr. Bart Op de Beeck [2]	Royal Belgian Radiological Society
Prof. dr. Birgit Weynand [1,2]	The Belgian Association of Clinical Cytology
Dr. Koen Traen [1,2] **Dr. Eric De Jonge** [1,2]	Vlaamse Vereniging voor Obstetrie en Gynaecologie
Dr. Bruno Vandermeersch [1] **Dr. Marc Wayembergh** [1,2]	Groupement des Gynécologues Obstétriciens de Langue Français de Belgique
Prof. dr Marc Van Eijkeren [1,2]	Belgische Vereniging voor Radiotherapie-Oncologie - Association Belge de Radiothérapie
Dr. Jean-Christophe Noel [2]	Belgian Society of Pathology
-	Domus Medica
-	Société Scientifique de Médicine Générale

[1] Attended the open meeting. [2] Gave feedback by email.

External Validators	
Dr. Frédéric Goffin	Université de Liège
Dr. Nick Reed	Beatson Oncology Centre, Glasgow
Dr. J. van de rVelden	AMC Amsterdam

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National Guidelines Cervical Cancer

INTRODUCTION

This document provides an overview of the clinical practice guidelines for cervical cancer. They are developed in collaboration with the KCE and the 'Integraal Kankercentrum Nederland' and by a panel of experts (see 'expert panel') comprising clinicians of different specialties and were reviewed by relevant professional associations (see 'external reviewers').

The aim of these guidelines is to assist all care providers involved in the care of patients with cervical cancer.

The guidelines presented cover a broad range of topics: diagnosis, staging, treatment, supportive therapy and follow up. Importantly, the guidelines will not address screening for cervical cancer.

For more in-depth information and the scientific background, we would like to ask the readers to consult the full scientific report at www.kce.fgov.be.

SEARCH FOR EVIDENCE

Sources

The present CPG was developed by adapting (inter)national CPGs to the Belgian context. This approach was recently structured in a formal methodology by the ADAPTE group, an international group of guideline developers and researchers [1]. If necessary, included guidelines were updated with more recent evidence.

To identify published CPGs on cervical cancer, OVID Medline, the National Guideline Clearinghouse and specific websites (Appendix 1) were searched. Both national and international CPGs were searched. A language (English, Dutch, French) and date restriction (2000 – 2010) were used. CPGs without references were excluded, as were CPGs without clear recommendations.

The search for peer-reviewed articles included a search in OVID Medline, EMBASE and the Cochrane Database of Systematic Reviews (see appendix for search strings). As for the CPGs, the search was limited to articles published in English, French and Dutch. For most questions, the search was focused on systematic reviews and randomized controlled trials (RCT). However, when these study designs were unavailable, the search was expanded to observational studies. For diagnostic questions, the search also included diagnostic accuracy studies. In general, systematic reviews not reporting the search strategy and/or the quality appraisal of the included studies were excluded.

All searches were run between December 2010 and May 2011.

Grade of recommendation

A grade of recommendation was assigned to each guideline using the GRADE system (Appendix 2) [2].

EXTERNAL REVIEW

Several professional associations were asked by the College of Oncology to appoint two representatives to act as an external reviewer of the draft guideline (see external reviewers). Not all associations appointed a representative.

External experts received the recommendations 3 weeks prior to the expert meeting. As a preparation of the meeting all invited experts were asked to score each recommendation on a 5-point Likert-scale to indicate their agreement with the recommendation, with a score of '1' indicating 'completely disagree', '2' indicating 'somewhat disagree', '3' indicating 'unsure', '4' indicating 'somewhat agree', and '5' indicating 'completely agree' (the experts were also able to answer 'not applicable' in case they were not familiar with the underlying evidence). In case an expert disagreed with the recommendation (score '1' or '2'), (s)he was asked to provide appropriate evidence. All scores were then anonymized and summarized into a median score, minimum score, maximum score and % of 'agree'-scores (score '4' and '5') to allow a targeted discussion (see appendix 5). The recommendations were then discussed during a face-to-face meeting on September 5th 2011. Based on this discussion a final draft of the recommendations was prepared. In appendix 5, an overview is provided of how the comments of the external experts were taken into account.

EPIDEMIOLOGY

In Belgium, cervical cancer is the 8th most frequent tumour in females (N=643 in 2008), with an age-standardised rate of 8.2/100 000 person years [3]. The mean age at diagnosis is 54 years. In 2008, 186 women died of cervical cancer, translating in an age-standardised rate of 1.8/100 000 person years. In comparison, the age standardised mortality rate in the Netherlands was 1.6/100 000 person years in 2008 (www.ikcnet.nl, accessed on August 2nd 2011).

National 5-year survival data are not yet available for Belgium. For the period 1997-2001, the Flemish Cancer Registry Network reported a 5-year observed survival of 65% and a relative survival of 68% for the Flemish Region [4]. Table 1 provides an overview of the 5-year relative survival in other countries.

Table 1: Cervical cancer 5-year relative survival in selected countries

Country	Period	5-year relative survival
Denmark	1999-2003	64%
Finland	1999-2003	68%
France	1994-1999	66%
Norway	1999-2003	70%
Sweden	1999-2003	66%
The Netherlands	2002-2004	67%
US	2001-2007	69%

TREATMENT OF HIGH-GRADE CIN

Treatment of CIN2/3 [5-12, 14-19]

Conclusions of the literature update

- The pooled progression rate to carcinoma in situ or cancer is estimated to be 20%, but estimations in case series varied widely (from 0% to

53%) [6; very low level of evidence].

- There are indications that delaying treatment of pregnant women with high-grade CIN is safe [6; low level of evidence].
- There are no indications of one clearly superior method of fertility-sparing treatment for CIN2 and 3. There is a need for sufficiently powered studies comparing the therapeutic outcomes of ablative and excisional therapy [7-8; low level of evidence].
- There are indications that cold knife conisation and probably both laser conisation and radical diathermy are associated with an increased risk of subsequent perinatal mortality and other serious pregnancy outcomes, unlike laser ablation and cryotherapy. There are also indications that large loop excision of the transformation zone was associated with obstetric morbidity, but an association with mortality and other serious obstetric outcomes could not be demonstrated but not excluded either [11; low level of evidence].
- There are indications that incomplete excision of CIN exposes women to a substantial risk of high-grade post-treatment disease [10; low level of evidence).
- It is plausible that retinoids are not helpful in the management of CIN [19; moderate level of evidence].

Final recommendations

- Cytological cervical abnormalities are classified into low-grade (LSIL) and high-grade squamous intraepithelial lesions (HSIL). The results of cervical biopsies are reported according to the CIN classification ***(1C)***.
- Women with biopsy-proven high-grade CIN (CIN2, CIN3, CGIN) require treatment, watchful waiting cannot be considered ***(1C)***.
- Treatment of pregnant women with high-grade CIN can be delayed until after the delivery ***(1C)***.
- Ablative and excisional therapies are both recommended treatment options for high-grade CIN ***(1B)***.
- Excisional techniques can be preferred over ablation in the majority of cases because they permit histological evaluation of the transformation zone ***(1C)***.
- The size and shape of the excised specimen should be determined by the colposcopic delineation of the lesion ***(expert opinion)***.
- The risk for adverse obstetric outcomes with excisional therapy should be weighed against a higher risk of recurrence and difficulties in evaluating complete removal of the lesion when applying ablative therapies ***(2B)***. In women requesting fertility conservation, ablation can be considered if the lesion is well-defined on colposcopy, not all 4 quadrants are involved, and if the intervention is therapeutic.
- Ablative therapy can only be considered if a number of additional conditions are fulfilled ***(1C)***:
    - The entire transformation zone must be visible;
    - One or more biopsies should be taken from the area or areas that colposcopically show the most severe change;
    - The result of the biopsy or biopsies should be available prior to the destructive therapy;
    - Cryotherapy should not be offered to women with large lesions, occupying more than 75% of the ectocervix, extending to the vaginal wall or extending more than 2 mm beyond the cryoprobe. This applies also to cold coagulation but not to radical diathermy;
    - There should be no evidence of invasive disease on cytology, colposcopy, or biopsy;
    - The Pap smear should not contain glandular atypical cells;
    - The destructive therapy should be carried out under colposcopic control by an experienced colposcopist;
    - There must be adequate follow-up.

- Women should be informed about the possible adverse obstetric outcomes of excisional therapy ***(1B)***.

Follow-up of CIN2/3 [5,6,13]

Conclusions of the literature update

- There are indications that most persistent/recurrent disease is detected within the first 24 months. However, there is clear evidence that there is a persistent long-term risk of invasive cancer for ten years after treatment based on observational studies [6; moderate level of evidence].
- There is conflicting evidence concerning the added value of colposcopy in addition to cytology for follow up after treatment for CIN [6; very low level of evidence].
- There are indications that HPV testing is more sensitive than cytology in the follow up after treatment, but it tends to be less specific. Implications for management of patients remain unclear [13; low level of evidence].

Final recommendations

- Women treated for high-grade disease can be proposed a follow-up cytology and HPV testing 6 months after the therapeutic intervention. In case of negative results, an additional confirmative cytology can be proposed after 1 year before returning to screening at routine interval ***(1C)***.

DIAGNOSIS AND STAGING OF INVASIVE CERVICAL CANCER

FIGO staging [20,21]

Clinical staging of cervical cancer is based on the FIGO staging system 21. Clinical examination and imaging are used for assessing T, N and M categories. In contrast with the TNM staging, FIGO no longer includes stage 0 (Tis). A comparison between the FIGO and TNM staging systems is provided in Table 2.

Table 2: Comparison between FIGO and TNM staging systems

TNM	Description	FIGO
Tis	In situ	-
T1	Confined to cervix	I
T1a	Diagnosed only by microscopy	IA
T1a1	Stromal invasion: depth ≤ 3 mm, horizontal spread ≤ 7 mm	IA1
T1a2	Stromal invasion: depth > 3 and ≤ 5 mm, horizontal spread ≤ 7 mm	IA2
T1b	Clinically visible or microscopic lesion > T1a2	IB
T1b1	≤ 4 cm	IB1
T1b2	> 4 cm	IB2
T2	Beyond uterus but not pelvic wall or lower third vagina	II
T2a	No parametrial invasion	IIA
T2a1	≤ 4 cm	IIA1

TNM	Description	FIGO
T2a2	> 4 cm	IIA2
T2b	Parametrial invasion	IIB
T3	Lower third vagina/ pelvic wall/ hydronephrosis	III
T3a	Lower third vagina	IIIA
T3b	Pelvic wall/hydronephrosis	IIIB
T4	Mucosa of bladder/rectum; beyond true pelvis	IVA
N1	Regional lymph node metastasis	
M1	Distant metastasis	IVB

Tumour characteristics

Conclusions of tumour characteristics CT [22-26]

- There are indications that CT has a low sensitivity (55%, 9 studies) to detect parametrial invasion [22; low level of evidence].
- Diagnostic accuracy studies indicate diverging sensitivities (9-100%) and specificities (67-100%) for CT to detect tumour invasion of the bladder and the urinary tract [22,24-26; low level of evidence].
- There are indications that CT has a low sensitivity (0-50%) for the detection of invasion of the rectum or the gastrointestinal tract. The reported specificities are moderate to high (85-100%) [22,25,26; low level of evidence].

Conclusions of tumour characteristics MRI [22,26-45]

- It is plausible that MRI has a low sensitivity (~75%) for the detection of parametrial invasion. Its specificity appears to be moderate to high [22,28-37; low level of evidence].
- Diagnostic accuracy studies indicate diverging sensitivities and moderate to high specificities for MRI to detect bladder and rectal invasion [22,26,36,38,39; low level of evidence].
- There are indications that MRI has a low sensitivity (range 0-87%) and a low-moderate specificity (range 72-95%) to detect vaginal invasion, although the results are divergent [32,33,36,40-42; low level of evidence].
- The reported sensitivities of MRI to detect invasion of the os interna are moderate (86%) to high (90%). However, the specificity is consistently high (93-98%) [29,41; low level of evidence].
- One diagnostic accuracy study found a high sensitivity and specificity of MRI to detect invasion of the myometrium [29; low level of evidence].

Lymph mode metastases [22,27,29,32,33,35,36, 46-67]

Conclusions of the literature update

- There are indications that CT and MRI have a low sensitivity but a high specificity to detect lymph node metastases [22,27,29,32,33,51,53; low level of evidence). These findings also specifically apply to pelvic lymph node metastases for CT and MRI [36,36,49,54; low level of evidence], and to para-aortic lymph nodes for MRI (35,49,52; low level of evidence).
- There are indications that PET has a low sensitivity and a high specificity for the detection of lymph node metastases [51; low level of evidence]. These findings also specifically apply to pelvic [49; low level of evidence] and para-aortic lymph node metastases [49,50; low level of evidence]. One diagnostic accuracy study found a low sensitivity and a high specificity for the detection of pelvic lymph nodes that were not

detected by MRI [55; low level of evidence].

- There are indications that PET/CT has a low sensitivity and a high specificity for the detection of lymph node metastases, although the evidence is heterogeneous [53,63,65; low level of evidence]. A low sensitivity and high specificity were specifically found for pelvic [54,59,60,64; low level of evidence] and para-aortic lymph node metastases [50,57,58; low level of evidence]. One diagnostic accuracy study found a low sensitivity and a high specificity for the detection of para-aortic lymph nodes that were not detected by MRI or CT [62; low level of evidence).

Surgical lymph node staging [51,68-77]

Conclusions of the literature update

- The available evidence indicates a moderate sensitivity of sentinel lymph node biopsy for the detection of lymph node metastases, although the results are conflicting [51,68-73; low level of evidence]

Distant metastases [56,58,78,79]

Conclusions of the literature update

- The dedicated literature about imaging techniques to detect distant metastases in patients with cervical cancer is limited.
- One diagnostic accuracy study indicated a low sensitivity but high specificity of CT and MRI for the detection of haematogenous bone metastases [78; low level of evidence].
- There are indications that PET and PET/CT have a high sensitivity and specificity to detect distant metastases [56,58; low level of evidence].
- There are indications that PET and PET/CT have a high sensitivity and specificity to detect bone metastases [56,78; low level of evidence].

Global staging accuracy [36,42,80,81]

Conclusions of the literature update

- There are indications that CT has a low sensitivity and a moderate specificity to detect stage IIB or higher [80; low level of evidence].
- The evidence on the ability of MRI to detect stage IIB or higher indicates a moderate sensitivity and specificity, but is conflicting [36,42,80; low level of evidence].

Tumour markers [82-86]

Conclusions of the literature update

- There are no indications that a high-risk group can be defined for lymph node metastases using a CA-125 determination [82,83; low level of evidence].
- There are no indications that a high-risk group for a tumour size of more than 4 cm can be defined using a SCCA determination [84, low level of evidence].
- There are no indications that a high-risk group for lymph node metastases can be defined using a SCCA determination [83-86; low level of evidence).

Histopathology [20,87-109]

Conclusions of the literature update

- A diagnosis of cervical cancer is made by the histopathological examination of cervical biopsies 20. As a rule, a LEEP/cone biopsy should be submitted entirely for histopathological evaluation.
- Several histological features can be used to stratify women to higher risk or lower risk of metastatic disease, recurrence or death 87, 88. These histological features should be included in the pathology report:
    - Tumour type 89-93: squamous carcinoma, adenocarcinoma or other, according to the WHO classification 94;
    - Tumour size
    - Extent of tumour, e.g. parametrial involvement
    - Depth of invasion: this is to be measured from the base of the epithelium
    - Lymphovascular space invasion
    - Status of resection margins: margin invasion by invasive or in-situ carcinoma should be specified;
    - Status of lymph nodes: the region and number of resected lymph nodes and the number of involved lymph nodes should be mentioned. Importantly, there is no current guidance on how isolated tumour cells (ITC) should be coded. Until further studies become available, patients with ITC should be coded N1 with a comment on how the cells were identified;
    - Tumour grade.
    - In addition, the pathology report should include the procedure (LEEP/cone biopsy, radical trachelectomy, radical hysterectomy, pelvic exenteration) and the tumour site.

Final recommendations on diagnosis and staging of invasive cervical cancer

- All patients with visible, biopsy proven cervical carcinoma should have an MRI scan of at least the pelvis ***(1C)***.
- Contrast-enhanced CT should be considered as an alternative to MRI in patients who have a medical contraindication for MRI ***(1C)***.
- PET/CT is recommended in tumours FIGO stage IB1 with suspicious pelvic lymph nodes and in large tumours FIGO stage IB2 and above ***(1C)***.
- Sentinel lymph node biopsy without lymphadenectomy is not recommended in patients with cervical cancer in routine clinical practice ***(1C)***.
- Tumour markers cannot be used for the diagnosis and staging of cervical cancer. However, they can be used for the monitoring of treatment response. Therefore, a pre-treatment baseline measurement can be considered ***(2C)***.
- Treatment options for patients with invasive cervical cancer should be discussed at the multidisciplinary team meeting ***(1C)***.

TREATMENT OF FIGO STAGE IA CERVICAL CANCER

Conclusions of the literature update [20,110-121]

- The recurrence rate in patients with cervical cancer FIGO stage IA1 treated with primary conization is low and seems to be limited to

patients with positive resection margins [110-114; very low level of evidence].

- Based on the available observational studies and case series, parametrial involvement seems to be very limited in patients with cervical cancer FIGO stage IA2. Lymph node involvement varies between 0% and 9.7%; adenocarcinomas and tumours without LVSI have a low risk of lymph node metastases [110,113,115; very low level of evidence].

Final recommendations

- In patients with cervical cancer FIGO stage IA1 and free margins of the conization specimen, no further treatment is needed ***(1C)***.
- In patients with a preliminary diagnosis of cervical cancer FIGO stage IA1 and positive margins of the conization specimen, repeat conization, total hysterectomy or utero-vaginal brachytherapy are options if the FIGO stage IA1 is confirmed histologically ***(2C)***.
- Based on the available evidence, parametrial involvement seems to be rare in patients with cervical cancer FIGO stage IA2, and hence a simple hysterectomy with systematic lymphadenectomy with the goal of at least 20 nodes is considered to be sufficient ***(2C)***.
- In patients with cervical cancer FIGO stage IA2 who are medically inoperable and without fertility wish, radical external radiotherapy and brachytherapy can be considered ***(2C)***.
- In case the preoperative staging indicates that postoperative treatment will be needed, concomitant cisplatin-based chemoradiotherapy is recommended instead of surgery ***(1C)***.

TREATMENT OF NON-METASTATIC CERVICAL CANCER

Stage IB1 and IIA1

Conclusions of the literature update [20,121-126]

- t is plausible that, compared to adjuvant radiotherapy alone, adjuvant cisplatin-based chemoradiotherapy significantly improves progression-free and overall survival at 3 years in women with early-stage cervical cancer and risk factors for recurrence (positive pelvic lymph nodes and/or positive margins and/or microscopic involvement of the parametrium) who undergo radical hysterectomy and pelvic lymphadenectomy [121; moderate level of evidence] (1B).
- There are indications that adjuvant cisplatin-based chemoradiotherapy is associated with a higher risk of severe adverse events than adjuvant radiotherapy alone [121; moderate level of evidence] (1B).

Final recommendations

- Patients with a clinical stage IA2, IB, or IIA carcinoma of the cervix and risk factors for recurrence (positive pelvic lymph nodes and/or positive margins and/or microscopic involvement of the parametrium) who have undergone radical hysterectomy and pelvic lymphadenectomy should be considered for adjuvant treatment with concurrent platinum-based chemoradiotherapy ***(1B)***.
- In case the preoperative staging indicates that postoperative treatment will be needed, concomitant cisplatin-based chemoradiotherapy is recommended instead of surgery ***(1C)***.

Stage IB2, IIA2, IIB, IIIA, IIIB and IVA

Primary chemoradiotherapy - thermoradiotherapy - brachytherapy [20,118,119,127-139]

Conclusions of the literature update

- It is demonstrated that concomitant platinum-based chemoradiotherapy is associated with an improved progression-free and overall survival compared to adjuvant radiotherapy alone in patients with stage IA-IVA cervical cancer [127,129,130,133; moderate level of evidence].
- It is demonstrated that chemoradiation increases acute haematological and gastrointestinal toxicity compared to radiation alone, requiring to consider the balance of risks and benefits before offering such aggressive treatment [129,131; moderate level of evidence].
- It is plausible that the addition of hyperthermia to radiotherapy improves local tumour control and overall survival in patients with IIB-IVA cervix carcinoma without increasing acute or late toxicity [136,137; moderate level of evidence].
- There are indications of benefits obtained with brachytherapy in terms of tumour control rate and survival in patients having I-III cervical cancer [129; low level of evidence].

Final recommendations

- In patients with cervical cancer FIGO stage IB-IVA considered suitable for radical radiotherapy treatment, concurrent chemoradiotherapy with a platinum-based chemotherapy is recommended, if fit enough ***(1B)***.
- The balance of risks and benefits should be discussed with the patient before offering chemoradiation for treatment of cervical cancer ***(1C)***.
- In patients with cervical cancer FIGO stage IB-IIIB, brachytherapy should be considered as a component of radical radiotherapy or chemoradiotherapy ***(1C)***.

Neoadjuvant treatment [20,140-146]

Conclusion of the literature update

- It is plausible that short cycle, dose-intensive neoadjuvant chemotherapy (NACT) before radiotherapy improves survival, whereas longer, less intensive schedules tended to show a detrimental effect of NACT [142; moderate level of evidence].
- It is plausible that neoadjuvant chemotherapy before surgery improves 5-year overall survival in patients with localised disease (FIGO stage IB-IIA) and in patients with locally advanced disease (FIGO stage IB bulky, IIB-IIIB) [142; moderate level of evidence].
- It is plausible that the following two alternative neoadjuvant strategies improve long-term outcomes [142; moderate level of evidence]: 1) A short cycle, dose intensive course of cisplatin-based chemotherapy prior to radiotherapy. 2) A similar chemotherapy regimen given prior to surgery (with or without radiotherapy).
- Due to important limitations (problem of heterogeneity in comparison 1 and potential confounding factors; small quantity of data available for comparison 2), the NACCCMA meta-analysis is not considered definitive evidence for NACT. At present the gold standard of treatment remains concomitant chemo/radiation [expert opinion].
- Results of EORTC 55994 trial are awaited to reconsider the place of NACT in the management of cervical cancer [expert opinion].

Final recommendations

- Evidence from EORTC 55994 trial is awaited to reconsider the place of NACT followed by surgery compared to concomitant chemoradiotherapy in the management of women with FIGO IB2, IIA>4cm or IIB cervical cancer.
- If NACT prior to surgery is chosen to treat patients with FIGO stage IB2, IIA, or IIB cervical cancer, then short cycle (≤ 14 days) and dose-intensive regimens (cisplatin ≥ 25 mg/m2) are recommended ***(1B)***.

MANAGEMENT OF METASTATIC AND RECURRENT DISEASE

Conclusion of the literature update [20,122,147-152]

- The only potentially curative option for recurrent disease is pelvic exenteration provided relapsed disease is confined to the central pelvis. The selection of operable patients can be optimized with a preoperative whole body PET or PET-CT scan, in addition to MRI and CT having confirmed the recurrent or persistent disease [20; low level of evidence].
- It is plausible that combination therapy improves response rate, progression-free and overall survival in stage IVB metastatic or recurrent cervical cancer compared to monochemotherapy based on cisplatin. Combination therapy induces higher toxicity, although it did not significantly reduce quality of life [149,150,151; moderate level of evidence].
- There are indications that paclitaxel plus cisplatin has superior results in median overall survival and response rate than topotecan plus cisplatin without higher toxicity [149,150; moderate level of evidence).
- Triplet combinations need to be evaluated in large phase III RCTs [expert opinion].

Final recommendations

- All recurrences should be discussed at the multidisciplinary oncological meeting ***(1C)***.
- Patients with a locoregional pelvic recurrence that is limited in size and not invading neighbouring structures, and who did not receive pelvic radiotherapy as part of their initial treatment, can be considered for resection or (chemo)radiotherapy ***(2C)***.
- In patients with recurrent cervical carcinoma confined to the central pelvis after earlier (chemo)radiotherapy, pelvic exenteration can be considered (1C). The selection of operable patients can be optimized with a preoperative whole body PET or PET/CT scan, in addition to MRI and CT having confirmed the recurrent or persistent disease ***(1C)***.
- In patients with cervical cancer FIGO stage IVB or recurrent cervical carcinoma and who are no candidate for curative (chemo)radiotherapy or surgery, palliative chemotherapy should be offered, after discussion of the relative benefits and risks, with either ***(1B)***:
    - cisplatin 50 mg/m2 on day 1 plus paclitaxel 135 mg/m2 every 3 weeks, or
    - cisplatin 50 mg/m2 on day 1 plus topotecan 0.75 mg/m2 on days 1 to 3 every 3 weeks
- Triplet combinations and targeted therapies need to be evaluated in large phase III RCTs ***(1C)***.

FERTILITY-SPARING TREATMENT

Conclusion of the literature update [20,110-114,153-169]

- The recurrence rate in patients with cervical cancer FIGO stage IA1 treated with primary conization seems to be low (range: 0-10%) and might be limited to patients with positive resection margins [110-114; very low level of evidence].
- There is no evidence that women with cervical cancer stage IA1, IA2 or IB1 and a tumour < 2 cm undergoing radical trachelectomy have increased recurrence rates compared with standard therapy (radical hysterectomy), but this cannot be excluded either [20,157-164,166; very low level of evidence].
- There are indications of higher recurrence rates in patients with a tumour size > 2 cm, although the absolute numbers are limited [20,157,159,163,166; very low level of evidence].
- No evidence is available on the differences in outcome between radical vaginal trachelectomy and radical abdominal trachelectomy.

Final recommendations

- In women requesting fertility conservation, radical trachelectomy and pelvic lymph node dissection can be considered, providing the tumour diameter is less than 2 cm ***(1C)***.
- An alternative experimental treatment might be neoadjuvant chemotherapy, pelvic lymph node dissection and conisation ***(2C)***.
- Cold knife conisation or large loop excision of the transformation zone (LLETZ) is adequate treatment for women with IA1 disease where fertility conservation is requested. If LVSI is present PLND needs to be considered ***(2C)***.
- Cold knife conisation or LLETZ combined with pelvic lymph node dissection may be adequate treatment in women with early stage disease and no LVSI (FIGO IA2 and microscopic IB1) requesting fertility conservation ***(2C)***.
- Women requesting fertility conservation should be informed of the potential additional risk of recurrence and of the experimental nature of trachelectomy ***(1C)***.

TREATMENT OF INVASIVE CANCER DURING PREGNANCY

Conclusion of the literature update [20,170]

- There is no evidence to suggest that pregnancy accelerates the natural history of cervical cancer. The prognosis of a pregnant patient with cervical cancer seems to be similar to that of a non-pregnant patient [20; very low level of evidence].
- The evidence seems to be favourable of immediate treatment for patients diagnosed with cervical cancer at or before 16 weeks of gestation, irrespective of stage [20; very low level of evidence].
- If gestational age is less than 20 weeks at diagnosis of advanced cervical cancer (FIGO IB2 or higher), evidence seems to be favourable of immediate delivery and treatment of the disease [20; very low level of evidence].

Final recommendations

- When cervical cancer is diagnosed during the first trimester of a wanted

pregnancy, a conservative approach is proposed to reach the second trimester ***(1C)***.

- Treatment of cervical cancer during the second trimester is determined by the stage ***(1C)***:
  - Stage IA1 disease is treated by a flat cone biopsy;
  - For stage IA2-1B1 less than 2 cm, NACT followed by conservative surgery (e.g. trachelectomy) can be considered in the absence of nodal metastasis;
  - For stage IB1 2-4 cm, lymphadenectomy is mandatory but can be performed after NACT. The potential to preserve the pregnancy depends mainly on the nodal status and the response to NACT;
  - For higher stages fertility-sparing treatment is not recommended.
- During the third trimester, foetal maturity is awaited and a caesarean delivery followed by standard treatment is proposed ***(1C)***.

SEXUAL MORBIDITY AFTER TREATMENT FOR CERVICAL CANCER

Conclusions of the literature update [20,171-177]

- There is limited evidence in favour of psycho-educational interventions to alleviate psychosexual morbidity [20,172; very low level of evidence].
- There is limited evidence in favour of topical oestrogens or benzydamine douches for the alleviation of post-radiotherapy vaginal complications [20,172,173; very low level of evidence].
- There is no evidence supporting the systematic use of vaginal dilation after radiotherapy [173; very low level of evidence].

Final recommendations

- Information about post-treatment female sexual function should be offered to patients by a relevantly trained healthcare professional using a model of care that involves addressing motivational issues and teaching behavioural skills ***(2C)***.
- Patients can be offered support sessions by a designated member of their care team, as soon as possible after treatment ***(2C)***.
- Topical oestrogens can be considered to alleviate post-(chemo)radiotherapy vaginal complications ***(2C)***.
- Vaginal dilation can be considered in patients treated with (chemo)radiotherapy ***(2C)***.

FOLLOW-UP AFTER TREATMENT FOR CERVICAL CANCER

Follow-up after primary treatment

Conclusions of the literature update [20,178,179]

- There are indications that 89-99% of cervical carcinoma recurrences are detected within 5 years after primary treatment [178; low level of evidence].

PET for the detection of (local or distant) cervical carcinoma recurrence

Conclusions of the literature update [49,78,180-183]

- There are indications that PET has a moderate to high sensitivity to detect a cervical carcinoma recurrence, but the evidence is conflicting. The specificity is low [49,180,181,183,; low level of evidence].
- There are indications that PET/CT has a high sensitivity to detect a cervical carcinoma recurrence in asymptomatic and symptomatic patients. The specificity is moderate to high, but the evidence is conflicting [180,181,183; low level of evidence].
- There are indications that PET has a high sensitivity and specificity to detect haematogenous bone metastases in patients with a suspicion of recurrence [78; low level of evidence].

SCCA for the detection of cervical carcinoma recurrence

Conclusions of the literature update [184-187]

- There are indications that SCCA has a low sensitivity but a high specificity for the detection of a cervical carcinoma recurrence [184-187; low level of evidence].
- There are indications that SCCA in combination with a gynaecological exam has a high sensitivity and specificity for the detection of a cervical carcinoma recurrence [184; low level of evidence].

Vaginal smear for the detection of cervical carcinoma recurrence

Conclusions of the literature update [188-189]

- There are indications that post-trachelectomy smears have a high specificity for the detection of a central recurring cervical carcinoma [189; very low level of evidence).

Final recommendations on follow-up after treatment

- A reasonable follow-up strategy involves follow-up visits every three to four months within the first two years, and every six to 12 months from years 3 to 5 ***(2C)***.
- History taking and clinical examination (including speculum exam with bimanual and pelvic/rectal examination) should be carried out during follow up of patients with cervical cancer to detect symptomatic and asymptomatic recurrence ***(1C)***.
- Cervical cytology or vault smears can be considered to detect asymptomatic recurrence of cervical cancer in cases where curative treatment of a central recurrence is an option and not previously treated with radiotherapy ***(2C)***.
- Imaging examinations (CT, MRI, PET, PET/CT) as part of routine follow-up in asymptomatic patients are not recommended ***(1C)***.
- SCCA can be considered during follow-up ***(1C)***.
- MRI of at least the pelvis should be considered initially to assess potential clinical pelvic recurrence in symptomatic patients ***(expert opinion)***.

- A PET/CT should be considered in all patients in whom recurrent or persistent disease has been demonstrated on clinical exam or MRI and in whom salvage therapy is being considered ***(1C)***.

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Appendix 1: Searched guideline websites and websites of oncologic organisations

Alberta Heritage Foundation For Medical Research (AHFMR)	**http://www.ahfmr.ab.ca/**
American Society of Clinical Oncology (ASCO)	**http://www.asco.org/**
American College of Surgeons (ACS)	**http://www.facs.org/cancer/coc/**
Cancer Care Ontario	**http://www.cancercare.on.ca/english/home/**
CMA Infobase	**http://mdm.ca/cpgsnew/cpgs/index.asp**
Guidelines International Network (GIN)	**http://www.g-i-n.net/**
National Comprehensive Cancer Network (NCCN)	**http://www.nccn.org/**
National Cancer Institute	**http://www.cancer.gov/**
Haute Autorité de Santé (HAS)	**http://bfes.has-sante.fr/HTML/indexBFES_HAS.html**
BC Cancer Agency	**http://www.bccancer.bc.ca/default.htm**
Institute for Clinical Systems Improvement (ICSI)	**http://www.icsi.org/index.asp**
National Health and Medical Research Council (NHMRC)	**http://www.nhmrc.gov.au/**
Scottish Intercollegiate Guidelines Network (SIGN)	**http://www.sign.ac.uk/**
New Zealand Guidelines Group (NZGG)	**http://www.nzgg.org.nz/**
Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC)	**http://www.fnclcc.fr/sor/structure/index-sorspecialistes.html**
National Institute for Health and Clinical Excellence (NICE)	**http://www.nice.org.uk/**

Appendix 2: GRADE system

Levels of evidence

Quality level	Definition	Methodological Quality of Supporting Evidence
High (A)	We are very confident that the true effect lies close to that of the estimate of the effect	RCTs without important limitations or overwhelming evidence from observational studies
Moderate (B)	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies
Low (C)	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect	RCTs with very important limitations or observational studies or case series
Very low (C)	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	

Definitions

Grade	Definition
Strong (1)	The desirable effects of an intervention clearly outweigh the undesirable effects, or clearly do not
Weak (2)	The desirable effects of an intervention probably outweigh the undesirable effects, or probably do not