COLLEGE OF ONCOLOGY

National Clinical Practice Guidelines

Cervical Cancer

Version 1.2010

Continue

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Invited professional associations	Reviewers
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* Two experts assigned and feedback received. *** Two experts assigned, but one feedback received.
***One or two experts assigned, but no feedback received. ****No experts assigned

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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 by a panel of experts (see 'expert panel') comprising clinicians of different specialties and were reviewed by relevant professional associations (see 'external reviewers').

The guidelines are based on the best evidence available at the time they are derived (date restriction 2009). The aim of these guidelines is to assist all care providers involved in the care of patients with cervical cancer.

The guidelines presented cover screening, diagnosis, treatment and follow up of cervical cancer.

SEARCH FOR EVIDENCE

Sources

The guidelines are adapted from the guidelines of the Flemish Society for Obstetrics and Gynaecology - Flemish Gynaecological Oncology Group which were revised in September 2008. They are based on existing clinical trials and international guidelines and a broad search on Medline.

Level of evidence

A level of evidence was assigned to each recommendation:

Level A: randomized studies, prospective cohort study

Level B: retrospective cohort study with consistent protocol, case-control studies, extrapolations from level A studies

Level C: case-series or extrapolations from level B studies

Level D: expert opinion

References are always provided for evidence levels A and B and sometimes for evidence level C.

EXTERNAL REVIEW

The guidelines prepared by the expert panel were circulated to the relevant professional associations (see 'external reviewers'). Each association was asked to assign two key persons to discuss the recommendations during an open meeting. As a preparation of the meeting all invited reviewers 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' (it was also possible to answer 'not applicable' in case they were not familiar with the underlying evidence). All scores were then summarized into a mean score and % of 'agree'-scores (score '4' and '5') to allow a targeted discussion. The recommendations were then discussed during a face-to-face meeting on April 21st 2010. Based on this discussion a final draft of the guidelines was prepared, and discussed by the expert panel by email.

CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN)

Epidemiology and aetiology

In Belgium, approximately 1800 new cases of cervical carcinoma in situ were reported in 2004 and almost 1700 in 2005 [1].

The evolution of CIN to invasive carcinoma occurs frequently but not always. 50% of CIN III evolves to invasive cervical cancer within 10 years, and 80% within 30 years. Each CIN may regress spontaneously but mainly the lower grades. When the basal membrane of the epithelial layer is infiltrated by carcinoma, it is considered an invasive cancer.

Risk factors for the development of CIN and cervix carcinoma are:

- Number of sexual partners (of the patient and her partner)
- Sexually transmitted diseases: mainly human papilloma virus (HPV) plays a central role.
- Young age at first sexual contact
- Smoking
- Low social class
- Reduced immunological resistance (transplants, AIDS, ...)
- Oral contraception

The key common factor in the development of CIN and cervical carcinoma is the number of sexual partners and HPV infection. Some HPV types rarely induce (pre-) malignant lesions, while other types (e.g. 16, 18, 31 and 33) are probably responsible for inducing and rapid evolution to CIN.

Screening

- Organized population based regular cytological screening every 3y for women aged 25 to 65 reduces the incidence of and the mortality from cervical cancer ***(evidence level A)*** [2].

Diagnosis and treatment

- Cervical intraepithelial neoplasia is defined as ***(evidence level D)***:
  - LSIL (Low-grade Squamous Intraepithelial Lesions): contains condyloma and CIN I
  - CIN I: low-grade epithelial changes with atypia, loss of maturation and proliferation encompassing the lower third of the epithelium; HPV-induced cell changes
  - HSIL (High-grade Squamous Intraepithelial Lesions): contains CIN II and CIN III
  - CIN II: high-grade epithelial changes with atypia, loss of maturation and proliferation in the lower two thirds of the epithelium.
  - CIN III: high-grade epithelial changes with atypia, loss of maturation and proliferation in the full thickness of the epithelium.
- A colposcopy should be performed in the following cases ***(evidence level D)***:
  - A Pap smear showing dysplasia.
  - A normal Pap smear but with contact bleedings.
  - First follow-up after 6 months of a treated CIN with positive section margins.
  - Every macroscopic suspicious lesion irrespective of the cytology.
  - A biopsy of a clinically suspicious lesion should be taken, even if

the cervical cytology is negative.

- If there is still doubt about the diagnosis after colposcopy and biopsies or discordance between cytology/colposcopy/biopsy, a diagnostic conisation is recommended ***(evidence level B)*** [2].
- Biopsy proven CIN I should not be treated unless persistent for at least 1y in which case ablation or excision can be considered ***(evidence level C)***.
- Excision of the lesion is recommended in case of CIN II and III ***(evidence level C)***.
- There is no indication to perform a hysterectomy unless for other indications as early detection of a recurrence is often more difficult after hysterectomy than after conisation ***(evidence level C)***.

Follow-up

- Cytology with HPV testing should be performed 6 months after excision. Further follow-up will depend on the results. Cytology should later be performed at least every year ***(evidence level C)***.

INVASIVE CERVICAL CANCER

Epidemiology and aetiology

In Belgium, about 20% of gynaecological cancers of the genital tract are cervical cancers. Approximately 600 women in Belgium will develop invasive cervical carcinoma. The average age is 50 years [1].

The frequency in the various countries depends mainly on screening and sexual promiscuity. In some developing countries, cervical carcinoma is the most frequent tumor in women.

Aetiology: see CIN

Five-year survival (FIGO Annual Report 2006)

Stage	Occurrence	5-year survival
I	40%	85%
II	30%	65%
III	25%	40%
IV	5%	10%
Total	100	65%

Diagnosis and staging

- A detailed history should be taken ***(evidence level D)***.
- For the classification of invasive cervical cancer the FIGO-2009 classification is recommended ***(evidence level D)*** (see appendix 1) [3].
- If cervical cancer is proven by biopsy the following examinations should be performed under general anesthesia ***(evidence level D)***:
  - Clinical gynaecological examination by a dedicated gynaecological oncologist and radiation oncologist
  - Biopsy for pathological diagnosis
  - Cystoscopy
  - If rectal invasion is suspected: rectoscopy
- When invasive cervical cancer is confirmed:
  - Biochemical studies ***(evidence level D)***
  - Routine blood count ***(evidence level D)***
  - Tumor markers for squamous cell carcinoma antigen (SCCA) and adenocarcinoma (CA125 is possible) ***(evidence level D)***
  - Chest X ray ***(evidence level D)***
  - Abdominal and pelvic CT ***(evidence level C)***
  - If manifest presence of para-aortic lymph nodes: Chest CT ***(evidence level C)***
  - PET-CT might improve the staging procedure and is recommended in large tumors FIGO IB2 and above ***(evidence level C)***
  - MRI of the pelvis is a valuable addition for investigating the size of the tumour and infiltration on the parametria and is recommended ***(evidence level C)***.
- In cases with FIGO stage IB2, IIA2, IIB, III and IVA without manifest para-aortic lymph nodes on (PET)/CT, a surgical para-aortic lymph node sampling can be considered ***(evidence level C)***.

Treatment

FIGO STAGE Ia1

- In case of free margins of the conisation specimen there is no indication for further surgical or radiotherapeutic treatment ***(evidence level C)***.
- In case of positive margins for invasive cancer of the conisation specimen and with no child wish, a total hysterectomy or utero-vaginal brachytherapy is recommended ***(evidence level C)***.
- In case of positive margins for invasive cancer of the conisation specimen and with a child wish a re-conisation can be considered ***(evidence level C)***.
- Utero-vaginal brachytherapy is an alternative in medically inoperable patients ***(evidence level C)***.

FIGO STAGE Ia2

- In case of Ia2 tumors a radical hysterectomy (type B1 or B2 according the Querleu-Morrow classification) (see appendix 2) with pelvic lymphadenectomy of at least 20 nodes is recommended ***(evidence level A)*** [4,5].
- Radical external radiotherapy and brachytherapy is an alternativie to radical hysterectomy leading to the same survival and is recommended in case of performance status of 3 or higher, or selected patients with an ASA classification score of 3, and all patients with an ASA classification score of 4 ***(evidence level A)*** [6].
- In case the preoperative staging examinations indicate that postoperative treatment will be needed, a treatment with concomitant chemoradiotherapy (weekly 6 courses Cisplatin 40mg/m²) is recommended ***(evidence level A)*** [7].

FIGO STAGE Ib1 AND IIa1

- In case of IB1 and IIA tumors of less than 4cm a radical hysterectomy (type C according the Querleu-Morrow classification, see appendix 2) with pelvic lymphadenectomy of at least 20 nodes is recommended ***(evidence level A)*** [4,5].
- Radical external radiotherapy and brachytherapy is an alternative to radical hysterectomy leading to the same survival and is recommended in case of performance status of 3 or higher, or selected patients with an ASA classification score of 3, and all patients with an ASA classification score of 4 ***(evidence level A)*** [6]
- In case the preoperative staging examinations indicate that postoperative treatment will be needed, a treatment with concomitant chemoradiotherapy (weekly 6 courses Cisplatin 40mg/m²) is recommended ***(evidence level A)*** [7].
- Postoperative (chemo)radiotherapy (weekly 6 courses Cisplatin 40mg/m²) should be considered in the following cases ***(evidence level A)*** [8];
  - Positive margins
  - If more than 1 positive lymph node
  - If the tumor is larger than 4cm
- There is not enough evidence for adjuvant surgery after complete remission following primary chemoradiotherapy ***(evidence level C)***.

FIGO STAGE Ib2 AND IIa2 AND IIb

- In cases with high risk factors (large tumor volume, pathological lymph nodes, unfavourable histology) where postoperative radiotherapy is likely, primary concomitant chemoradiotherapy with pelvic field should be considered ***(evidence level A)*** [6].
- In case of radiotherapy 3D MRI guided brachytherapy is recommended ***(evidence level C)*** [9].
- In cases where preoperative staging shows that postoperative treatment is unlikely (due to favourable tumor volume, no evidence for pathological lymph nodes, favourable performance status/ASA) a radical hysterectomy type C with pelvic lymphadenectomy of at least 20 nodes can be considered ***(evidence level D)***.
- Neoadjuvant platinum based chemotherapy followed by radical surgery can be considered ***(evidence level A)*** [10,11].
- Postoperative (chemo)radiotherapy (weekly 6 courses Cisplatin 40mg/m²) should be considered in the following cases ***(evidence level A)*** [8]:
  - Positive margins
  - If one or more positive lymph nodes
  - If the tumor is larger than 4cm

FIGO STAGE IIIb AND IVa

- In cases with high risk factors (large tumor volume, pathological lymph nodes, unfavorable histology) where postoperative radiotherapy is likely, primary concomitant chemoradiotherapy with pelvic field should be considered ***(evidence level A)*** [5]. In case of radiotherapy 3D MRI guided brachytherapy should be recommended ***(evidence level C)*** [12].
- In case of hydronephrosis with a functional kidney and performance status less than 4, stenting of the ureter prior to radiotherapy should be considered ***(evidence level C)***.
- In case of a vesicovaginal fistual due to tumor infiltration a Bricker ileostomy or continent bladder can be considered ***(evidence level D)***.

FIGO STAGE IVb (based on inguinal or para-aortic lymph nodes only)

- In case of proven metastatic para-aortic lymph nodes, extended radiotherapy field to the para-aortic nodes can be considered ***(evidence level C)***.
- In case of negative (PET)CT and metastatic para-aortic lymph nodes on surgical staging platinum based chemotherapy can be considered prior to the para-aortic radiotherapy ***(evidence level D)*** [13].
- In case of proven inguinal lymph nodes metatasis the radiation field is extended to the inguinal region ***(evidence level C)***.

FIGO STAGE IVb (with distant metastases)

- Platinum based doublet combination chemotherapy (topotecan or paclitaxel) is recommended ***(evidence level C)***.

Follow-up

- Follow-up consultations could be provided every 3 months in the first two years, every 6 months until 5 years after diagnosis, and every year after 5 years ***(evidence level D)***.

- Cytological vaginal or cervical follow-up is recommended in case curative treatment of the recurrent disease is possible ***(evidence level D)***.
- Routine imaging examinations to screen for distant recurrent disease are not recommended ***(evidence level D)***.

Treatment of recurrent disease

- In case of pelvic relapse chemoradiotherapy is recommended if no primary or adjuvant radiotherapy was given ***(evidence level C)***.
- In case of central relapse without distant metastases and following prior radiotherapy, a pelvic exenteration should be considered ***(evidence level C)***.
- In case of distant metastases platinum based doublet combination chemotherapy (topotecan or paclitaxel) is recommended ***(evidence level C)***.
- In case of chemotherapeutic treatment monitoring of the tumor markers (SCC or CA125) can be useful ***(evidence level D)***.

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FIGO Staging 2009 [3]

Stage I: The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded)

Stage Ia : Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion ≤5 mm and largest extension ≥7 mm
- Ia1: Measured stromal invasion of ≤3.0 mm in depth and extension of ≤7.0 mm
- Ia2: Measured stromal invasion of >3.0 mm and not >5.0 mm with an extension of not >7.0 mm

Stage Ib : Clinically visible lesions limited to the cervix uteri or pre-clinical cancers greater than stage IA *
- Ib1 Clinically visible lesion ≤4.0 cm in greatest dimension
- Ib2 Clinically visible lesion >4.0 cm in greatest dimension

Stage II: Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina

Stage IIa : Without parametrial invasion
- IIa1 Clinically visible lesion ≤4.0 cm in greatest dimension
- IIa2 Clinically visible lesion >4 cm in greatest dimension

Stage IIb : With obvious parametrial invasion

Stage III: The tumor extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or non-functioning kidney**

Stage IIIa : Tumor involves lower third of the vagina, with no extension to the pelvic wall

Stage IIIb : Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney

Stage 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

Stage IVa : Spread of the growth to adjacent organs

Stage IVb : Spread to distant organs

* All macroscopically visible lesions—even with superficial invasion—are allotted to stage IB carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.00 mm and a horizontal extension of not >7.00 mm. Depth of invasion should not be >5.00mm taken from the base of the epithelium of the original tissue—superficial or glandular. The depth of invasion should always be reported in mm, even in those cases with "early (minimal) stromal invasion" (~1 mm). The involvement of vascular/lymphatic spaces should not change the stage allotment.

** On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. All cases with hydronephrosis or non-functioning kidney are included, unless they are known to be due to another cause.

Classification of radical hysterectomy [4]

Type		Description
Type A		Extrafascial hysterectomy, in which the position of the ureters is determined by palpation or direct vision (after opening of the ureteral tunnels) without freeing the ureters from their beds. The paracervix is transected medial to the ureter, but lateral to the cervix. The uterosacral and vesicouterine ligaments are not transected at a distance from the uterus. Vaginal resection is generally at a minimum, routinely less than 10 mm, without removal of the vaginal part of the paracervix (paracolpos).
Type B	B1	Partial resection of the uterosacral and vesicouterine ligaments is a standard part of this category. The ureter is unroofed and rolled laterally, permitting transection of the paracervix at the level of the ureteral tunnel. The caudal (posterior, deep) neural component of the paracervix caudal to the deep uterine vein is not resected. At least 10 mm of the vagina from the cervix or tumour is resected
	B2	B1 with additional removal of the lateral paracervical lymph nodes.
Type C	C1	Transection of the uterosacral ligament at the rectum and vesicouterine ligament at the bladder The ureter is mobilised completely. 15–20 mm of vagina from the tumour or cervix and the corresponding paracolpos is resected routinely, depending on vaginal and paracervical extent and on surgeon choice. The sacrouterine ligament is transected after separation of the hypogastric nerves. The nerve is identified systematically and preserved by transection of only the uterine branches of the pelvic plexus. The bladder branches of the pelvic plexus are preserved in the lateral ligament of the bladder (ie, lateral part of bladder pillar). If the caudal part of the paracervix is transected, careful identifi cation of bladder nerves is needed.
	C2	C1 without preservation of autonomic nerves. The paracervix is transected completely, including the part caudal to the deep uterine vein.
Type D	D1	Resection of the entire paracervix at the pelvic sidewall along with the hypogastric vessels, exposing the roots of the sciatic nerve.13 There is total resection of the vessels of the lateral part of the paracervix; these vessels (ie, inferior gluteal, internal pudendal, and obturator vessels) arise from the internal iliac system.
	D2	D1 plus resection of the entire paracervix with the hypogastric vessels and adjacent fascial or muscular structures.

Lymph-node dissection

Four areas or levels are defined according to corresponding arterial anatomy and radicality of the procedure
Level 1: external and internal iliac
Level 2: common iliac (including presacral)
Level 3: aortic infra-mesenteric
Level 4: aortic infrarenal

