COLLEGE OF ONCOLOGY

National Clinical Practice Guidelines

Endometrial Cancer

Version 1.2010

Continue

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Royal Belgian Radiological Society **	Prof. dr. Bart Op de Beeck
The Belgian Association of Clinical Cytology **	Prof. dr. John-Paul Borgers
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Domus Medica ****	-
Société Scientifique de Médicine Générale ****	-

* 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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ENDOMETRIAL CANCER

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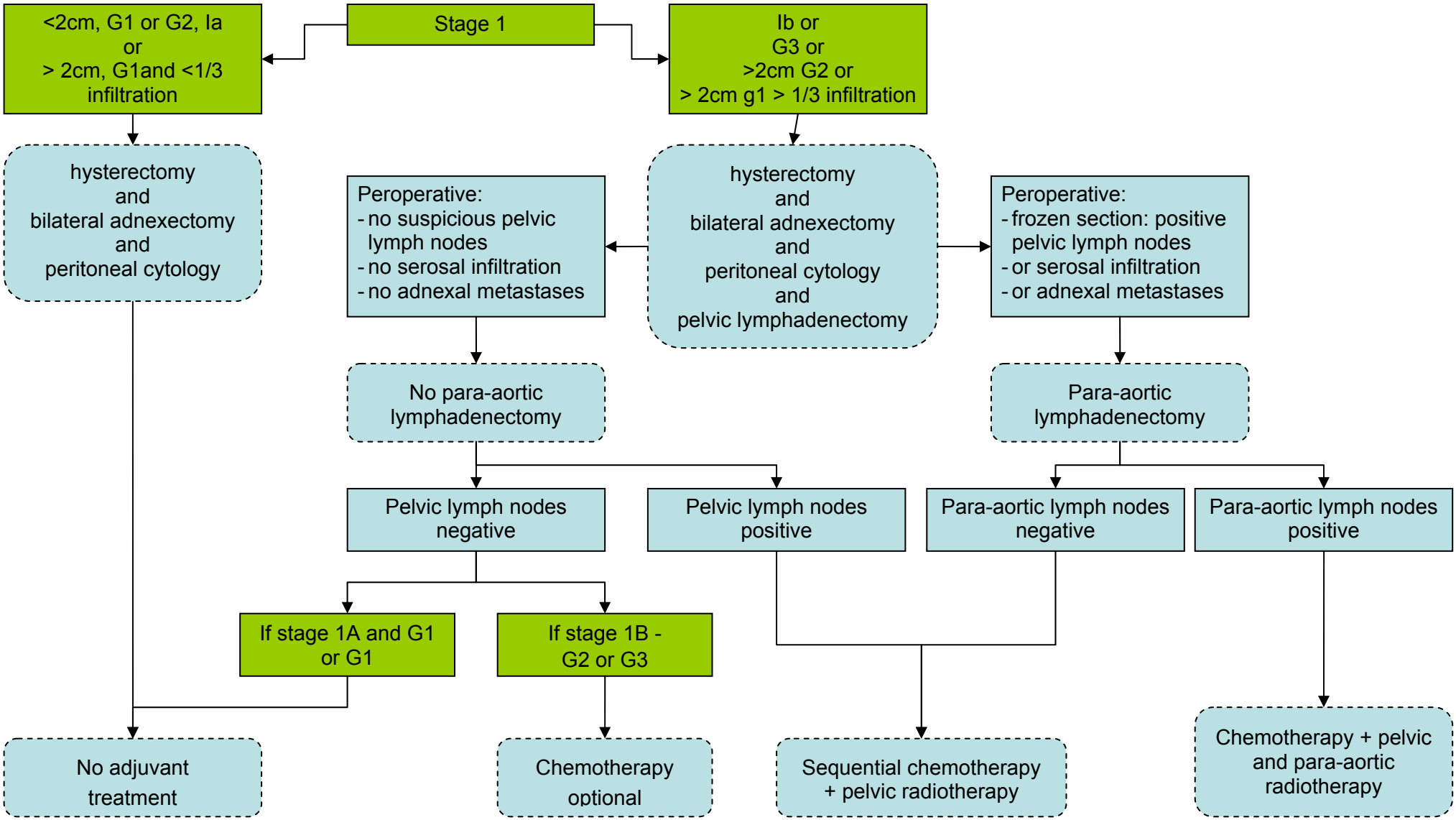

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National Guidelines Endometrial Cancer

INTRODUCTION

This document provides an overview of the clinical practice guidelines for endometrial 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 ovarian cancer.

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

SEARCH FOR EVIDENCE

Sources

The guidelines are adapted from the guidelines of the Flemish Association for Obstetrics and Gynaecology 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.

EPIDEMIOLOGY

In Belgium, approximately 1320 new cases of cancer of the corpus uteri are being recorded yearly [1]. In Flanders endometrial cancer is the third most common cancer in women after breast and colon cancer. The incidence of 24.7 per 100,000 women in Flanders is similar to that in other Western European countries. Approximately 80% of endometrial cancer is of the endometrioïd type. The term 'endometrioïd' refers to endometrium-like glands with varying differentiation.

The non-endometroïde tumors constitute approximately 10% of endometrial cancers and include serous and clear cell carcinoma (see Appendix 1). The serous carcinoma is the most common type of non-endometrioïde endometrial cancer [2,3].

SCREENING

- There is no evidence for routine screening ***(evidence level D)***.
- Patients with family history suggesting high risk for endometrial cancer (Hereditair Non-Polyposis Colorectaal Carcinoma (HNPCC) or familial endometrial cancer) should undergo genetic counseling ***(evidence level C)***.
- MMR (mismatch repair) mutation carriers should be routinely screened with gynaecological ultrasound and cervicovaginal cytology starting at 30 years and yearly thereafter ***(evidence level C)***.
- Hysterectomy and bilateral salpingo-oophorectomy is recommended with proven HNPCC after completion of the child wish and certainly from the age of 40 ***(evidence level C)*** [4].
- Patients receiving tamoxifen have a slightly increased incidence of endometrial cancer but routine screening is not recommended unless there is postmenopausal vaginal bleeding ***(evidence level C)*** [5].

DIAGNOSIS AND STAGING

- A detailed history including family and personal history (menopausal status) should be taken ***(evidence level D)***.
- A complete clinical examination including gynaecological examination should be done ***(evidence level D)***.
- The following pre-operative examinations should be performed:
  - Biochemical studies
    - Preoperative blood test ***(evidence level D)***
    - Serum tumormarkers: cancer antigen 125 (*CA* 125) is recommended ***(evidence level D)***
  - Gynaecological (vaginal) ultrasound is valuable if performed by a physician with experience in this field ***(evidence level C)***.
  - Endometrial biopsy for histological confirmation (Pipelle de Cornier).
  - MRI of the pelvis is an efficient examination, for estimating the extent of the tumor in the uterus and can be recommended if the gynaecological ultrasound provides unsufficient information ***(evidence level B)*** [6,7].
  - Abdominal and pelvic (if no pelvic MRI available) CT ***(evidence level C)***.
  - (Pre-operative) Chest X-ray ***(evidence level D)***.
  - Hysteroscopy is not recommended in patients with clear suspicion of endometrial cancer on gynaecological ultrasound

due to the increased incidence of the presence of malignant cells intraperitoneally after this procedure ***(evidence level C)***.
- In case of suspicion of metastatic para-aortic lymph nodes a thoracic CT or whole body PET/CT is recommended for full staging ***(evidence level C)***.
- Other examinations (e. g. cystoscopy, bone scan, rectoscopy) as clinically indicated ***(evidence level D)***.

- For evaluation of cervical infiltration a fractionated curettage could be performed ***(evidence level D)***.
- For the classification of invasive endometrial cancer the FIGO-2009 classification is recommended ***(evidence level D)*** (see Appendix 2).

TREATMENT OF OPERABLE PATIENS

SURGICAL FIGO-2009 STAGE I ENDOMETRIOID CARCINOMA

- In case a pelvic lymphadenectomy is performed, the removal of at least 6 nodes from each side is recommended ***(evidence level C)***.
- Sentinel node procedure in endometrial cancer remains experimental ***(evidence level C)***.
- Para-aortic lymphadenectomy up to renal vessels should be considered if metastatic pelvic nodes, or metastases to the adnex or growth through the serosa is present ***(evidence level C)*** [8].
- In case of adjuvant pelvic radiotherapy is needed, 3D conformal planning for a total dose of 50 Gy (fraction size of 1.8-2 Gy) is recommended, preferably with belly board in prone position when feasible ***(evidence level C)***.
- Adjuvant chemotherapy can be considered in high-risk cases. In case of chemotherapy the preferred regimen is paclitaxel/carboplatinum ***(evidence level C)*** [9].

SURGICAL FIGO-2009 STAGE II ENDOMETRIOID CARCINOMA

- In young patients with a good performance status a Wertheim-Meigs surgery (radical hysterectomy + bilateral adnexectomy + pelvic with or without para-aortic lymphadenectomy) and peritoneal cytology is recommended ***(evidence level C)***.
- In case of clear margins and N0 status adjuvant radiotherapy is not recommended ***(evidence level D)***.
- In case of adjuvant pelvic radiotherapy, 3D conformal planning for a total dose of 50 Gy (fraction size of 1.8-2 Gy) is recommended, preferably with belly board in prone position when feasible ***(evidence level C)***.
- Adjuvant chemotherapy can be recommended in surgical FIGO 2009 stage II In case of chemotherapy the preferred regimen is paclitaxel/carboplatinum ***(evidence level C)*** [9].

SURGICAL FIGO-2009 STAGE III ENDOMETRIOID CARCINOMA

- In case of IIIA based on serosal or adnexal infiltration adjuvant chemotherapy is recommended ***(evidence level C)***.
- In case of chemotherapy the preferred regimen is paclitaxel/carboplatinum ***(evidence level C)***.
- In case of clinical infiltration of the vagina or parametria, radiotherapy is usually the preferred treatment. In case of surgical stage IIIB on final

pathology after standard surgery, postoperative radiotherapy is recommended. This includes central or whole pelvic radiotherapy or brachytherapy ***(evidence level C)***.

- In case of IIIC and good performance status postoperative sequential chemotherapy and radiotherapy is recommended. In case of C1 pelvic radiotherapy is recommended. In case of C2 pelvic and para-aortic radiotherapy ***(evidence level C)*** [10].
- In case of adjuvant pelvic radiotherapy, 3D conformal planning for a total dose of 50 Gy (fraction size of 1.8-2 Gy) is recommended, preferably with belly board in prone position when feasible ***(evidence level C)***.
- In case of non resected macroscopic pelvic and/or para-aortic lymph nodes, a supplemental dose of 10-16 Gy is recommended ***(evidence level C)***.

TREATMENT OF MEDICALLY INOPERABLE PATIENTS

- In case of intraperitoneal metastases outside the pelvis neoadjuvant chemotherapy can be considered [11]. If no progressive disease after 3 cycles, interval debulking followed by 3 cycles of chemotherapy can be considered ***(evidence level C)***.
- In case of extra-abdominal or parenchymal liver metastasis surgery is not recommended ***(evidence level D)***.
- In case of a hormone receptor negative tumor chemotherapy can be considered ***(evidence level C)***.
- In case of a hormone receptor positive tumor, a progestagen treatment is recommended ***(evidence level C)***. In case of progression after first line hormonal treatment, second line hormonal treatment can be considered ***(evidence level C)***.
- In case of chemotherapy the preferred regimen is paclitaxel/carboplatinum ***(evidence level C)***.
- In case of IA and a tumor less than 2 cm and grade 1 and in case of IA and a tumor less or equal than 2 cm and grade 2, LDR, PDR or HDR brachytherapy to an equivalent dose of 85 GyEQ D2 to the tumor and 60 Gy to the serosal surface is recommended ***(evidence level C)***.
- The preferred imaging technique for brachytherapy is MRI ***(evidence level C)***.
- In stage IB, II and IIIB pelvic radiotherapy with 3D conformal planning for a total dose of 50 Gy (fraction size of 1.8-2 Gy) is recommended, preferably with belly board in prone position when feasible followed by LDR, PDR or HDR brachytherapy to a total equivalent dose of 85 GyEQ D2 to the tumor and 60 Gy to the serosal surface ***(evidence level C)***.
- In women with a uterus of less than 8cm and less than 4cm diameter brachytherapy to a dose of 60 Gy is recommended ***(evidence level C)***.
- In other cases external pelvic radiotherapy (50 Gy) followed by a brachytherapy boost (10 Gy) 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)***.

- Clinical examination and cytological vaginal follow-up is recommended at every follow-up consultation in all cases who can be treated with curative intent at the time of recurrence, e.g. patients who did not receive postoperative radiotherapy or who might be candidates for exenterative surgery ***(evidence level C)***.
- Routine imaging examinations to screen for distant recurrent disease are not recommended ***(evidence level C)***.

TREATMENT OF CARCINOSARCOMA / CLEAR CELL CARCINOMA / SEROUS CARCINOMA

- In case of stage I, II and III a hysterectomy + bilateral salpingoophorectomy + pelvic lymphadenectomy + omentectomy + cytology of peritoneal fluid + peritoneal biopsies are recommended ***(evidence level C)***.
- In case of stage IV neoadjuvant chemotherapy can be considered. If no progressive disease after 3 cycles, interval debulking followed by 3 cycles of chemotherapy can be considered ***(evidence level C)***. A paclitaxel/carboplatinum regimen is recommended.
- In case of stage I and II there is no evidence for adjuvant chemotherapy ***(evidence level C)***.
- In case of metastatic pelvic or para-aortic lymph nodes radiotherapy is recommended ***(evidence level D)***.

TREATMENT OF RECURRENT DISEASE

- In case of a solitary metastases surgical resection and/or radiotherapy should be considered ***(evidence level C)***.
- In case of local recurrence in a previously irradiated region, exenterative surgery can be considered in selected cases. If surgery is not indicated re-radiation can be considered ***(evidence level C)***.
- In case of local recurrence and no previous radiotherapy, radiotherapy/brachytherapy is recommended. Surgery can be considered in selected cases prior to radiotherapy. Surgery following radiotherapy can be considered ***(evidence level C)***.
- In case of distant metastasis and a progesteron receptor positive tumor or if the hormone status is unknown, a progestagen treatment can be considered ***(evidence level C)***. In case of progression after first line hormonal treatment, second line hormonal treatment can be considered ***(evidence level C)***.
- In case of distant metastasis and a hormone receptor negative tumor chemotherapy should be considered ***(evidence level C)***. In case of negative receptors response after hormonal treatment is not excluded but rare.
- A paclitaxel/carboplatinum regimen is recommended. In older patients or important co-morbidities carboplatinum single agent can be considered ***(evidence level C)***.

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Histological subtypes

The histological subtype is an important prognostic factor. Frequency of endometrial cancer cell types is as follows:

1. Endometrioid (75%–80%): The prognosis depends mainly on the staging. In stage 1 the prognosis depends on the depth of the myometrial infiltration , histopathological grading, status of the lymph nodes and age.
    1. Ciliated adenocarcinoma
    2. Secretory adenocarcinoma
    3. Papillary or villoglandular
    4. With squamous differentiation: The prognosis depends on the histopathological grading of the glandular component
2. Uterine papillary serous carcinoma (5-10%): 5-year survival 25%
3. Clear cell (4%): 5-year survival 40%
4. Mucinous (1%)
5. Squamous cell (<1%)
6. Mixed (5-10%)
7. Undifferentiated (very rare)
8. Malignant mixed Müllerian tumor
    1. Low grade malignant: adenosarcoma
    2. High grade malignant: carcinosarcoma

FIGO Staging 2009 (surgical staging)

Stage I: Tumor confined to the corpus uteri
Stage Ia G 123 : no invasion or < ½ of the myometrium
Stage Ib G 123 : invasion of ≥ ½ of the myometrium

Stage II: Tumor invades cervical stroma (but does not extend beyond the uterus). Endocervical epithelial involvement only is classified as stage I.

Stage III: Local and/or regional spread of the tumor
Stage IIIa G 123 : invasion of the serosa and/or adnexes (positive peritoneal cytology has to be reported separately and is in itself not sufficient to be classified as stage III)
Stage IIIb G 123 : Invasion of the vagina or parametria
Stage IIIc G 123 : pelvic and/or para-aortic lymph nodes metastasis
IIIc1: Pelvic lymph nodes metastasis
IIIc2: Para-aortic lymph nodes metastasis

Stage IV: Tumor invades bladder mucosa and/or bowel mucosa, and/or distant metastasis
Stage IVa G 123 : invasion of bladder mucosa and/or bowel mucosa
Stage IVb G 123 : distant metastasis with involvement of intra-abdominal and/or inguinal lymph nodes

G1, 2 of 3 is the histopathological grading

