COLLEGE OF ONCOLOGY

National Clinical Practice Guidelines

Gynaecological Sarcomas

Version 1.2010

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Gynaecological Sarcomas Guidelines Expert Panel

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External reviewers

Invited professional associations	Reviewers
Belgian Society of Medical Oncology *	Dr. Gino Pelgrims Dr. Aldrik Nielander
Royal Belgian Radiological Society **	Prof. dr. Bart Op de Beeck
The Belgian Association of Clinical Cytology **	Prof. dr. John-Paul Borgers
Vlaamse Vereniging voor Obstetrie en Gynaecologie **	Dr. Koen Traen
Groupement des Gynécologues Obstétriciens de Langue Français de Belgique **	Dr. Michel Coibion
Belgische Vereniging voor Radiotherapie-Oncologie - Association Belge de Radiothérapie ***	-
Belgian Society of Pathology ****	-
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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GYNAECOLOGICAL SARCOMAS

National Guidelines Gynaecological Sarcomas

INTRODUCTION

This document provides an overview of the clinical practice guidelines for gynaecological sarcomas. 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

Gynaecological sarcomas are rare. They can occur in all gynaecologic organs (uterus, ovary, cervix, vagina or vulva), however they are most frequent in the uterine body. Main types are leiomyosarcoma and endometrial stromal sarcoma. Rhabdomyosarcoma is extremely rare and is most common in newborns and young girls (vaginal, sometimes cervical). The other sarcomas occur in later life (mean 65 years +).

HISTOLOGY AND PROGNOSTIC FACTORS

Leiomyosarcoma

Diagnosis is based on the mitotic index, atypia and coagulation necrosis. However, all variations are possible and form the basis for a distinction between atypical and mitotic active leiomyomas, smooth muscle cell tumors with unknown malignant potential (STUMP) and leiomyosarcoma.

Major prognostic factors are stage and myometrial invasion depth.

Endometrial stromal sarcoma

The histological picture of the stromal nodule and endometrial stromal sarcoma (ESS), earlier called the low-grade endometrial stromal sarcoma, is similar. They contain spindle-shaped cells with a pleomorphism of the core and mitotic activity in more than 90% of the cases is lower than 3/10 HPF. In more than half of the cases mitosis are absent. In exceptional cases, up to 15 mitosis per 10HPF are described.

The distinction between a nodule and an ESS can only be made on a hysterectomy specimen. An endometrial nodule has a sharp border towards the myometrium while and ESS infiltrates the myometrium and sometimes the surrounding vessels.

Undifferentiated sarcoma

Uterine endometrial undifferentiated sarcomas, often show a pronounced pleomorphism, anaplasia, abnormal mitotic figures, high mitotic activity (> 20/10 HPF) and necrosis.

Five-year survival

The five years survival in uterine leiomyosarcoma and undifferentiated uterine sarcoma is estimated at ±50% in stage I and II and ±10% in stages III-IV. Pure mesenchymal tumors metastasize quickly and hematogenously (frequent in lung and liver). The prognosis is worse if after primary surgery residual tumor is left behind.

DIAGNOSIS AND STAGING

- A detailed history including family and personal history 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)***
    - Abdomino-pelvic and thoracic CT ***(evidence level C)***
    - Gynaecological (vaginal) ultrasound carried out by a physician

with experience in this field ***(evidence level D)***.

- 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 C)*** [1,2].
- In case of a fixed tumor as indicated:
  - Biopsy for pathological diagnosis
  - Cystoscopy
  - Barium enema
  - Rectoscopy or coloscopy

SURGICAL TREATMENT

High grade sarcoma and leiomyosarcoma of the uterus

- A total hysterectomy is the standard of care ***(evidence level C)***. Routine systematic pelvic or para-aortic lymphadenectomy is not indicated.
- In case of young patients the ovaries should not be removed unless needed for complete surgical resection ***(evidence level C)***.
- Extensive debulking surgery is not recommended ***(evidence level C)***.
- In the absence of necrosis and standard smooth muscle differentiation the diagnosis of sarcoma is made in the presence of moderate to severe cellular atypia and a mitotic index of 10 mitoses per 10 HPF (high power field).
- In the absence of necrosis and epitheloid or myxoid differentiation the diagnosis of sarcoma is made in the presence of moderate to severe cellular atypia and a mitotic index of 5 mitoses per 10 HPF.
- In the presence of necrosis there is no minimal number of mitoses to classify a tumor as a sarcoma.

Endometrial stromal sarcoma

- In case of endometrial stromal sarcomas (i.e. low grade endometrial stromal sarcoma) a hysterectomy should be performed. A bilateral salpingo-oophorectomy can be performed ***(evidence level C)***. Resection of metastatic lesions should be considered.

ADJUVANT TREATMENT

High grade sarcoma and leiomyosarcoma

- Adjuvant treatment with chemotherapy is not recommended ***(evidence level C)*** [3].
- Adjuvant pelvic radiotherapy is not recommended ***(evidence level A)*** [4].

Endometrial stromal sarcoma

- In case of endometrial stromal sarcoma adjuvant treatment with 250mg MPA can be considered ***(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)***.
- Routine imaging examinations to screen for distant recurrent disease are not recommended ***(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 D)***.
- Routine imaging examinations to screen for recurrent disease are not recommended ***(evidence level D)***.

TREATMENT OF RECURRENT OR PRIMARILY ADVANCED DISEASE

High grade sarcoma and leiomyosarcoma

- In case of a solitary recurrent disease surgery and/or radiotherapy can be considered ***(evidence level C)***.
- Chemotherapy with adriamycin/epirubicin or ifosfamid in monotherapy or in combination are used in first line. Yondelis or gemcitabin with taxotere is recommended at progression ***(evidence level C)***.

Endometrial stromal sarcoma

- Surgery is recommended ***(evidence level C)***.
- Treatment with progetagens is recommended and should be sustained until progression ***(evidence level C)***.
- In case of progression after respons with progestagens a treatment with tamoxifen or LHRH agonists or aromatase inhibitors can be considered ***(evidence level C)***.
- In case of progression after treatment with tamoxifen or LHRH agonists or aromatase inhibitors, chemotherapy can be considered (chemotherapy for soft tissue sarcomas or in clinical trial) ***(evidence level C)***.

References

1 Kinkel K, Kaji Y, Yu KK, et al. Radiologic staging in patients with endometrial cancer: a meta-analysis. Radiology 1999; 212(3):711-718.

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4 Reed NS, Mangioni C, Malmström H, Scarfone G, Poveda A, Pecorelli S, Tateo S, Franchi M, Jobsen JJ, Coens C, Teodorovic I, Vergote I, Vermorken JB; European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group. Phase III randomised study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I and II: an European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group Study (protocol 55874). Eur J Cancer. 2008; 44(6):808-18

