COLLEGE OF ONCOLOGY

National Clinical Practice Guidelines

Vulvar-Vaginal Cancer

Version 1.2010

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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
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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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VULVAR-VAGINAL CANCER

National Guidelines Vulvar-Vaginal Cancer

INTRODUCTION

This document provides an overview of the clinical practice guidelines for vulvar and vaginal 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 early 2010). The aim of these guidelines is to assist all care providers involved in the care of patients with vulvar cancer.

The guidelines presented cover screening, diagnosis, treatment and follow up of vulvar and vaginal 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

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.

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EPIDEMIOLOGY

In Belgium, 162 new cases of vulvar carcinoma and 45 new cases of vaginal carcinoma were reported in 2006 [1].

Traditionally vulvar pre-invasive and invasive pathology affects postmenopausal women, although younger women can be diagnosed with this condition, often based on HPV infection.

The vulvar intra-epithelial neoplasia (VIN) among young women is related to an HPV infection and is also more common in smokers. In contrast, in older women VIN usually develops in dystrophic lesions (lichen scleroticus and atroficus). Because of these different etiopathogenesis lesions among young women are more frequently multifocal while older women have more frequently a unifocal lesion.

HISTOLOGICAL TYPES AND FIVE-YEAR SURVIVAL

Histological types

Epithelial carcinoma
- Vulvar intra-epithelial neoplasia (VIN)
  - Squamous type with or without koilocytosis
  - Non-squamous type
    - Morbus Paget
    - Melanoma in situ
- Invasive vulvar carcinoma
  - Invasive squamous carcinoma
    - Superficial invasive squamous carcinoma
    - Verrucoid carcinoma
  - Verruceus carcinoma (giant condyloma of Buschke-Löwenstein)
  - Basocellular carcinoma
- Other types
  - Carcinoma of the Bartholin glands
  - Carcinoma of the urethra

Invasive melanoma

Mesenchymal tumors

Five-year survival [2]

Stage	Occurence	5-year survival
I	34%	78%
II	28%	59%
III	26%	43%
IV	8%	11%
Total		59%

VULVAR INTRA-EPITHELIAL NEOPLASIA (VIN)

Diagnosis

- A biopsy of a clinically suspicious lesion should be taken under vulvascopy including the anal region ***(evidence level D)***.
- As CIN is associated with VIN a cervical cytology should be performed ***(evidence level C)***.
- The International Society for the Study of Vulvar Disease (ISSVD)

recommends not to use a grading any more ***(evidence level D)***.

- The histological changes previously encompassed within the term VIN 1 will be described as flat condyloma or HPV effect ***(evidence level D)***.
- VIN, usual type, is related to a human papillomavirus (HPV) high-risk type infection in most of the cases and includes the previously called VIN 2 and VIN 3. The diagnosis is often made in association with a multifocal limited invasive squamous cell carcinoma around the age of 40-45 ***(evidence level D)***.
- The less common type of VIN lesion is termed VIN, differentiated type. This type of VIN is a highly differentiated lesion. The epithelium does not contain koilocytosis because it is not associated with HPV. It is seen primarily in older women, with a previous history of lichen sclerosus. The diagnosis is often made late in association with keratinising squamous cell carcinomas ***(evidence level C)***.

Treatment

- In case of flat condyloma or HPV effect a wait and see attitude is recommended ***(evidence level D)***.
- Excision of the lesion or laser vaporisation is recommended in case of VIN usual type and differentiated type ***(evidence level D)*** [3].
- In case of section margins involved by VIN only a wait and see policy is recommended ***(evidence level D)***.

Follow-up

- Clinical examination and optionally vulvar cytology should be performed every 6 months in the first two years after excision. Further follow-up will depend on the results. Vulvoscopy on indication ***(evidence level D)***.

INVASIVE VULVAR CANCER

Screening

- No evidence for screening ***(evidence level D)***.

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)***
        - Serum tumormarkers: squameus cell cancer antigen (SCCA) can be considered ***(evidence level D)***
    - Vulvoscopy with biopsy for histological confirmation ***(evidence level D)***.
    - Cervical cytology***(evidence level D)***.
    - Abdominal and pelvic CT ***(evidence level D)***.
    - MRI can be considered in advanced cases, for instance anal or urethral invasion ***(evidence level D)***.
    - PET/CT can be considered in case of suspicious inguinofemoral lymph nodes ***(evidence level D)***.
    - (Pre-operative) Chest X-ray ***(evidence level D)***.
    - FNAC or core biopsy in case of suspicious inguinal lymph nodes should be considered ***(evidence level D)***.
    - Other examinations (e. g. cystoscopy, rectoscopy) as clinically indicated ***(evidence level D)***.

- For the classification of invasive vulvar cancer the FIGO-2009 classification is recommended ***(evidence level D)*** (see appendix 1).
- The histopathological report should describe the following:
    - Histological type
    - Grade of differentiation
    - Maximal diameter
    - Depth of the stromal invasion
    - Surgical margins
    - Minimal free resection margin (mm)
    - Lymphovascular involvement
    - Presence associated VIN lesions
    - Number of positive lymph nodes and total number of lymph nodes removed

Treatment of stage I FIGO-2009

- In case of stage Ia a wide local excision (partial vulvectomy) without lymphadenectomy is recommended ***(evidence level C)***. A pathological resection margin of > 8mm should be obtained (clinically 1 to 2 cm) ***(evidence level C)***.
- In case of stage Ib a partial (or hemi) vulvectomy should be performed ***(evidence level C)***. A pathological resection margin of > 8mm should be obtained (clinically 1 to 2 cm) ***(evidence level C)***.
- In case of multifocal lesions a total vulvectomy is recommended ***(evidence level C)***.
- In stage Ib a sentinel procedure of the inguinofemoral lymph nodes is recommended, if the tumor is less than 4 cm and not multifocal. In case of central lesions a bilateral sentinel procedure is needed ***(evidence level A)*** [3].
- In case of positive sentinel a bilateral inguinofemoral lymphadenectomy is needed ***(evidence level B)*** [4].
- For the tumors larger than 4cm or multifocal a complete unilateral or bilateral inguino-femoral lymphadenectomy should be performed. In case of lateral lesions a unilateral lymphadenectomy is recommended. In case of central lesions a bilateral lymphadenectomy is needed ***(evidence level B)*** [3,4].

Treatment of stage II & III FIGO-2009

- Preoperative platinum based chemotherapy or (chemo)radiotherapy can be considered ***(evidence level C)***.
- In case of stage II a total or partial vulvectomy with bilateral inguinofemoral lymphadenectomy should be performed ***(evidence level C)***. A pathological resection margin of > 8mm should be obtained (clinically 1 to 2 cm) ***(evidence level C)***.
- In case of stage III a total or partial vulvectomy with bilateral inguinofemoral lymphadenectomy should be performed ***(evidence level C)***. A pathological resection margin of > 8mm should be obtained (clinically 1 to 2 cm) ***(evidence level C)***.
- In case of anal extension treatment as recommended for stage IV should be performed ***(evidence level C)***.
- Postoperative vulvar radiotherapy (optionally with concomitant platinum based chemotherapy) is considered in the following cases ***(evidence level D)***:
    - Lesions of > 4cm diameter
    - Microscopic resection margin < 8mm
    - Evidence of extensive lymphovascular involvement
- Postoperative radiotherapy (optionally with concomitant chemotherapy) of the inguinofemoral and external iliacal lymph nodes is recommended

in the following cases ***(evidence level D)***:

- Macroscopic metastatic inguinofemoral lymph nodes
- > 2 microscopically affected lymph nodes

Treatment of stage IV FIGO-2009

- Radiotherapy is recommended in case of stage IVA ***(evidence level C)***. Concommitant cisplatin should be considered ***(evidence level D)***.
- Alternatively neoadjuvant chemotherapy followed by surgery or radiotherapy can be considered ***(evidence level C)***.
- According to the response sequential exenterative surgery (response < 75% after 45 Gy) can be considered ***(evidence level C)***. In case of complete response a total dose of 60 Gy is recommended. In case of partial response a total dose of 65 Gy is recommended ***(evidence level D)***.
- Treatment with platinum based chemotherapy (in combination with paclitaxel or gemcitabine) with palliative intent can be considered in case of stage IVB ***(evidence level D)***.

Follow-up

- Follow-up consultations 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 is recommended at every follow-up consultation. Vulvar cytology might be considered ***(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 a solitary metastases surgical resection and/or (platinum based chemo)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 ***(evidence level C)***.
- Treatment with platinum based chemotherapy (in combination with paclitaxel or gemcitabine) with palliative intent can be considered ***(evidence level C)***.

VULVOPERINEAL PAGET'S DISEASE

- Vulvoperineal Paget's disease is a malignant epithelial neoplasm characterized by growth of adenocarcinoma cells within the epidermis of the vulva or perineum
- Paget's disease is often multifocal or extending subepidermal underneath normal looking skin ***(evidence level D)***.
- A biopsy of a clinically suspicious lesion should be taken ***(evidence level D)***.
- A vulvoscopy should be performed ***(evidence level D)***.
- Wide excision or radiotherapy should be performed. Paget's disease is very radiosensitive. Local electron or 4-field photon field including wide margins should be performed ***(evidence level D)***.

VAGINAL INTRAEPITHELIAL NEOPLASIA (VAIN) AND INVASIVE VAGINAL CARCINOMA

Vaginal intraepithelial neoplasia

- VAIN is defined as preinvasive squamous cell carcinoma limited to the vaginal epithelium.
- A biopsy of a clinically suspicious lesion should be taken ***(evidence level D)***.
- 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
    - Follow-up of a treated VAIN
    - Every macroscopic suspicious lesion irrespective of the cytology
- VAIN can be treated with local excision, or ablation or vaporisation. In case of multifocal lesions a local treatment with 5-FU can be considered ***(evidence level C)***.

Invasive vaginal cancer

- Tumors of the upper half of the vagina are treated like cervical carcinoma (see guidelines cervical cancer).
- Tumors of the lower half of the vagina are treated like vulvar carcinoma (see guidelines invasive vulvar cancer).

References

1 Cancer incidence in Belgium, 2004-2005, Belgian Cancer Registry, Brussels 2008.
2 Beller U, Quinn MA, Benedet JL, Creasman WT, Ngan HY, Maisonneuve P, Pecorelli S, Odicino F, Heintz AP. Carcinoma of the vulva. FIGO 6th Annual Report on the Results of Treatment in Gynecological Cancer. Int J Gynaecol Obstet. 2006;95 Suppl 1:S7-27.
3 Van der Zee AG, Oonk MH, De Hullu JA, Ansink AC, Vergote I, Verheijen RH, Maggioni A, Gaarenstroom KN, Baldwin PJ, Van Dorst EB, Van der Velden J, Hermans RH, van der Putten H, Drouin P, Schneider A, Sluiter WJ. Sentinel node dissection is safe in the treatment of early-stage vulvar cancer. J Clin Oncol. 2008;26(6):884-9.
4 Iversen T. New approaches to treatment of squamous cell carcinoma of the vulva. Clin Obstet Gynecol. 1985;28(1):204-10.

FIGO Staging 2009 (surgical staging)

Stage I: **Tumor confined to the vulva or vulva and perineum**
Stage Ia: Tumour ≤ 2cm with stromal invasion of ≤ 1mm
Stage Ib: Tumour > 2cm with stromal invasion of > 1mm

Stage II: **Tumor with extension to adjacent perineal structures: lower third urethra, lower third vagina, anus**

Stage III: **Stage I or II tumour with spread to the lymph nodes**
Stage IIIa: A single lymph node ≥ 5 mm OR 1 or 2 lymph nodes < 5 mm
Stage IIIb: 3 or more lymph nodes < 5 mm OR 2 or more lymph nodes ≥ 5 mm
Stage IIIc: Lymph nodes with extracapsular spread

Stage IV:
Stage IVa: Tumor with extension to the following structures: upper 2/3 urethra, upper 2/3 vagina, bladder mucosa, rectal mucosa, or fixed to pelvic bone OR fixed or ulcerated regional lymph node metastasis
Stage IVb : Distant metastasis (including pelvic lymph node metastasis)

