European Society of Gynaecological Oncology Guidelines for the Management of Patients With Vulvar Cancer

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Objective: The aim of this study was to develop clinically relevant and evidence-based guidelines as part of European Society of Gynaecological Oncology's mission to improve the quality of care for women with gynecologic cancers across Europe.

Methods: The European Society of Gynaecological Oncology Council nominated an international development group made of practicing clinicians who provide care to patients with vulvar cancer and have demonstrated leadership and interest in the management of patients with vulvar cancer (18 experts across Europe). To ensure that the statements are evidence based, the current literature identified from a systematic search has been reviewed and critically appraised. In the absence of any clear scientific evidence, judgment was based on the professional experience and consensus of the development group (*expert agreement*). The guidelines are thus based on the best available evidence and expert agreement. Prior to publication, the guidelines were reviewed by 181 international reviewers including patient representatives independent from the development group.

Results: The guidelines cover diagnosis and referral, preoperative investigations, surgical management (local treatment, groin treatment including sentinel lymph node procedure, reconstructive surgery), radiation therapy, chemoradiation, systemic treatment, treatment of recurrent disease (vulvar recurrence, groin recurrence, distant metastases), and follow-up.

Key Words: Algorithms, Guidelines, Quality indicators, Vulvar cancer

(*Int J Gynecol Cancer* 2017;27: 832–837)

The objectives of the guidelines are to improve and to homogenize the management of patients with vulvar cancer. The guidelines are intended for use by gynecologic oncologists, general gynecologists, surgeons, pathologists, radiotherapists, medical and clinical oncologists, general practitioners, palliative care teams, and allied health professionals. The guidelines cover diagnosis and referral, preoperative investigations, surgical management (local treatment, groin treatment including sentinel lymph node [SLN] procedure, reconstructive surgery), radiation therapy,

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The authors declare no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal's Web site (www.ijgc.net).

ISSN: 1048-891X
DOI: 10.1097/IGC.0000000000000975

chemoradiation, systemic treatment, treatment of recurrent disease (vulvar recurrence, groin recurrence, distant metastases), and follow-up for patients with vulvar cancer and provides information for discussion with patients and carers. This report does not include any economic analysis of the strategies. These guidelines apply to adults older than 18 years with squamous cell carcinoma of the vulva. These guidelines do not address patients with other vulvar cancer histologies.

RESPONSIBILITIES

These guidelines are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. These guidelines make no representations or warranties of any kind whatsoever regarding their content, use, or application and disclaim any responsibility for their application or use in any way.

METHODS

The guidelines were developed using a 5-step process (Fig. 1). The strengths of the process include creation of a multidisciplinary international development group, use of scientific evidence and/or international expert consensus to support the guidelines, and use of an international external review process (physicians and patients). This development process involved 2 meetings of the international development group, chaired by Prof Ate A. G. van der Zee and Dr Maaike H. M. Oonk (University Medical Center Groningen, the Netherlands).

Step 1: Nomination of Multidisciplinary International Development Group

The European Society of Gynaecological Oncology (ESGO) Council nominated practicing clinicians who care for vulvar cancer patients and have demonstrated leadership in clinical management of patients through research, administrative responsibilities, and/or committee membership to serve on the expert panel. The objective was to assemble a multidisciplinary panel. It was therefore essential to include professionals from relevant disciplines (gynecologic oncology, medical oncology, pathology, radiation oncology) so that their perspectives would contribute to the validity and acceptability of the guidelines. The experts of the multidisciplinary international development group were required to complete a declaration of interest form and to promptly inform the ESGO Council if any change in the disclosed information occurred during the course of the project.

Step 2: Identification of Scientific Evidence

To ensure that the statements were evidence based, the current literature was reviewed and critically appraised. A systematic literature review of the studies published between January 1980 and September 2015 was carried out using the MEDLINE database (Appendix 1, http://links.lww.com/IGC/A468). The literature search was limited to publications in English. Priority was given to high-quality systematic reviews, meta-analyses, and randomized controlled trials, but lower levels of evidence were also evaluated. The search strategy excluded editorials, letters, and in vitro studies. The reference list of each identified article was reviewed for other potentially relevant articles. The bibliography was also to be supplemented by additional references provided by the international development group. Another bibliographic search was carried out to identify previous initiatives using a systematic literature search in MEDLINE database (no restriction in the search period) and a bibliographic search using selected evidence-based medicine Web sites (Appendix 2, http://links.lww.com/IGC/A469). After the selection and critical appraisal of the articles (N = 256; Appendix 1), a summary of the scientific evidence was developed.

Step 3: Formulation of Guidelines

The multidisciplinary expert group developed guidelines for diagnosis and referral, preoperative investigations, surgical management (local treatment, groin treatment including SLN procedure, reconstructive surgery), radiation therapy, chemoradiation, systemic treatment, treatment of recurrent disease (vulvar recurrence, groin recurrence, distant metastases), and follow-up. The guidelines were retained if they were supported by sufficient high-level scientific evidence and/or when a large consensus among experts was obtained. By default,

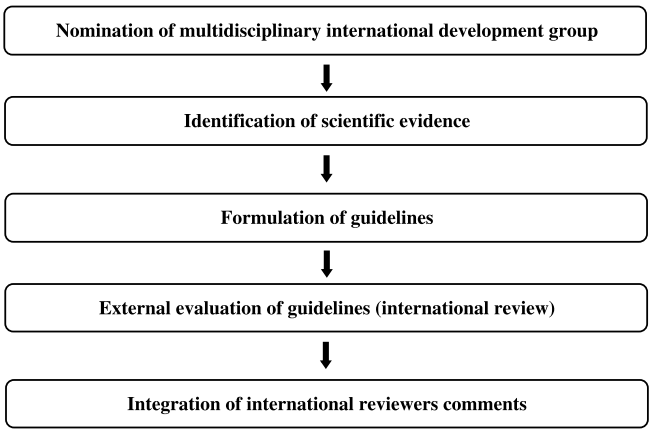

FIGURE 1. Development process.

a guideline was the clinical approach that was unanimously recognized by the development group as being the criterion-standard clinical approach. If an approach was judged to be acceptable but was not unanimously recognized as a criterion-standard clinical approach, indication was given that it was still subject to discussion and/or evaluation. In the absence of any clear scientific evidence, judgment was based on the professional experience and consensus of the development group (*expert agreement*). The reliability and quality of the evidence given throughout this article have been graded following the SIGN grading system (Table 1).

Step 4: External Evaluation of the Guidelines—International Review

The ESGO Council established a large panel of practicing clinicians who provide care to vulvar cancer patients. The objective was to assemble a multidisciplinary panel. The 181 international reviewers were independent from the multidisciplinary expert group. International reviewers were asked to evaluate each guideline according to their relevance and feasibility in clinical practice (only physicians). Quantitative and qualitative evaluations of the guidelines were proposed to be performed. Patients were asked to qualitatively evaluate each guideline (according their experience, preferences, feelings, etc).

TABLE 1. Grades of recommendations

A	At least 1 meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population; or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rates as 2++
D	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+
✓	Recommended best practice based on the clinical experience of the guideline development group

1++, High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias; 1+, well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias; 2++, high-quality systematic reviews of case-control or cohort studies or high-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal; 2+, well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal; 3, nonanalytic studies, for example, case reports, case series; 4, expert opinion.

Step 5: Integration of International Reviewers Comments

Responses of the 181 external reviewers were pooled and discussed by the international development group to finalize the guidelines. The complete report of the guidelines for the management of patients with squamous cell carcinoma of the vulva is available online at the ESGO Web site (https://guidelines.esgo.org/).

GUIDELINES

Diagnosis and Referral

For accurate treatment planning (SLN procedure: yes/no, expected unilateral or bilateral lymph drainage, visibility of scar, etc), the localization of the primary tumor is important. Therefore, excision biopsy should be avoided. In case of multifocal macroinvasive vulvar cancer, the patient is not eligible for SLN detection, and inguinofemoral lymphadenectomy should be performed. Because vulvar cancer is a rare disease and outcome of, for example, the SLN procedure is related to experience of the treating physician, treatment should be centralized in centers with adequate experience in the treatment of this disease.

In any patient suspected of having vulvar cancer, diagnosis should be established by a punch/incision biopsy. Excision biopsy should be avoided for initial diagnosis, because this may obstruct further treatment planning (*expert agreement*). In patients with multiple vulvar lesions, all lesions should be biopsied separately (with clear documentation of mapping) (*expert agreement*). All patients with vulvar cancer should be referred to a gynecologic oncology center and treated by a multidisciplinary gynecologic oncology team (*expert agreement*).

Staging System

The TNM classification[1] and the FIGO staging system[2,3] classify vulvar cancer on the basis of the size of the tumor (T), whether the cancer has spread to lymph nodes (N), and whether it has spread to distant sites (M). By convention, the depth of invasion is defined from the epithelial-stromal junction of the most superficial adjacent dermal papilla to the deepest point of invasion of the tumor.[4] Inguinal and femoral nodes are the initial sites of regional spread, and involvement of pelvic lymph nodes is considered distant metastasis. The FIGO staging system was last reviewed in 2009 by the FIGO Committee on gynecologic oncology[2,3] in close collaboration with the American Joint Commission on Cancer and the Union of International Cancer Control. It should be noted that as part of this revised FIGO staging system the pathologist must report not only the number of nodes with metastatic disease but also the size of the metastases and the presence or absence of extranodal spread. The development group recommends using the TNM classification because it more accurately reflects the status of the primary tumor and lymph nodes.

Vulvar cancer should be staged according to FIGO and/or TNM classification (throughout these recommendations, advanced stage of disease is defined as clinical T3 and/or N3) (*expert agreement*).

Preoperative Investigations

Size and invasion depth of the lesion, distance to the midline, and palpation of the lymph nodes all determine the choice for primary treatment. Involvement of clitoris, anus, and/or urethra often means that these structures will need to be radically excised together with the primary tumor. Such information is important for treatment planning and informing the patient. In case of clitoral/anal/urethral involvement, primary radio(chemo)therapy might be an alternative.

In patients with primary unifocal vulvar cancer less than 4 cm, inguinofemoral lymphadenectomy should be performed immediately instead of SLN procedure if lymph node metastases are diagnosed preoperatively. Computed tomography (CT) or positron emission tomography (PET)/CT can be performed to rule out involvement of pelvic nodes and to decide whether to perform pelvic nodal debulking. Presence of distant metastases should also be evaluated because their presence or absence may influence the radicality of treatment of the primary tumor and the regional lymph nodes.

Preoperative workup should at least include clear documentation of clinical examination (size of lesion, distance to the midline/clitoris/anus/vagina/urethra and palpation of lymph nodes). Picture or clinical drawing is advised (*expert agreement*). Evaluation of the cervix/vagina/anus is recommended (*expert agreement*). Prior to SLN biopsy, clinical examination and imaging of the groins (either by ultrasound, PET/CT, or magnetic resonance imaging) are required to identify potential lymph node metastases (*grade C*). Suspicious nodes (at palpation and/or imaging) should be analyzed by fine-needle aspiration or core biopsy when this would alter primary treatment (*expert agreement*). Further staging with CT thorax/abdomen and pelvis is recommended where there is a clinical suspicion of or proven (nodal) metastatic disease and/or advanced-stage disease (*expert agreement*). The pathology report on preoperative biopsy should at least include histological type and depth of invasion (*expert agreement*).

Surgical Management

Vulvectomy, in addition to radical local excision, can be considered in tumors with extensive premalignant disease to reduce the risk of local recurrence. Data on surgical margins are conflicting. Therefore, the development group advises to consider narrow margins when this means clitoris/anus can be preserved.

Treatment of advanced-stage vulvar cancer often involves multiple treatment modalities. Treatment planning is often individualized in advanced stage and depends on primary tumor characteristics and presence of regional and/or distant metastases. Also, comorbidity and/or frailty of the patient influences treatment planning. Therefore, a multidisciplinary setting is needed to optimize treatment planning.

In case of enlarged groin nodes, either inguinofemoral lymphadenectomy followed by radiotherapy or groin node debulking followed by radiotherapy can be considered. When imaging shows enlarged pelvic nodes, debulking of these nodes is recommended with adjuvant radiotherapy, because radiotherapy alone will probably not sterilize large nodal pelvic disease.

Vulvar squamous cell carcinoma does arise either as consequence of transforming human papillomavirus infection with the precursor lesion vulvar intraepithelial neoplasia (VIN) or independent of human papillomavirus with the precursor lesion differentiated VIN, often in association with lichen planus and lichen sclerosus.[5] However, data are insufficient to recommend separate therapy schemes based on etiology.

For local treatment, radical local excision is recommended (*grade C*). Consider additional, more superficial resection of differentiated VIN in addition to radical local excision of invasive tumors (*expert agreement*). In multifocal invasive disease, radical excision of each lesion as a separate entity may be considered. Vulvectomy may be required in cases with multifocal invasion arising on a background of extensive vulvar dermatosis (*expert agreement*). The goal of excision is to obtain tumor-free pathological margins. Surgical excision margins of at least 1 cm are advised. It is acceptable to consider less wide margins, where the tumor lies close to midline structures (clitoris, urethra, anus) and preservation of their function is desired (*expert agreement*). When invasive disease extends to the pathological excision margins of the primary tumor, re-excision is treatment of choice (*expert agreement*). Patients with advanced-stage disease should be evaluated in a multidisciplinary setting to determine the optimal choice and order of treatment modalities (*expert agreement*).

For groin treatment, it should be performed for tumors greater than pT1a (*grade C*). For unifocal tumors less than 4 cm without suspicious groin nodes on clinical examination and imaging (any modality), the SLN procedure is recommended (*grade B*). For tumors 4 cm or greater and/or in case of multifocal invasive disease, inguinofemoral lymphadenectomy by separate incisions is recommended. In lateral tumors (medial border >1 cm from midline), ipsilateral inguinofemoral lymphadenectomy is recommended. Contralateral inguinofemoral lymphadenectomy may be performed when ipsilateral nodes show metastatic disease (*grade C*). When lymphadenectomy is indicated, superficial and deep femoral nodes should be removed (*grade D*). Preservation of the saphenous vein is recommended (*grade C*). The optimal management of the groin (full inguinofemoral lymphadenectomy or isolated removal only) for enlarged, proven metastatic nodes remains to be defined (*expert agreement*). Where enlarged (>2 cm) pelvic nodes are identified, their removal should be considered (*expert agreement*).

Reconstructive surgery: availability of reconstructive surgical skills as part of the multidisciplinary team is required in early- and advanced-stage disease (*expert agreement*).

SLN Procedure

In tumors involving the midline, absence of bilateral drainage should be considered as a false-negative procedure at the site of no drainage. Multiple sectioning and immunohistochemistry allow more accurate evaluation of the SLN.

The SLN procedure is recommended in patients with unifocal cancers of less than 4 cm, without suspicious groin

nodes (*grade B*). Use of radioactive tracer is mandatory; use of blue dye is optional (*grade B*). Lymphoscintigram is advised to enable the preoperative identification, location, and number of SLNs (*grade C*). Intraoperative evaluation and/or frozen sectioning of the SLN can be performed in an attempt to prevent a second surgical procedure. Caution is warranted because of an increased risk of missing micrometastases on final pathology due to the loss of tissue arising from processing for frozen-section assessment (*grade C*). When an SLN is not found (method failure), inguinofemoral lymphadenectomy should be performed (*expert agreement*). Where metastatic disease is identified in the SLN (any size): inguinofemoral lymphadenectomy in the groin with the metastatic SLN should be performed (*grade C*). For tumors involving the midline, bilateral SLN detection is mandatory. When only unilateral SLN detection is achieved, an inguinofemoral lymphadenectomy in the contralateral groin should be performed (*expert agreement*). Pathological evaluation of SLNs should include serial sectioning at levels of at least every 200 μm. If the hematoxylin-eosin sections are negative, immunohistochemistry should be performed (*grade C*).

Radiation Therapy

When possible without damaging structures such as anus, urethra, and clitoris, re-excision is preferred in case of positive margins in the light of the significant short- as well as long-term morbidity associated with the necessary relatively high dose of radiotherapy to the vulvar skin.

Adjuvant radiotherapy should start as soon as possible, preferably within 6 weeks of surgical treatment (*expert agreement*). When invasive disease extends to the pathological excision margins of the primary tumor, and further surgical excision is not possible, postoperative radiotherapy should be performed (*expert agreement*). In case of close but clear pathological margins, postoperative vulvar radiotherapy may be considered to reduce the frequency of local recurrences. There is no consensus for the threshold of pathological margin distance below which adjuvant radiotherapy should be advised (*expert agreement*). Postoperative radiotherapy to the groin is recommended for cases with more than 1 metastatic lymph node and/or presence of extracapsular lymph node involvement (*grade B*). Adjuvant radiotherapy for metastatic groin nodes should include the ipsilateral groin area and where pelvic nodes are nonsuspicious on imaging the distal part of the iliac nodes with an upper limit at the level of the bifurcation of the common iliac artery (*expert agreement*). Based on evidence from other squamous cell cancers such as cervical, head and neck, and anal cancer, the addition of concomitant, radiosensitizing chemotherapy to adjuvant radiotherapy should be considered (*grade C*).

Chemoradiation

Definitive chemoradiation (with radiation dose escalation) is the treatment of choice in patients with unresectable disease (*grade C*). In advanced-stage disease, neoadjuvant chemoradiation should be considered in order to avoid exenterative surgery (*grade C*). Radiosensitizing chemotherapy, preferably with weekly cisplatin, is recommended (*grade C*).

Systemic Treatment

Data in vulvar cancer are insufficient to recommend a preferred schedule in a palliative setting (*grade D*).

Treatment of Recurrent Disease

Local recurrences should be treated as primary tumors with wide local excision and inguinofemoral lymphadenectomy in case of depth of invasion of more than 1 mm and not previously performed groin dissection. Computed tomography of the thorax/abdomen or PET/CT thorax/abdomen is recommended to examine the presence of additional metastases, which presence may influence treatment planning. Imaging might also be helpful in determining the possibility of surgical resection.

For treatment of vulvar recurrence, radical local excision is recommended (*expert agreement*). For vulvar recurrence with a depth of invasion of more than 1 mm and previous SLN removal only, inguinofemoral lymphadenectomy should be performed (*expert agreement*). The indications for postoperative radiotherapy are comparable to those for the treatment of primary disease (*expert agreement*).

For treatment of groin recurrence, restaging by CT (or PET/CT) of the thorax/abdomen/pelvis is recommended (*expert agreement*). Preferred treatment is radical excision when possible, followed by postoperative radiation in radiotherapy-naive patients (*expert agreement*). Based on evidence from other squamous cell cancers such as cervical and anal cancer, the addition of radiosensitizing chemotherapy to postoperative radiotherapy should be considered (*expert agreement*). Definitive chemoradiation is recommended when surgical treatment is not possible (*expert agreement*).

For treatment of distant metastases, systemic (palliative) therapy may be considered in individual patients (see Systemic Treatment) (*expert agreement*).

Follow-up

There is no evidence for best follow-up schedule. Because local recurrences may occur many years after primary treatment, lifelong follow-up is advised. Because patients with associated VIN or lichen sclerosus/planus have a higher risk of local recurrence, more intensive follow-up may be indicated.

The optimal follow-up schedule for vulvar cancer is undetermined (*expert agreement*). After primary surgical treatment, the following follow-up schedule is suggested:

- first follow-up 6 to 8 weeks postoperatively
- first 2 years every 3 to 4 months
- third and fourth year biannually
- afterward, long-term follow-up, especially in case of predisposing vulvar disease

Follow-up after surgical treatment should include clinical examination of the vulva and groins (despite the well-recognized low sensitivity of palpation to identify groin recurrences, available data do not support routine use of imaging of the groins in follow-up) (*expert agreement*).

After definitive (chemo)radiation, the following follow-up schedule is suggested:

- first follow-up visit 10 to 12 weeks after completion of definitive (chemo)radiation
- first 2 years every 3 to 4 months
- third and fourth year biannually
- afterward, long-term follow-up, especially in case of predisposing vulvar disease

At first follow-up visit 10 to 12 weeks after definitive (chemo)radiation, CT or PET/CT is recommended to document complete remission (*expert agreement*).

ACKNOWLEDGMENTS

The authors thank the Guidelines, Recommendations and Quality Assurance Committee of the ESGO. The authors also thank the 181 international reviewers for their participation (Appendix 3, http://links.lww.com/IGC/A470). The authors also wish to express gratitude to the Institut National du Cancer (INCa, France) for providing the main funding for this work.

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