POCKET GUIDELINES

Based on

ESGO Guidelines for the management of patients with Vulvar cancer
- Update 2023 -

As part of its mission to improve the quality of care for women with gynaecological cancers across Europe, the European Society of Gynaecological Oncology (ESGO) first published in 2017 evidence-based guidelines in order to improve the management of patients with vulvar cancer within a multidisciplinary setting. Given the body of new evidence addressing the management of vulvar cancer, ESGO decided to update these evidence-based guidelines and moreover to cover new topics in order to provide comprehensive guidelines on all relevant issues of diagnosis and treatment in vulvar cancer.

The updated guidelines cover comprehensively diagnosis and referral, staging, pathology, preoperative investigations, surgical management (local treatment, groin treatment, sentinel lymph node procedure, reconstructive surgery), (chemo)radiotherapy, systemic treatment, treatment of recurrent disease (vulvar, inguinal, pelvic and distant recurrences), and follow-up.

The guidelines were developed using a five-step process as defined by the ESGO Guideline Committee:

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Nomination of multidisciplinary international development group</th>
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<tr>
<td>Step 2</td>
<td>Identification of scientific evidence</td>
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<td>Formulation of guidelines</td>
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<td>External evaluation of guidelines (international review)</td>
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<td>Step 5</td>
<td>Integration of international reviewers’ comments</td>
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The objective of these ESGO Guidelines is to improve the quality of care for women with vulvar cancer across Europe and worldwide. They are intended for use by all health professionals who are involved in the management of patients with vulvar cancer, across all allied disciplines.

These guidelines do not include any economic analysis of the strategies. 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.
To ensure that the statements were evidence based, the current literature was reviewed and critically appraised. Systematic literature review of relevant studies published between September 2015 and April 2022 was carried out.

The guidelines were adopted if they were supported by sufficient high level of scientific evidence and/or when a large consensus among experts was obtained. Adapted version of the “Infectious Diseases Society of America-United States Public Health Service Grading System” was used to define the level of evidence and grade of recommendation for each of the recommendations:

**LEVELS OF EVIDENCE**

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well conducted, randomised trials without heterogeneity</td>
</tr>
<tr>
<td>II</td>
<td>Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity</td>
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<tr>
<td>III</td>
<td>Prospective cohort studies</td>
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<tr>
<td>IV</td>
<td>Retrospective cohort studies or case-control studies</td>
</tr>
<tr>
<td>V</td>
<td>Studies without a control group, case reports, and/or expert opinions</td>
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**GRADES OF RECOMMENDATIONS**

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<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>A</td>
<td>Strong evidence for efficacy with a substantial clinical benefit, strongly recommended</td>
</tr>
<tr>
<td>B</td>
<td>Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended</td>
</tr>
<tr>
<td>C</td>
<td>Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs…), optional</td>
</tr>
<tr>
<td>D</td>
<td>Moderate evidence against efficacy or for adverse outcome, generally not recommended</td>
</tr>
<tr>
<td>E</td>
<td>Strong evidence against efficacy or for adverse outcome, never recommended</td>
</tr>
</tbody>
</table>
ESGO would like to thank the international development group for their constant availability, work, and for making possible the development of these guidelines for the management of patients with vulvar cancer (see below). ESGO is also very grateful to the 206 international external reviewers for their participation (list available on the ESGO website).

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General recommendations

Planning of staging investigations and treatment should be made on a multidisciplinary basis (generally at a tumour board meeting) and based on the comprehensive and precise knowledge of prognostic and predictive factors for oncological outcome, side effects, and quality of life.

Patients should be carefully counselled about the suggested diagnostic and treatment plan and potential alternatives, including risks and benefits of all options.

Treatment should be undertaken by a dedicated team of specialists in the diagnosis and management of vulvar cancer.

Enrolment of patients with vulvar cancer in clinical trials is encouraged.

Centralization of care in specialized centres and referral network is encouraged.

Supportive care and psychological support should be offered to all patients with vulvar cancer throughout their pathway.

Diagnosis and referral

Inspection of the vulva is indicated for women with vulvar symptoms.

Clinical drawing and/or photographs are recommended.

In any patient with suspected vulvar cancer, diagnosis should be established by a punch/incision biopsy. Excision biopsy should be avoided for initial diagnosis, as this may hinder further treatment planning.

In patients with multiple vulvar lesions, all lesions should be biopsied separately with clear documentation of mapping.

All patients with vulvar cancer should be referred to a centre specialised in vulvar disease and treated by a multidisciplinary gynaecological oncology team.

Staging

Currently there is limited alignment between the 8th edition of TNM and FIGO 2021 classifications, and lack of evidence to base treatment on the FIGO 2021 staging. Therefore, TNM classification is advised.

Throughout these recommendations, advanced stage of disease is defined as clinical ≥T3 and/or ≥N2.

The method used to determine tumour status (T), lymph node (LN) status (N), and systemic status (M) should be documented.
Pathology

The surgeon should secure the specimen in a way that allows accurate orientation by the pathologist. The anatomical site of a vulvar cancer should be clearly indicated. LN basins and/or sentinel lymph node (SLN) should be sent as separate specimens.

The pathology reports must include:

- Specimen dimensions
- Tumour dimensions
- Histological type (5th edition of the WHO classification 2020)
- Depth of invasion (including at least A, and preferably B method)
- Tumour margin status (distance tolateral and deep resection planes in mm)
- Presence or absence of lymphovascular space invasion (LVSI) and perineural invasion
- Presence or absence of premalignant disease, including presence in resection margins

The origin/designation of all tissue blocks should be recorded (block code). This information should be documented in the pathology report and is particularly important in case of external review.

Immunohistochemistry for p16 (surrogate marker for human papillomavirus (HPV) infection) or molecular testing for HPV is mandatory to correctly classify HPV association. For HPV-independent carcinoma and for differentiated VIN, p53 immunohistochemistry is recommended.

Pathological evaluation of SLN should include at least 3 sections per mm. If the hematoxylin and eosin sections are negative, immunohistochemistry for cytokeratin should be performed.

Preoperative investigations

Pre-operative work-up includes a medical history; general assessment and inventory of co-morbidities; frailty assessment; clinical examination; biopsy of all suspicious areas followed by pathologic review; and imaging as indicated.

Clinical examination should document tumour site (labia majora/minora/Bartholin gland, clitoris, mons pubis, or perineum) and laterality (if relevant); tumour focality; the size of each lesion separately; the closest distance to midline and infiltration of and distance to the urethra/vagina/anus; tumour mobility. Photograph or clinical drawing is recommended.

In advanced stage, bimanual vaginal and rectal examination should be considered.
Palpation of the inguinal LN should be included to assess laterality, site, size, mobility, consistency, skin over the nodes.

Evaluation of cervix/vagina/anus including cytology and HPV test from cervix/vagina are recommended.

For pT1a tumours (tumour ≤2 cm confined to the vulva and/or perineum, with stromal invasion ≤1 mm), no further imaging is required.

In patients considered for SLN procedure, imaging of inguinofemoral LN by ultrasound is recommended.

In all other cases, systemic staging (including pelvic LN and distant organs) by computed tomography (CT) (chest/abdomen/pelvis) or [18F]Fluorodeoxyglucose-positron emission tomography-computed tomography (18-FDG-PET-CT) is recommended.

Suspicious inguinal nodes (on imaging) should be assessed by ultrasound guided fine-needle aspiration or core biopsy if this would alter primary treatment.

If the invasive tumour clinically involves surrounding tissues (≥T2 tumours) or if the finding is equivocal, evaluation of extra-vulvar structures (septa, urethra, bladder, vagina, cervix and anal canal) with magnetic resonance imaging (MRI) is recommended.

In specialized centres with available trained ultrasound examiner, transvaginal/transrectal/perineal ultrasound can be an option in determining local staging.

Use of a structured report and a standardised imaging protocol is recommended.

Equivocal distant metastasis should be biopsied (if possible) to avoid inappropriate treatment.

**Surgical management**

**Local management**

Radical local excision is recommended with the aim to obtain histological tumour-free margins.

Extending primary excision in a superficial fashion to include adjacent differentiated VIN is highly recommended.

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.

The optimal radicality of the excision remains to be defined. It is acceptable and often desirable to limit radicality in order to preserve structure and function (e.g. preservation of midline structures such as clitoris, anus and urethra).

When invasive disease extends to the excision margins of the primary tumour, re-excision is the treatment of choice if feasible.

Advanced stage patients should be evaluated in a multidisciplinary setting to determine the optimal choice and order of treatment modalities.
Groin management

Groin treatment should be performed for tumours >T1a (method of measurement of depth of invasion according to the 8th version of the TNM classification).

Surgical bilateral evaluation should be performed for non-lateralized tumours (medial border <1 cm from midline).

For unifocal tumours <4 cm without suspicious inguinofermal LN on clinical examination and imaging the SLN procedure is recommended.

For tumours ≥4 cm and/or in case of multifocal invasive disease inguinofermal lymphadenectomy by separate incisions is mandatory. In lateralized tumours at least ipsilateral inguinofermal lymphadenectomy should be performed.

Contralateral inguinofermal lymphadenectomy may be performed when ipsilateral lymphadenectomy has demonstrated metastatic disease.

When lymphadenectomy is indicated, superficial and deep femoral nodes should be removed.

Preservation of the saphenous vein is recommended.

The optimal management of the groin for enlarged, proven metastatic nodes (inguinofemoral lymphadenectomy or isolated removal/debulking only) remains to be defined and treatment needs to be individualized.

Reconstructive surgery

Availability of reconstructive surgical skills as part of the multidisciplinary team is required in early as well as advanced stage disease. The type of reconstruction is based on patients/tumour characteristics and experience of the surgical team.
The SLN procedure is recommended in patients with unifocal cancers of <4 cm, >T1a, without suspicious inguinofemoral nodes.

There are insufficient data to confirm the efficacy and safety of the SLN procedure in the case of recurrent disease.

Use of radioactive tracer (Tc99/nanocolloid) is mandatory.

Combination detection techniques with isotope and either blue dye or indocyanine green (ICG) are recommended.

When used as part of combination technique, ICG appears more effective than blue dye in the detection of the SLN although the imaging protocol is still to be defined.

Lymphoscintigraphy is advised to enable the preoperative identification, location and number of SLN.

Intraoperative frozen section is optional balancing the importance of accurate measurement of size of LN metastasis and increased risk of missing micrometastases on final pathology against the impact of a second surgical procedure.

When a SLN is not found (method failure), inguinofemoral lymphadenectomy should be performed.

For tumours involving the midline, bilateral SLN detection is mandatory. When only unilateral SLN detection is achieved, contralateral inguinofemoral lymphadenectomy should be performed.

When tumour cells, both metastases and isolated tumour cells (ITC), are identified in the SLN, additional treatment to the involved inguinofemoral area is indicated.

When macrometastatic (>2 mm) disease is identified in the SLN, inguinofemoral lymphadenectomy of the affected site should be performed.

Inguinofemoral lymphadenectomy can safely be omitted in favour of radiotherapy when micrometastatic disease (≤2 mm) or isolated tumour cells are identified in the metastatic SLN.

For patients undergoing a bilateral SLN procedure, who are found to have unilateral metastasis, the incidence of contralateral metastasis is low and further treatment may be limited to the affected groin.
**Adjuvant radiotherapy/Chemoradiotherapy**

Postoperative radiotherapy to the vulva:

- When invasive disease extends to the pathological excision margins of the primary tumour, and further surgical excision is not feasible, postoperative radiotherapy to the vulva is indicated.
- In case of close but clear pathological margins with extensive LVSI, perineural involvement or LN involvement, postoperative vulvar radiotherapy may be considered on individualized basis to reduce the frequency of local recurrences.

Postoperative radiotherapy to the inguinofemoral region:

- SLN metastasis ≤2 mm and ITC can be treated with postoperative radiotherapy as a safe alternative to inguinofemoral lymphadenectomy with less long-term side effects.
- After inguinofemoral lymphadenectomy:
  - Radiotherapy is recommended for cases with more than 1 metastatic LN and/or extra capsular spread.
  - Concurrent radiosensitising chemotherapy should be considered.

Target volume and dose for adjuvant (chemo)radiotherapy should be defined on individual basis according to tumour and patient characteristics.

Radiotherapy should be started as soon as possible (total time from surgery to completion of radiotherapy preferably less than 104 days). Treatment breaks should be avoided.

Radiotherapy should be performed with intensity modulated radiotherapy techniques.

**Primary chemoradiotherapy**

Primary chemoradiotherapy should be performed in a specialized gynaecological radiotherapy centre.

Primary chemoradiotherapy is the treatment of choice in patients with unresectable disease and should be considered for tumours which would otherwise need exenterative surgery with stoma formation.

Appropriate tumour and LN imaging (MRI and/or 18-FDG-PET-CT) should be performed prior to commencing chemoradiotherapy.

Assessment of response should be performed at 12 weeks following completion of treatment (clinically, imaging and/or biopsy if residual tumour is suspected). In case of residual disease surgery should be considered.

Treatment breaks should be avoided, as a prolonged treatment time of >50 days is associated with higher recurrence rates for primary therapy.
Systemic treatment

Neoadjuvant chemotherapy for locally advanced disease

In selected patients, not eligible/fit for upfront surgery or chemoradiotherapy, neoadjuvant platinum-based combination chemotherapy may be considered after a multidisciplinary assessment.

Systemic treatment for metastatic or recurrent unresectable disease

Platinum-based combination chemotherapy should be considered as first-line treatment for metastatic or recurrent unresectable disease.

Although the best combination partner for platinum is unclear, cisplatin or carboplatin and paclitaxel could be considered the preferred regimen.

Based on cervical cancer data, the addition of pembrolizumab in cases with PD-L1 expression with combined positive score ≥1 and/or bevacizumab to platinum-based chemotherapy may be considered for selected patients in first line, although these drugs do not have specific approval for vulvar cancer.

After progressing to platinum-based first-line chemotherapy, there are no standard treatments. Immune checkpoint inhibitors can be considered as mono-therapy.

Chemotherapy or epidermal growth factor receptor targeting inhibitors may be considered as possible alternatives, taking into account that there is no specific approval for any drug.

Follow-up

The optimal follow-up schedule for vulvar cancer is undetermined.

The follow-up strategy should be individualised in terms of intensity, duration and procedures, taking into account individual risk assessment.

Counselling patients about signs of recurrence and adverse short-term, long-term and late side effects of treatment remains an important part of survivorship care.

After treatment with curative intent, the following follow-up schedule is suggested:

- First follow-up 6-8 weeks after the end of treatment
- First two years every 3-4 months
- Third to fifth year biannual/annual
- Long-term surveillance may be appropriate in individuals with ongoing predisposing vulvar disease or treatment related side effects

Follow-up visits should include, at a minimum, a symptom review and a complete physical examination of the vulva, skin bridge and inguinal LN.

Imaging and laboratory tests should be performed only based on risks of recurrence, symptoms, or findings suggestive of recurrence and/or side effects.
**Treatment of recurrent disease**

**General recommendations**

All patients with a recurrence after primary vulvar cancer should be discussed by a multidisciplinary team and treated at a specialized centre.

Before treatment of recurrent disease, vulvar examination, with biopsies from all suspicious areas is recommended. Evaluation with ultrasound, MRI, and/or CT (or 18-FDG-PET) of the thorax/abdomen/pelvis should be performed. When suspecting nodal or distant recurrence, a biopsy is recommended if feasible.

In case of incurable recurrent disease, early palliative care referral should be offered.

**Treatment of local recurrence**

For treatment of vulvar recurrence, radical local excision is recommended.

Since many vulvar recurrences could be classified as new primary disease, arising from underlying premalignant skin conditions, surgical groin re-staging should be considered in clinically negative inguinofemoral LN.

In case of resection of the tumour with involved margins, re-excision (if feasible) or post-operative radiotherapy is recommended.

In locally advanced disease definitive (chemo)radiotherapy is recommended in radiotherapy-naïve patients. In selected cases, pelvic exenteration can be considered.

**Treatment of inguinofemoral and pelvic LN recurrence**

Preferred treatment of an inguinofemoral nodal recurrence is inguinofemoral lymphadenectomy or debulking of suspicious inguinofemoral LN, followed by (chemo)radiotherapy in radiotherapy-naïve patients.

In case of pelvic LN recurrence with or without inguinofemoral LN recurrence, (chemo)radiotherapy is recommended.

Debulking of enlarged pelvic LN may be considered prior to commencing the treatment.

In previously irradiated women, complete resection and/or stereotactic radiotherapy can be considered for oligometastatic inguinofemoral/pelvic disease.

Systemic therapy may be an option when local therapies are not feasible.

Based on evidence from other squamous cell cancers such as cervical and anal cancer, the addition of radio sensitizing chemotherapy to radiotherapy can be considered.
Treatment of distant recurrence

For treatment of distant metastases, systemic therapy may be considered. Stereotactic radiotherapy or surgery can be considered for oligometastatic disease.

Supportive care

Dedicated supportive services should be available in any specialized centre for vulvar cancer treatment.

Women should be given information about potential consequences of treatment and have multi-disciplinary holistic support available at all stages of care.

Access to specialist psycho-sexual and psychosocial counselling services is required.

Patients should receive information on decreasing risk of lymphoedema following inguinofemoral lymphadenectomy, with access to specialized lymphoedema services if required.

Palliative care

Early palliative care referral is strongly recommended as an important step towards improved symptom control and end-of-life care.

Radiotherapy is indicated for palliation of symptoms related to pelvic disease including bleeding, ulceration, pain and/or systemic disease.

Hypofractionated small volume external beam radiation therapy can be used for treating primary disease in patients not fit for radical treatment or in pre-irradiated, inoperable patients.

Palliative surgery can be considered in selected cases.