

Diagnosis, Therapy and Follow-up Care of Vulvar Cancer and its Precursors. Guideline of the DGGG and DKG (S2k-Level, AWMF Registry Number 015/059, November 2015)

Diagnostik, Therapie und Nachsorge des Vulvakarzinoms und seiner Vorstufen.
Leitlinie der DGGG und DKG (S2k-Level, AWMF-Registernummer 015/059, November 2015)

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Key words

- vulvar cancer
- diagnosis
- therapy
- vulvar intraepithelial neoplasia

Schlüsselwörter

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- Diagnostik
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- VIN



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Abstract

Purpose: This is an official guideline, published and coordinated by the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO, Study Group for Gynecologic Oncology) of the Deutsche Krebsgesellschaft (DKG, German Cancer Society) and the Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG, German Society for Gynecology and Obstetrics). The number of cases with vulvar cancer is on the rise, but because of the former rarity of this condition and the resulting lack of literature with a high level of evidence, in many areas knowledge of the optimal clinical management still lags behind what would be required. This updated guideline aims to disseminate the most recent recommendations, which are much clearer and more individualized, and is intended to create a basis for the assessment and improvement of quality care in hospitals.

Methods: This S2k guideline was drafted by members of the AGO Committee on Vulvar and Vaginal Tumors; it was developed and formally completed in accordance with the structured consensus process of the Association of Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, AWMF).

Recommendations: 1. The incidence of disease must be taken into consideration. 2. The diagnostic pathway, which is determined by the initial findings, must be followed. 3. The clinical and therapeutic management of vulvar cancer must be done on an individual basis and depends on the stage of disease. 4. The indications for sentinel lymph node biopsy must be evaluated very carefully. 5. Follow-up and treatment for recurrence must be adapted to the individual case.

Zusammenfassung

Ziel: Offizielle Leitlinie, publiziert und koordiniert von der Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) in der Deutschen Krebsgesellschaft (DKG) und der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe (DGGG). Vulvakarzinome nehmen an Anzahl stetig zu, während die Kenntnisse über das optimale klinische Management wegen der früheren Seltenheit und dem daraus resultierenden Mangel an Literatur-Evidenz dem Bedarf an vielen Stellen noch hinterherhinken. Dieses Leitlinien-Update soll die aktuell deutlich klareren und individualisierten Behandlungsempfehlungen möglichst weit verbreiten und die Grundlage für eine Qualitätsmessung und Qualitätssteigerung in Kliniken bieten.

Methoden: Die vorliegende S2k-Leitlinie wurde von den Mitgliedern der Kommission Vulva- und Vaginaltumoren der AGO entworfen und in einem methodisch überwachten Konsensusverfahren der Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) strukturiert entwickelt und formal abgeschlossen.

Empfehlungen: 1. Beachtung der Inzidenz. 2. Einhaltung der abgestuften Diagnostik in Abhängigkeit vom Ausgangsstadium. 3. Individualisiertes klinisch-therapeutisches Management der Vulvakarzinome in Abhängigkeit vom Stadium. 4. Ausgewogene Indikationsstellung zur Sentinel-Lymphknoten-Biopsie. 5. Adaptierte Nachsorge und Behandlung im Rezidivfall.

I Information on the Guideline

Guidelines program of the DGGG, OEGGG and SGGG

Information on the guidelines program is available at the end of the guideline.

Citation format

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Guideline documents

The complete long version of this guideline with a summary of the conflicts of interest of all authors, a short version and a PDF slide version for PowerPoint is available in German on the homepage of the AWMF:

<http://www.awmf.org/leitlinien/detail/II/015-059.html>

Numbering

This text is a condensed version which has omitted chapters on more generalized issues. Nevertheless, to make it easier to find the respective passages in the long version, the numbering of chapters and tables and figures in “IV – Guideline” and the numbering of the recommendations and statements corresponds to the numbering used in the long version.

Authors

See **Table 1**.

Abbreviations

AGO	Study Group for Gynecologic Oncology (Arbeitsgemeinschaft Gynäkologische Onkologie)
AWMF	Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften)
CT	computed tomography
DKG	German Cancer Society (Deutsche Krebs Gesellschaft)
DGGG	German Society for Gynecology and Obstetrics (Deutsche Gesellschaft für Gynäkologie und Geburtshilfe)
dVIN	differentiated vulvar intraepithelial neoplasia
EC	expert consensus
FDG	fluorodeoxyglucose
FDG-PET	fluorodeoxyglucose positron emission tomography
Gy	gray
HIV	human immunodeficiency virus
HPV	human papillomavirus
HSIL	high-grade squamous intraepithelial lesion
IMRT	intensity-modulated radiation therapy
ISSVD	International Society for the Study of Vulvo-vaginal Disease
Laser	light amplification by stimulated emission of radiation
LD	max. longitudinal diameter
LN	lymph nodes
LND	lymphadenectomy
L-status	extent of lymphatic vessel infiltration in pTNM staging

LSIL	low-grade squamous intraepithelial lesion
MRI	magnetic resonance imaging
p53	53-kilodalton tumor suppressor protein
PET-CT	positron emission tomography-computed tomography
Pn-status	extent of perineural sheath infiltration in pTNM staging
pTNM	pathologic TNM staging
R1	microscopic evidence of tumor
R2	macroscopic evidence of tumor
RKI	Robert Koch Institute
R-status	extent of residual tumor using the pTNM tumor classification system
TD	max. transverse diameter
TNM	UICC staging system for malignant tumors
UICC	Union internationale contre le cancer
uVIN	classic or usual vulvar intraepithelial neoplasia
VAIN	vaginal intraepithelial neoplasia
VIN	vulvar intraepithelial neoplasia
V-status	invasion of veins in pTNM staging

II Application of the Guideline

Purpose and objectives

The purpose of this guideline is to optimize the management of patients with vulvar cancer by describing and summarizing current medical standards. The recommendations developed and described in this guideline are intended as a basis for quality management in oncology. The quality indicators (listed in both the long and the short version) derived from this guideline can be used for the purpose of scientific quality control and to certify treatment centers. The aim is to maintain and improve the quality of the oncological care available in Germany based on scientifically verified recommendations.

Targeted areas of patient care

The guideline provides information on the characteristics of vulvar cancer and the optimal diagnostic work-up and treatment. It should serve as the basis for a discussion of individual treatment plans by an interdisciplinary board. The clinical information has been incorporated into comments on the most important psychosocial events, the various rehabilitation strategies and the most suitable follow-up care for patients with this neoplasm.

Target audience

This S2k guideline targets all physicians and professionals involved in the outpatient and/or inpatient care of patients with vulvar cancer. This guideline can additionally serve as an important source of information for affected patients and their relatives.

Period of validity

The validity of this guideline was confirmed in December 2015 by the respective committees of the DKG and the DGGG and will remain valid until December 2020. If there should be important changes to the available evidence, then amendments to the guideline can be published prior to its expiry date after a careful review of the new evidence in accordance with the methodology published by the AWMF.

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III Methodology of the Guideline

The methodology used to compile this guideline was based on a stratified classification system. The rules are prescribed by the AWMF rulebook (version 1.0). Guidelines are differentiated into lowest level (S1), intermediate level (S2) and highest level (S3). The lowest level is defined as a collection of recommendations for action compiled by a non-representative group of experts. In 2004 the S2 category was subdivided into 2 sublevels: systematic evidence-based (S2e) and structurally consensus-based (S2k). The highest level (S3) integrates both approaches.

This guideline corresponds to the level: S2k

The text of the clinical guideline was drawn up and the statements/recommendations were developed by the members of the AGO Committee on Vulvar and Vaginal Tumors after a systematic literature search. The text and all statements/recommendations were jointly reviewed by all members of the committee. The accompanying chapters on psychosocial aspects were taken from other (S3) gynecologic oncology guidelines and adapted to take account of the specific issues of vulvar cancer. The highlighted statements and recommendations were agreed upon in a consensus conference after a structured process. The participants in the consensus conference consisted of mandate holders from involved and associated scientific medical societies and professional associations working alongside patients' representatives from various self-help groups. This guideline was confirmed in December 2015 by the Guideline Committee of the DGGG and the DKG. More details on the development and consensus process used for this guideline are available in the long version.

Recommendations

The individual recommendations have been formulated in such a way that they indicate the level of requirement for each recommendation. There are three levels of requirement. The level of requirement depends on the ratio between the benefits and the disadvantages of alternative approaches. The terms "must/must not" indicate a strong recommendation (high level of requirement), "should/should not" indicate a simple recommendation (mid-level requirement), and "can" or "may"/"cannot" or "may not" signify an open recommendation (limited level of requirement). The guidelines are not mandatory; they consist of recommendations compiled by a panel of experts, with different levels of requirement for each recommendation. In every individual clinical case, the physician must examine the relevance and appropriateness of the recommendation; if the recommendation is contraindicated, the physician must make a decision after carefully weighing up the options. This also applies to strong recommendations.

Statements

If statements by specialists are included in this guideline that are not intended as recommendations for action, but rather simply for the purpose of presentation, these are referred to as "statements". For these statements, it is *not* possible to indicate evidence levels.

Consensus strength

As part of a structured consensus agreement process (S2k/S3 level), the eligible participants at the meeting agree on the statements and recommendations that were drawn up. During this process, significant modifications to the wording may occur. Sub-

sequently, the consensus strength is determined based on the number of participants (● Table 2).

Expert consensus

Table 2 Classification of consensus strength.

Symbol	Consensus strength	Agreement in percent
+++	Strong consensus	Agreement of > 95% of the participants
++	Consensus	Agreement of > 75–95% of the participants
+	Majority agreement	Agreement of > 50–75% of the participants
–	No consensus	Agreement of < 50% of the participants

As the name suggests, "expert consensus" refers to consensus decision specifically for recommendations/statements without a prior systematic literature search (S2k) or based on the missing evidence (S2e/S3). The term "expert consensus (EC)" to be used is synonymous with terms from other guidelines such as "good clinical practice (GCP)" or "clinical consensus point (CCP)". The recommendation strength is graded similarly to the aforementioned classification without the use of the symbols and is expressed in purely semantic terms ("must"/"must not" or "should"/"should not" or "may"/"does not need to").

IV Guideline

1 Epidemiology and Risk Factors

1.1 VIN: incidence, tumor staging

Consensus-based statement 1. S1

The incidence of VIN is on the rise. The mean age at diagnosis has decreased significantly (**expert consensus**).

Strength of consensus (++++)

VIN are divided into:

- ▶ undifferentiated (usual type, classic) VIN = uVIN
- ▶ differentiated (differentiated type) VIN = dVIN

The prognosis of untreated VIN varies widely. VIN can persist, disappear again or develop into invasive cancer. One study reported that approximately 10% of cases with VIN (8 out of 88 patients), experienced progression to invasive carcinoma within 1–8 years [1]. Half of these cases had additional risk factors such as pelvic radiation therapy of the lower genital tract or immunosuppression. Spontaneous remission occurred particularly among patients younger than 35 years of age [2].

1.2 Paget's disease of the vulva

Extramammary Paget's disease is rare and accounts for only around 1% of vulvar malignancies. The disease is most common in the 7th decade of life; the mean age at diagnosis is 69 years. Concurrent malignancies are identified in 30% of cases, with breast cancer and urothelial cancer reported to be the most common concurrent tumor types [3–5].

1.3 Invasive carcinoma

Consensus-based statement 1. S2

The incidence of invasive vulvar cancer has increased significantly and stands currently at 5.8/100 000 women/year. The mean age at diagnosis has decreased significantly (**expert consensus**).

Strength of consensus (+++)

Vulvar cancer is the fourth most common cancer of the female genital tract. The number of new cases with vulvar cancer has doubled in the last 10 years [6], meaning that the overall incidence of vulvar cancer is increasing. According to data of the RKI, the incidence of vulvar cancer in Germany in 2010 was 4.6/100 000 women/year with around 3200 new cases annually. The estimated figures for 2014 are an incidence of 5.8/100 000 women/year with 4000 new cases of vulvar cancer in that year (www.rki.de/Krebs/DE/Content/Publikationen/Krebs-in-Deutschland/kid-2013-c51-vulva.pdf). In 2010, the relative 5-year survival rate in Germany for all stages of disease was 71%.

1.4 Risk factors

Keratinizing vulvar cancers are not associated with HPV infection. Degenerative and chronic inflammatory skin diseases are important risk factors for this type of cancer, particularly lichen sclerosus which is associated with a 4–5% lifelong risk of cancer [7]. Non-keratinizing squamous cell carcinoma of the vulva tends to be associated with HPV infection and usually occurs in younger women (mean age at diagnosis is 55 years). Other risk factors include smoking [8–11] and immunosuppression, e.g. after organ transplantation or due to HIV infection.

2 Prevention and Early Detection

2.1 Primary prevention

Consensus-based statement 2. S3

Primary prevention of the subgroup of HPV-associated invasive vulvar cancers and their precursor lesions is possible by avoiding genital infection with HPV (**expert consensus**).

Strength of consensus (+++)

Consensus-based recommendation 2. E1

HPV vaccination should* also be recommended in the context of preventing VIN lesions and vulvar cancer [12] (**expert consensus**).

Strength of consensus (+++ 2 biased)

* Note: used analogously to “should” as defined for the S3 guideline on HPV vaccination

Vaccination with one of the prophylactic HPV vaccines is considered a means of primary prevention, as around 85% of all high-grade VIN lesions (HSIL) and approximately 40% of all vulvar cancers are positive for HPV [13–15]. The two most common forms of HPV associated with VIN are types 16 and 18 while the types most commonly associated with vulvar cancer are types 16 and 33. Based on the currently available data, HPV vaccination should be recommended as it additionally serves to prevent VIN lesions and vulvar cancer (see also “S3 Guideline on the Prevention of HPV-associated Neoplasia through Vaccination”, AWMF registry number 082/002). According to the recommendation of the German Standing Vaccination Committee (STIKO) at the Robert Koch Institute published in August 2014 [16], HPV vaccination is recommended for all young girls aged between 9 and 14 years. All

girls who have not received the vaccination by this age should be vaccinated before they reach the age of 17 years.

2.2 Secondary prevention

Consensus-based recommendation 2. E2

There is no specific screening to detect vulvar cancer and its precursor lesions. Examination of all of the vulva must be an essential part of gynecological cancer screening (**expert consensus**).

Strength of consensus (+++)

3 Structure of Care

Consensus-based recommendation 3. E3

Patients with vulvar cancer should be managed by an interdisciplinary and interprofessional team. This team should consist of a cross-sectoral network of persons from all relevant medical specialties and professions. This is most easily achievable in a certified center (**expert consensus**).

Strength of consensus (++)

Minority vote: The following 3 organizations do not support the last sentence: VulvaKarzinom-Selbsthilfegruppe e.V. [Vulvar Cancer Self-help Group]; Berufsverband der Frauenärzte e.V. (BVF) [Professional Association of German Gynecologists]; Deutsche Röntgengesellschaft e.V. (DRG) [German Radiological Society].

Consensus-based recommendation 3. E4

All cases of vulvar cancer must be presented to and discussed by an interdisciplinary tumor board (**expert consensus**).

Strength of consensus (++)

4 Pathology

4.1 Classification of precancerous lesions

(Table 3)

Consensus-based recommendation 4. E5

The terminology and morphological diagnosis of precancerous vulvar lesions (vulvar intraepithelial neoplasia, VIN) must be based on the nomenclature used in the most current version of the WHO classification (**expert consensus**).

Strength of consensus (+++)

4.3 Paget’s disease of the vulva

Consensus-based recommendation 4. E6

To exclude or detect (micro-)invasion, biopsied specimens should be examined in step sections to obtain a histological verification of Paget’s disease of the vulva (**expert consensus**).

Strength of consensus (+++)

4.4 Morphology of invasive vulvar cancer

Consensus-based statement 4. S4

Micrometastasis is defined as histological evidence of tumor cells in lymph nodes with a diameter of ≥ 0.2 mm but not more than 2 mm (**expert consensus**).

Strength of consensus (+++)

Table 3 Nomenclature for HPV-associated and non-HPV-associated precancerous vulvar lesions [17–24].

Source	Description				
	Condylomatous lesion	Mild dysplasia	Moderate dysplasia	Severe dysplasia, carcinoma in situ	HPV-negative lesions with atypical keratinocytes in the basal cell layer
WHO 2003	VIN 1		VIN 2	VIN 3	VIN 3
ISSVD* 2005	HPV-associated changes		classic VIN, usual type, u-VIN		differentiated VIN, d-VIN
WHO 2014	low-grade squamous intraepithelial lesion LSIL**		high-grade squamous intraepithelial lesion HSIL**		differentiated type vulvar intraepithelial neoplasia (d-VIN)
ISSVD* 2015#	low grade squamous intraepithelial lesion (flat condyloma or HPV effect)		high grade squamous intraepithelial lesion (VIN usual type)		intraepithelial neoplasia, differentiated type

* ISSVD = International Society for the Study of Vulvo-vaginal Disease [22, 23]

** The term VIN is used synonymously in the WHO classification.

Information issued by the ISSVD and sent to members in 2015 by J. Bernstein (Chairman of the 2013–2015 ISSVD Terminology Committee)

<http://issvd.org/wp-content/uploads/2015/09/2015-ISSVD-VIN-terminology-for-the-website-v5.pdf>

4.5 Preparation of tissue samples

4.5.1 Diagnostic biopsies

Consensus-based recommendation 4. E7

Biopsied material which was sampled because of a suspicion of VIN must be examined in step sections (**expert consensus**).

Strength of consensus (+++)

Consensus-based recommendation 4. E8

The information in the findings report must include evidence for VIN, the type of VIN, the presence or absence of any dermatologic disorder, the presence or absence of virus-associated changes, and the presence or absence of invasion (**expert consensus**).

Strength of consensus (+++)

4.5.2 Tissue samples after local (radical) excision, (radical) vulvectomy and lymphadenectomy

Consensus-based recommendation 4. E9

Morphological examination of tissue specimens must be carried out such that all therapeutically and prognostically relevant parameters can be determined. The diagnosis must be based on the most recent relevant WHO classification of tumor types and use the most recent TNM classification for staging (**expert consensus**).

Strength of consensus (+++)

Consensus-based recommendation 4. E10

The pathologist's report on the findings in the vulvar samples and on vulvar cancer must include the following information:

- ▶ histological type according to the WHO classification
- ▶ tumor grade
- ▶ evidence/absence of lymphatic vessel or blood vessel invasion (L-status and V-status)
- ▶ evidence/absence of perineural sheath infiltration (Pn-status)
- ▶ staging (pTNM)
- ▶ maximum depth of invasion and extent of tumor (in mm) for stages pT1a and pT1b
- ▶ 3-dimensional tumor size in cm (from pT1b)
- ▶ metric data on the minimal distance from the cancer or VIN to the vulvar resection margin
- ▶ after resection of the vulvo-vaginal, vulvo-anal area and/or urethra, metric data on the minimal width of the vulvo-vaginal, vulvo-anal or urethral resection margin

- ▶ metric data on the minimal width of the soft tissue resection margin (basal margin)

- ▶ R-classification (UICC), where relevant (**expert consensus**)

Strength of consensus (+++)

Consensus-based recommendation 4. E11

When surgery is indicated for vulvar cancer, every lymph node resected during lymphadenectomy must be submitted for histological examination (**expert consensus**).

Strength of consensus (+++)

Consensus-based recommendation 4. E12

Lymph nodes with diameters of up to 0.3 cm should be completely embedded; larger lymph nodes should be halved along their longitudinal plane and also completely embedded for examination (**expert consensus**).

Strength of consensus (+++)

Consensus-based recommendation 4. E13

The findings report on lymph node preparations must include the following information:

- ▶ the number of lymph nodes with tumor involvement compared to the overall number of resected lymph nodes together with information about the site of resection (which side, bilateral/unilateral, inguinal/pelvic)
- ▶ the absence/presence of extracapsular growth of the lymph node metastasis
- ▶ the presence of isolated tumor cells in the lymph node along with any evidence of lymphatic vessel infiltration into perinodal adipose tissue and/or the lymph node capsule
- ▶ maximum diameter of the metastasis (**expert consensus**)

Strength of consensus (+++)

For more details on information which should be included in the histological reporting of lymph nodes specimens, cf. [25–27].

4.5.3 Sentinel lymph nodes

Consensus-based recommendation 4. E14

Sentinel lymph nodes resected from patients with vulvar cancer must be completely embedded and examined in step sections. In addition, lymph nodes which are morphologically unremarkable on H&E must be examined by immunohistochemistry (so-called ultrastaging) (**expert consensus**).

Strength of consensus (+++)

Table 4 Prognostic factors for vulvar cancer \geq stage pT1b.

Name	Standard factor	Risk/prognostic factor	Relevant for therapy
Tumor stage	yes	yes	yes
Lymph node status	yes	yes	yes
Size of inguinal LN metastasis	yes	yes	yes
Number of inguinal LN positive for metastatic disease	yes	yes	yes
Extracapsular growth of inguinal LN metastasis	yes	yes	yes
Perineural sheath infiltration (Pn-status)	yes	unclear	no
Lymphatic vessel infiltration (L-status)	yes	unclear	no
Invasion of the vein (V-status)	yes	unclear	no
Resection margins (residual tumor status; R-status)	yes	yes	yes
Depth of invasion in mm	yes	yes	no
Grade	yes	unclear	no
3-dimensional tumor size in cm	yes	unclear	no
Ulceration of the cancer	no	no	no
Multifocal carcinoma	yes	unclear	yes (surgery)
Peritumoral VIN	yes	unclear	yes (surgery)
Histological tumor type	yes	yes	yes (LND yes/no)
Evidence of HPV in the cancer	no	unclear	no
Pattern of invasion	no	unclear	no
Extent of metastasis in the affected LN	no	unclear	no
Bilateral inguinal LN metastasis	yes	no	yes
Immunohistochemical ultrastaging of LN for metastasis	no	unclear	unclear
Molecular marker	no	no	no

4.6 Morphologic prognostic factors

Established prognostic factors for vulvar cancer include the tumor stage, the presence of inguinal or pelvic lymph node metastasis [28–37]; the size of regional lymph node metastases, the presence of extracapsular growth and the number of lymph nodes with metastatic disease [30, 31, 35, 36, 38–44]. The individual criteria for tumors \geq stage pT1b are listed in [Table 4](#).

5 Diagnosis

5.1 Medical history

Consensus-based recommendation 5. E15

Early symptoms of vulvar cancer and its precursor lesions are often unspecific or absent. Therapy-resistant symptoms which persist for several weeks must be investigated in a detailed clinical work-up (**expert consensus**).

Strength of consensus (+++)

5.2 Clinical examination

Consensus-based recommendation 5. E16

If symptoms are suspicious for vulvar cancer, the diagnosis must be primarily based on the clinical work-up. The basis of the clinical work-up is careful inspection of the area with additional vulvoscopy and palpation of the area including the inguinal region. Biopsies must be taken if findings are suspicious (**expert consensus**).

Strength of consensus (+++)

The following methods are used to identify precancerous lesions and carcinomas:

- ▶ clinical examination, consisting of inspection and palpation
- ▶ vulvoscopy with the application of acetic acid

5.4 Histological work-up

Consensus-based recommendation 5. E17

All suspicious lesions must be examined histologically (**expert consensus**).

Strength of consensus (+++)

5.5 Cancer staging prior to starting treatment

Consensus-based recommendation 5. E18

If there is evidence of invasion, the following examinations must be done prior to starting treatment:

- ▶ determination of the depth of infiltration
- ▶ gynecological examination of the entire anogenital area
 - ▶ determination of the clinical tumor size (vulvoscopy in preparation for surgery)
 - ▶ determination of tumor location and extent of tumor spread as well as documentation of any extension of the tumor to the urethra, vagina, anus, bones
 - ▶ determination of multicentric status
 - ▶ examination of regional lymphatic pathways (palpation of the inguinal region, imaging depending on tumor stage)

(expert consensus)

Strength of consensus (+++)

Imaging work-up should only be done for tumors with a diameter > 2 cm or where there is infiltration of the urethra, vagina or anus. MRI is the imaging method of choice to assess local tumor extension because of its superior soft tissue contrast; contrast-enhanced CT is used to search for distant metastasis [45, 46]. Published data on the appropriate imaging method to detect inguinal lymph node metastasis in patients with primary vulvar cancer are summarized in [Table 5](#).

5.5.4 Examination of regional lymphatics (Table 5)

Table 5 Imaging method of choice to detect inguinal lymph node metastasis [47–55].

Imaging method	MRI	MRI	MRI	MRI	MRI	CT	FDG-PET	US	US	US
LN size	≥ 10 mm	≥ 10 mm	≥ 8 mm	≥ 5 mm	> 8 mm	> 10 mm		> 8 mm	long axis/ short axis ratio < 2	≥ 4 mm
Location	TD*	TD	TD	TD	TD deep/ femoral	LD#				
Sensitivity	89%	86%	52%	87%	50%	58%	67%	83%	87%	76%
Specificity	91%	82%	89%	81%	100%	75%	95%	90%	69%	91%
Negative predictive value	91%	64%	89%			58%	86%	97%	48%	88%
Positive predictive value	89%	94%	52%			75%	86%	62%	94%	83%
References	Hawnaur	Singh	Bipat	Kataoka	Sohaib	Land	Cohn	Abang Mo- hammed	Land	de Gregorio

* TD = max. transverse diameter, # LD = max. longitudinal diameter

5.6 Diagnostic work-up for advanced tumors

Consensus-based recommendation 5. E19

Imaging and endoscopy should only be used for specific indications (**expert consensus**).

Strength of consensus (+++)

Consensus-based recommendation 5. E20

The search for distant metastasis should only be done in patients with advanced vulvar cancer (FIGO > II) (**expert consensus**).

Strength of consensus (+++)

5.5 Staging

Staging is done in accordance with the FIGO and TNM classification systems. The final diagnosis is based on the findings at surgery and the results of the histopathological examination of surgical specimens (Table 6).

7 Treatment of VIN and Paget's Disease

Consensus-based statement 7. S5

There is no reliable data on the adequate margin of healthy tissue when resecting HSIL, including multifocal HSIL (**expert consensus**).

Strength of consensus (+++)

Consensus-based recommendation 7. E31

HSIL and dVIN lesions must either be resected by histologically complete excision or removed by laser evaporation until tissue margins are healthy. Excision should be used to treat dVIN lesions while laser evaporation is the treatment of choice for HPV-associated HSIL (**expert consensus**).

Strength of consensus (+++)

The use of topical 5% imiquimod represents an 'off-label' use. According to recent data, response rates of up to 50% have been reported for HSIL; however, long-term follow-up data are lacking [58–63].

Table 6 FIGO/TNM classification of vulvar cancer [56, 57].

UICC	FIGO	Tumor spread
	Tis	Carcinoma in situ, vulvar intraepithelial neoplasia (VIN) 3
T1	I	Tumor confined to the vulva or vulva and perineum
T1a	IA	Maximum size of lesion: 2 cm or less, stromal invasion less than 0.1 cm
T1b	IB	Maximum size of lesion: > 2 cm, stromal invasion > 0.1 cm
T2	II	Tumor has infiltrated one of the following adjacent structures: lower third of the urethra, vagina or anus
T3	IVA	Tumor has infiltrated one of the following adjacent structures: upper two thirds of the urethra, vagina, bladder mucosa, rectal mucosa or fixed to bone
N0		No regional lymph node metastasis
N1		Regional lymph node metastasis with the following characteristics:
N1a	IIIA(ii)	1 or 2 lymph node metastases, each smaller than 0.5 cm
N1b	IIIA(i)	1 lymph node metastasis, 0.5 cm or larger
N2		Regional lymph node metastasis with the following characteristics:
N2a	IIIB(ii)	3 or more lymph node metastases, each smaller than 5 mm
N2b	IIIB(i)	2 or more lymph node metastases, 5 mm or larger
N2c	IIIC	Lymph node metastasis with extracapsular spread
N3	IVA(ii)	Fixed or ulcerated regional lymph node metastasis
M0		No distant metastasis
M1	IVB	Any distant metastasis (including pelvic lymph node metastasis)

Consensus-based recommendation 7. E32

The primary treatment for extramammary Paget's disease consists of surgical excision of the lesion. Surgical excision should include wide excision margins extending well into healthy tissue, both in the horizontal and the vertical planes.

Depending on the location and size of the lesion, plasty may be considered to cover the defect, with careful attention paid to any comorbidities (**expert consensus**).

Strength of consensus (+++)

8 Surgical Treatment of Invasive Carcinoma

8.1 Standard treatment for primary vulvar cancer

The appropriate treatment should be decided on by an interdisciplinary (gynecologic oncology, radiation therapy, pathology, anesthesiology) board.

8.2 Surgery of the vulva

Consensus-based recommendation 8. E33

The surgical specimen must be excised in such way that an R0 resection status is achieved on all sides. The minimum tumor-free tissue margin should be at least 3 mm on histological examination (**expert consensus**).

Strength of consensus (+++)

While the ultimate goal is excision with a margin of healthy tissue, whether by local excision or vulvectomy, the following general principle applies: the greater the distance between the tumor and the edge of the resection margin, the lower the probability of local recurrence. It is not possible to define an evidence-based cut-off for the minimum width of tumor-free resection margins. The expert consensus can be summarized as follows: the margin of healthy tissue must be at least 3 mm (measured histologically); clinical dissection should therefore extend even further. In individual cases, after informing the patient about the potentially higher risk of recurrence, accepting quite narrow ablation margins may be the right thing to do, for example to avoid resection of the clitoris or of the external urethral orifice. The goal of resection into healthy tissue does not just apply to tumors with invasive growth but also includes potential intraepithelial neoplastic neoplasia (VIN) directly adjacent to the tumor.

Consensus-based recommendation 8. E34

If vulvectomy is indicated and there is no increased risk of skin bridge metastasis, the approach must be the triple incision technique, i.e. vulvectomy and lymphadenectomy are performed using different incisions (**expert consensus**).

Strength of consensus (+++)

Local radical excision must, wherever possible, be the surgical method of choice. Complete vulvectomy should only be performed if it is unavoidable due to tumor spread. If it is necessary to perform complete vulvectomy, the recommended approach is the triple incision technique, i.e. vulvectomy and inguinal lymphadenectomy are performed using different incisions.

Consensus-based recommendation 8. E35

After local excision or vulvectomy, primary reconstruction plasty (pudendal flaps, Limberg flaps or others) should be considered; careful attention is necessary to ensure tension-free coverage of the wound, good functionality and appearance (**expert consensus**).

Strength of consensus (+++)

Reconstructive plasty to cover the wound [64] after resection with a focus on functionality and body image should not just be performed in younger patients but should be done in all patients, irrespective of age, as this makes it more likely that coverage of the defect will be tension-free and will prevent wound dehiscence with longer secondary healing in all age groups.

When deciding whether reconstructive surgery is indicated it is important to take account of any patient comorbidities such as age, diabetes mellitus, hypertension, or nicotine abuse.

8.3 Recommendations for treatment according to stage

8.3.1 Stage T1

Consensus-based recommendation 8. E36

Unifocal stage T1a or T1b vulvar cancer must be treated by local resection into healthy tissue (radical local excision) (**expert consensus**).

Strength of consensus (+++)

8.3.2 Stage T2

Consensus-based statement 8. S6

Depending on the clinical status, local radical excision or vulvectomy combined with resection of any involved structures of the urethra, vagina, or anus is indicated for stage T2 disease.

Primary radio(chemo)therapy is an alternative if surgery would otherwise put continence at risk (**expert consensus**).

Strength of consensus (+++)

8.3.3 Stage T3 (equivalent to FIGO stage IVA)

Consensus-based recommendation 8. E37

Primary radiochemotherapy should be done if stage T3 (= FIGO stage IVA) lesions are present to preserve the function of adjacent organs (micturition and/or defecation) where possible. Alternatively, patients should receive neoadjuvant radio(chemo)-therapy to reduce the extent of subsequent surgery (**expert consensus**).

Strength of consensus (+++)

Consensus-based recommendation 8. E38

If there is infiltration into adjacent organs and/or fistula formation, primary exenteration should be performed if there is no distant metastasis.

Primary exenteration should also be done as a palliative therapy when infiltration into adjacent organs and/or fistula formation has occurred (**expert consensus**).

Strength of consensus (+++)

9 Lymphatic Vessel Surgery

9.1 Lymphatic drainage of the vulva

The lymphatics of the vulva drain exclusively to the inguinal and femoral lymph nodes. There is no risk of skip metastasis to the pelvic lymph nodes.

9.2 Extent of lymphadenectomy

Consensus-based recommendation 9. E39

Systematic inguinofemoral lymphadenectomy (= surgical staging of the inguinal region) must always include removal of both the superficial (inguinal) and the deep (femoral) lymph nodes below the cribriform fascia (**expert consensus**).

Strength of consensus (+++)

The rule of thumb is that at least 6 lymph nodes should be resected from either side [57].

Consensus-based recommendation 9. E40

Staging of the inguino-femoral lymph nodes must not be done in cases with stage pT1a vulvar cancer (infiltration depth 1 mm or less), basal cell carcinoma, or verrucous carcinoma of the vulva (**expert consensus**).

Strength of consensus (+++)

Consensus-based recommendation 9. E41

Surgical staging of the inguino-femoral lymph nodes must be done in cancers where the infiltration depth is more than 1.0 mm (\geq pT1b) (**expert consensus**).

Strength of consensus (+++)

9.3 Lateral tumor and contralateral LN

Consensus-based recommendation 9. E42

Contralateral lymph node staging may be dispensed with in lateral cancers (> 1 cm distance to the midline) with diameters of less than 2 cm if the ipsilateral lymph nodes are histologically tumor-free. Surgical staging of the contralateral side must be performed in all other cases (**expert consensus**).

Strength of consensus (+++)

9.4 Complications of inguino-femoral lymphadenectomy

Inguino-femoral lymphadenectomy is associated with significant morbidity [65–70]:

- ▶ impaired wound healing in 14–44% of cases
- ▶ lymphoceles in 13–40% of cases
- ▶ lymphedema (requiring treatment) of the leg in 20–35% of cases

9.5 Sentinel lymphadenectomy

Consensus-based recommendation 9. E43

Patients with unifocal primary tumor with a diameter < 4 cm and clinically negative inguino-femoral lymph nodes must be informed about the benefits and possible oncologic risks of sentinel lymphadenectomy and of systematic inguino-femoral lymphadenectomy. If no sentinel lymphadenectomy is performed, patients must undergo inguino-femoral lymphadenectomy (**expert consensus**).

Strength of consensus (+++)

Consensus-based recommendation 9. E44

The following conditions must be met for sentinel lymph node biopsy to be indicated:

- ▶ maximum tumor diameter at skin level < 4 cm
- ▶ unifocal tumor
- ▶ inguino-femoral lymph nodes must be clinically and sonographically unremarkable
- ▶ team must be experienced in marking sentinel lymph nodes
- ▶ ultrastaging of the lymph nodes must be done with additional immunohistochemical examination by a pathologist
- ▶ the patient must be informed in detail about the benefits and possible oncologic risks of the method
- ▶ the patient must be followed up regularly (good patient compliance) (**expert consensus**)

Strength of consensus (+++)

9.6 Pelvic lymph nodes

Pelvic lymphadenectomy can be considered as part of a multimodal treatment plan with additional radiation therapy in patients who undergo tumor debulking if there is evidence of enlarged pelvic LN. Pelvic lymphadenectomy may be considered in patients with inguinal lymph node metastasis and an increased risk of pelvic LN involvement when the aim is to avoid adjuvant pelvic radiation therapy if pelvic LN are negative.

10 Radiotherapy and Radiochemotherapy

10.1 Postoperative (adjuvant) radiotherapy

10.1.1 Postoperative tumor bed irradiation

Consensus-based recommendation 10. E45

Postoperative irradiation of the tumor bed must be done after R1/R2 resection.

Tumor bed irradiation should be considered if the resection margin in health tissue is 3 mm (in the histological specimen) or less and a second resection is not possible or/and functionally not expedient or the patient does not want it (**expert consensus**).

Strength of consensus (+++)

10.1.2 Postoperative irradiation of the inguinal lymphatics

Consensus-based recommendation 10. E46

Postoperative irradiation of the affected inguinal region(s) should be done:

- ▶ if lymph node involvement is present with involvement of 2 or more inguinal lymph nodes, irrespective of the size of the metastases
- ▶ if one lymph node is affected and the metastasis is at least 5 mm or larger
- ▶ always if extracapsular growth is present (FIGO IIIC)
- ▶ if fixed/ulcerated lymph nodes are present (FIGO IVAii) (**expert consensus**)

Strength of consensus (+++)

10.1.3 Postoperative irradiation of pelvic lymphatics

Consensus-based recommendation 10. E47

To avoid overtreatment and unnecessary therapy-related toxicity, postoperative irradiation of the pelvic lymphatics should be reserved for patients with histologically verified pelvic lymph node metastasis (**expert consensus**).

Strength of consensus (+++)

Laparoscopic or extraperitoneal pelvic lymphadenectomy is recommended to obtain the histological lymph node status if

- ▶ lymph node involvement is present with involvement of 2 or more inguinal lymph nodes, irrespective of the size of the metastases
- ▶ one inguinal lymph node is affected and the metastasis is at least 5 mm or greater
- ▶ extracapsular growth in an inguinal lymph node is present (FIGO IIIC)
- ▶ fixed/ulcerated inguinal lymph nodes are present (FIGO IVAii)

Irradiation of the pelvic lymphatics should only be done if lymph nodes are positive [71].

Table 7 Follow-up for vulvar cancer; examinations and intervals.

Interval (years)	Frequency (months)	Mandatory examinations	Symptom-related examination	Comments
1–3	every 3 months	history, clinical examination	imaging	biopsy of suspicious region
4–5	every 6 months	history, clinical examination	imaging	biopsy of suspicious region
≥ 6	every 12 months	history, clinical examination	imaging	biopsy of suspicious region

10.2 Primary radiotherapy

10.2.1 Primary radiochemotherapy

Primary radiochemotherapy can be administered to treat invasive cancer if the patient requests it (to preserve the organ) or if the cancer is inoperable.

10.2.2 Neoadjuvant radiochemotherapy

In patients with locally advanced vulvar cancer, chemoradiation may achieve a reduction in tumor size in 63–92% of cases, making the cancer operable [72].

10.2.3 Simultaneous chemotherapy

As with other squamous cell carcinomas, combined radiochemotherapy can also be used to treat locally advanced vulvar cancer. The most common combination is 5-fluorouracil with cisplatin or mitomycin C.

11 Systemic Therapy

The experience with systemic therapy to treat vulvar cancer is very limited.

11.1 Neoadjuvant chemotherapy

Neoadjuvant chemotherapy is not yet an established treatment option to treat vulvar cancer. Platinum-based combination chemotherapy has a reported clinical response rate of up to 80% and complete pathological remission rates of up to 45% [73]. In contrast to primary radiochemotherapy (cf. relevant chapter on the indications for and administration of primary radiochemotherapy) the goal of neoadjuvant chemotherapy is subsequent surgical resection. When making the decision for treatment, this approach can be considered for selected patients in a suitable general state of health.

16 Follow-up

Consensus-based recommendation 16. E61

Follow-up must consist of:

- ▶ disease-specific history
 - ▶ symptom-related history: palpated tumor, pain, pruritus, vaginal discharge, bleeding, leg edema, propensity for swelling, symptoms of scarring and stenosis, micturition anomalies
 - ▶ clinical examination:
 - ▶ inspection and palpation of the external and internal genitalia including the inguinal lymphatics and the rectum
 - ▶ speculum examination
 - ▶ broad indication for biopsy of suspicious findings
- (expert consensus)**

Strength of consensus (+++)

Consensus-based recommendation 16. E62

If lichen sclerosis of the vulva is present, this will significantly affect the probability of recurrence or new-onset of vulvar cancer. Lifelong follow-up must therefore be done in patients with this condition **(expert consensus)**.

Strength of consensus (+++)

Consensus-based recommendation 16. E63

The routine use of imaging methods is not indicated in follow-up but can be helpful when the status is unclear or suspicious for recurrence. Determination of the tumor marker SCC must not be part of follow-up **(expert consensus)**.

Strength of consensus (+++)

Consensus-based statement 16. S8

Colposcopy of the cervix, vagina, vulva and anus is an additional useful examination **(expert consensus)**.

Strength of consensus (+++)

Consensus-based recommendation 16. E64

Lifelong follow-up should be done in patients with treated HSIL or d-VIN **(expert consensus)**.

Strength of consensus (+++)

16.1 Follow-up intervals (◉ Table 7)

17 Locoregional Recurrence and Distant Metastasis

The majority of all recurrences occur within the first 2 years after primary therapy [6, 28, 74–84]. Around 65% of these recurrences are detected clinically during routine follow-up [74].

17.2 Diagnostic work-up for suspicion of recurrence

If there is a suspicion of vulvar cancer recurrence the first step should consist of histological verification. Once the recurrence has been verified histologically, a diagnostic work-up to determine the extent of spread of disease should be done, particularly if there is inguinal recurrence. This diagnostic work-up can consist of MRI of the pelvis, CT of the thorax/abdomen and possibly scalene node biopsy [85]. FDG-PET-CT at primary diagnosis has a high predictive value in the search for distant metastasis.

17.4 Treatment of local recurrence without involvement of the urethra or anus

Consensus-based recommendation 17. E65

Treatment of local recurrence should consist of resection with cancer-free resection margins (R0) **(expert consensus)**.

Strength of consensus (+++)

17.5 Treatment of local recurrence when R0 resection is not possible

Consensus-based recommendation 17. E66

The treatment of choice for inoperable recurrence should be chemoradiotherapy or radiation therapy (**expert consensus**).

Strength of consensus (+++)

Consensus-based recommendation 17. E67

If locoregional recurrence occurs in a previously irradiated region and surgery or repeated radiotherapy is not an option, the patient should receive palliative care (**expert consensus**).

Strength of consensus (+++)

17.6 Treatment of recurrence with involvement of the urethra, vagina and anus

Staging of the lesion should be done prior to starting any treatment. If recurrence involves adjacent organs such as the urethra and/or anus, then primary radio(chemo)therapy is usually indicated if the patient has not previously had radiotherapy. If distant metastasis has been excluded, one treatment option is pelvic exenteration. The few existing studies have reported a 5-year survival rate of 31–38%, with longer survival times documented for individual cases [86–91].

17.7 Treatment of inguinal recurrence

Consensus-based recommendation 17. E68

Distant metastasis must be excluded prior to carrying out radical surgery for inguinal and/or pelvic recurrence (**expert consensus**).

Strength of consensus (+++)

Inguinal or pelvic recurrence is usually a sign that treatment can only be palliative rather than curative; the prognosis is poor, with a 5-year survival rate of 5–27%. In patients who have not had prior radiation therapy, local excision followed by radiotherapy or radiochemotherapy should be performed. If the affected inguinal region was previously treated with adjuvant radiotherapy, the only remaining option is that of best supportive care [92,93].

17.9 Treatment for distant metastasis

Consensus-based recommendation 18. E69

Because of the poor response rates, monotherapy should be the systemic therapy of choice. The diagnostic criteria for prescribing systemic therapy should be very strict (**expert consensus**).

Strength of consensus (+++)

17.10 Note on radiochemotherapy

When considering whether radiation therapy is indicated to treat recurrence of vulvar cancer, there is always the question whether it should take the form of straightforward radiotherapy or be administered in the form of radiochemotherapy. Unfortunately, there are no comparative randomized studies available which would clarify this issue.

Note

Chapters on more general topics which did not exclusively apply to vulvar cancer such as the chapters on **Patient Information** (6), **Supportive Therapy** (12), **Psychooncology and Quality of Life** (13), **Rehabilitation** (14), **Integrative Medicine** (15) and **Palliative Medical Care** (18) can be consulted in the long version of the guideline.

During the compilation of this guideline, **quality indicators** were developed as part of the methodological framework; they are included in a separate chapter in the long version of this guideline (19).

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