ESGO
European Society of Gynaecological Oncology

VULVAR CANCER

GUIDELINES

- Complete report -

The European Voice of Gynaecological Oncology

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1 Introduction

Vulvar cancers are relatively uncommon and affect predominantly elderly women. The vast majority are squamous cell carcinomas. The objectives of the guidelines are to improve and to homogenize the management of patients with vulvar cancer. The guideline is intended for use by gynaecological oncologists, general gynaecologists, surgeons, pathologists, radiotherapists, medical and clinical oncologists, general practitioners, palliative care teams, and allied health professionals.

The guideline covers diagnosis and referral, preoperative investigations, surgical management (local treatment, groin treatment, reconstructive surgery), sentinel lymph node procedure, radiation therapy, 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 complete report does not include any economic analysis of the strategies. These guidelines apply to adults over the age of 18 years with squamous cell carcinoma of the vulva. These guidelines do not address patients with other vulvar cancer histologies.

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.

2 Acknowledgements

The European society of gynaecological oncology (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. ESGO is also very grateful to the external panel of physicians and patients (international reviewers) for their participation. The names of the participants in each group are listed on Appendix 1.

ESGO also wishes to express sincere gratitude to the Institut National du Cancer (INCa, France) for providing the main funding for this work.

3 Method

The guidelines were developed using a five-step process (see figure 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, use of an international external review process (physicians and patients), and management of potential conflicts of interests. This development process involved two meetings of the international development group, chaired by Professor Ate van der Zee and Dr Maaike Oonk (University Medical Center Groningen, Netherlands).

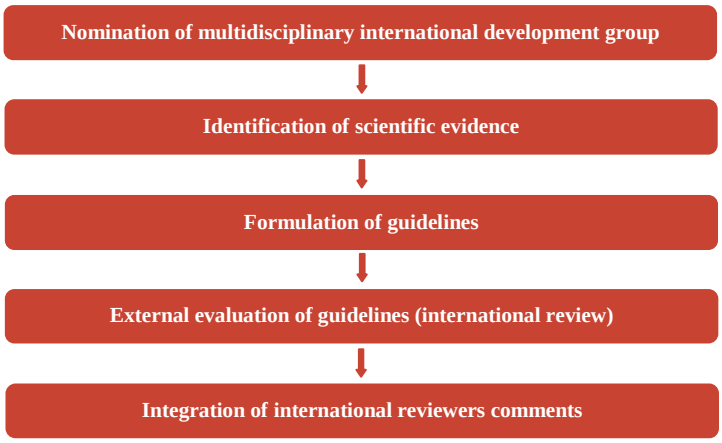


Figure 1. Development process

3.1 Nomination of multidisciplinary international development group

The ESGO Council nominated practicing clinicians that 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 (gynaecological oncology, medical oncology, pathology, radiation oncology, surgery) so that their perspectives would contribute to the validity and acceptability of the guidelines. The list of the development group is available in Appendix 1.1.

3.2 Identification of scientific evidence

To ensure that the statements made in this document are 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. This search used indexing terms as follows: accuracy, adverse effects, bilateral en bloc dissection, biopsy, chemotherapy (primary, neoadjuvant, adjuvant), chemoradiation (primary, neoadjuvant, adjuvant), chemotherapeutic agents, detection rate, diagnosis, en bloc dissection, exenteration (anterior, posterior, total), follow-up, frozen sections, groin lymph node involvement, groin node metastasis, histology, histological examination, imaging, inguinofemoral lymph node dissection, laboratory testing, local excision, lymph node dissection, lymphadenectomy, (inguinofemoral or deep, inguinal or superficial, ipsilateral, pelvic), lympho-vascular invasion, margin, node dissection, operation, pathology, pathology report, pelvic-lymph node dissection, perioperative care, physical examination, postoperative complications, preoperative care, preoperative workup, quality of life, radiotherapy (primary, neoadjuvant, adjuvant), radiation (primary, neoadjuvant, adjuvant), radical local excision, reconstructive surgery, sensibility, sentinel lymph node assessment, sentinel lymph node biopsy, sentinel lymph node dissection, specificity, staging, surgical management, surgical outcome, surgical procedures, surgical resection, surveillance, survival rate, survival analysis, systemic treatment, targeted therapy, toxicity, treatment outcome, tumour margin, vulvar cancer (early and/or advanced stages), vulvectomy (radical, simple, modified, hemi).

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 papers. 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, indexing terms: clinical practice guidelines, evidence-based medicine, guidelines, methodology, recommendations, vulvar cancer) and a bibliographic search using selected websites (see Appendix 2). All retrieved articles have been methodologically and clinically appraised. After the selection and critical appraisal of the articles, a summary of the scientific evidence has been developed.

3.3 Formulation of guidelines

During the first meeting (December 4, 2015), the Development group developed guidelines for diagnosis and referral, preoperative investigations, surgical management (local treatment, groin treatment, reconstructive surgery), sentinel lymph node procedure, 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, a guideline is the clinical approach that is unanimously recognized by the Development group as being the criterion-standard clinical approach. If an approach is judged to be acceptable but is not unanimously recognized as a criterion-standard clinical approach, indication is given that it is 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 document has been graded following the SIGN grading system (see Appendix 3).

3.4 External evaluation of the guidelines - International review

The ESGO Council established a large panel of practicing clinicians that provide care to vulvar cancer patients and patients. The objective was to assemble a multidisciplinary panel. These international reviewers are independent from the development 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.). The list of international reviewers (N = 181) is available in Appendix 1.2.

3.5 Integration of international reviewers comments

Responses were be pooled and discussed by the international development group to finalize the guidelines.

4 Management of conflicts of interest

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 this work.

5 Summary of guidelines

5.1 Diagnosis and referral

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

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

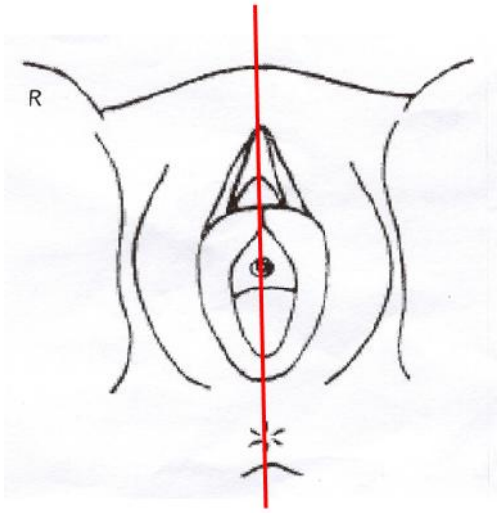
✓ All patients with vulvar cancer should be referred to a Gynaecological oncology centre (GOC) and treated by a multidisciplinary gynaecological oncology team.

5.2 Staging system

✓ Vulvar cancer should be staged according to FIGO and/or TNM classification[1].

5.3 Preoperative investigations

✓ Preoperative work-up should at least include clear documentation of clinical exam (size of lesion, distance to the midline/clitoris/anus/vagina/urethra and palpation of lymph nodes). Picture or clinical drawing is advised (see below).



✓ Evaluation of the cervix/vagina/anus is recommended.

C Prior to sentinel lymph node biopsy, clinical examination and imaging of the groins (either by ultrasound, (positron emission tomography-)computed tomography ((PET-)CT), or magnetic resonance imaging (MRI)) are required to identify potential lymph node metastases.

✓ Suspicious nodes (at palpation and/or imaging) should be analysed by fine-needle aspiration (FNA) or core biopsy when this would alter primary treatment.

[1] Throughout these recommendations advanced stage of disease is defined as clinical T3 and/or N3.

✓ 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.

✓ The pathology report on preoperative biopsy should at least include histological type and depth of invasion.

5.4 Surgical management

Local treatment

C Radical local excision is recommended.

✓ Consider additional, more superficial resection of differentiated vulvar intraepithelial neoplasia (d-VIN) in addition to radical local excision of invasive tumours.

✓ 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 goal of excision is to obtain tumour-free pathological margins. Surgical excision margins of at least 1 cm are advised. It is acceptable to consider less wide margins where the tumour lies close to midline structures (clitoris, urethra, anus) and preservation of their function is desired.

✓ When invasive disease extends to the pathological excision margins of the primary tumour, reexcision is treatment of choice.

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

Groin treatment

C Groin treatment should be performed for tumours > pT1a.

B For unifocal tumours < 4 cm without suspicious groin nodes on clinical examination and imaging (any modality) the sentinel lymph node procedure is recommended.

C For tumours ≥ 4 cm and/or in case of multifocal invasive disease inguinofemoral lymphadenectomy by separate incisions is recommended. In lateral tumours (medial border > 1 cm from midline) ipsilateral inguinofemoral lymphadenectomy is recommended. Contralateral inguinofemoral lymphadenectomy may be performed when ipsilateral nodes show metastatic disease.

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

C Preservation of the saphenous vein is recommended.

✓ The optimal management of the groin (full inguinofemoral lymphadenectomy or isolated removal only) for enlarged, proven metastatic nodes remains to be defined.

✓ Where enlarged (> 2 cm) pelvic nodes are identified, their removal should be considered.

Reconstructive surgery

✓ Availability of reconstructive surgical skills as part of the multidisciplinary team is required in early as well as advanced stage disease.

5.5 Sentinel lymph node procedure

B The sentinel lymph node procedure is recommended in patients with unifocal cancers of < 4 cm, without suspicious groin nodes.

B Use of radioactive tracer is mandatory, use of blue dye is optional.

C Lymphoscintigram is advised to enable the preoperative identification, location and number of sentinel lymph nodes.

C Intraoperative evaluation and/or frozen sectioning of the sentinel lymph node 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.

✓ When a sentinel lymph node is not found (method failure), inguinofemoral lymphadenectomy should be performed.

C Where metastatic disease is identified in the sentinel lymph node (any size): inguinofemoral lymphadenectomy in the groin with the metastatic sentinel lymph node.

✓ For tumours involving the midline: bilateral sentinel lymph node detection is mandatory. Where only unilateral sentinel lymph node detection is achieved, an inguinofemoral lymphadenectomy in the contralateral groin should be performed.

C Pathological evaluation of sentinel lymph nodes should include serial sectioning at levels of at least every 200 µm. If the H&E sections are negative, immunohistochemistry should be performed.

5.6 Radiation therapy

✓ Adjuvant radiotherapy should start as soon as possible, preferably within 6 weeks of surgical treatment.

✓ When invasive disease extends to the pathological excision margins of the primary tumour, and further surgical excision is not possible, postoperative radiotherapy should be performed.

✓ 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.

B Postoperative radiotherapy to the groin is recommended for cases with > 1 metastatic lymph node and/or presence of extracapsular lymph node involvement.

✓ Adjuvant radiotherapy for metastatic groin nodes should include the ipsilateral groin area and where pelvic nodes are non-suspicious on imaging, the distal part of the iliac nodes with an upper limit at the level of the bifurcation of the common iliac artery.

C Based on evidence from other squamous cell cancers such as cervical, head & neck, and anal cancer, the addition of concomitant, radiosensitising chemotherapy to adjuvant radiotherapy should be considered.

5.7 Chemoradiation

C Definitive chemoradiation (with radiation dose escalation) is the treatment of choice in patients with unresectable disease.

C In advanced stage disease neoadjuvant chemoradiation should be considered in order to avoid exenterative surgery.

C Radiosensitising chemotherapy, preferably with weekly cisplatin, is recommended.

5.8 Systemic treatment

D Data in vulvar cancer are insufficient to recommend a preferred schedule in a palliative setting.

5.9 Treatment of recurrent disease

Treatment of vulvar recurrence

✓ Radical local excision is recommended.

✓ For vulvar recurrence with a depth of invasion > 1 mm and previous sentinel lymph node removal only, inguinofemoral lymphadenectomy should be performed.

✓ The indications for postoperative radiotherapy are comparable to those for the treatment of primary disease.

Treatment of groin recurrence

✓ Restaging by CT (or PET-CT) of the thorax/abdomen/pelvis is recommended.

✓ Preferred treatment is radical excision when possible, followed by postoperative radiation in radiotherapy naïve patients.

✓ Based on evidence from other squamous cell cancers such as cervical and anal cancer, the addition of radiosensitising chemotherapy to postoperative radiotherapy should be considered.

✓ Definitive chemoradiation when surgical treatment is not possible.

Treatment of distant metastases

✓ Systemic (palliative) therapy may be considered in individual patients (see systemic treatment).

5.10 Follow-up

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

✓ After primary surgical treatment the following follow-up schedule is suggested:

- First follow-up 6-8 weeks postoperative
- First two years every three-four 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 vulva and groins.[2]

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

- First follow-up visit 10-12 weeks post completion of definitive (chemo)radiation.
- First two years every three-four months
- Third and fourth year biannually
- Afterward, long-term follow-up, especially in case of predisposing vulvar disease.

At first follow-up visit 10-12 weeks post definitive (chemo)radiation CT or PET-CT is recommended to document complete remission.

[2] Despite the well-recognized low sensitivity of palpation to identify groin recurrences, currently available data do not support routine use of imaging of the groins in follow-up.

6 Diagnosis and referral

6.1 Summary of available scientific evidence

No directly applicable clinical studies have been identified.

6.2 Previous initiatives

Four previous[1-4] initiatives presenting guidelines on diagnosis and referral were identified.

6.3 Development group comments

For accurate treatment planning (sentinel lymph node (SLN) procedure: yes/no; expected uni-or bilateral lymph drainage; visibility of scar; etc.) the localization of the primary tumour 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 e.g. the SLN procedure is related to experience of the treating physician, treatment should be centralized in centres with adequate experience in the treatment of this disease.

6.4 Guidelines

✓ In any patient suspected for vulvar cancer, diagnosis should be established by a punch/incision biopsy. Excision biopsy should be avoided for initial diagnosis, as this may obstruct 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 GOC and treated by a multidisciplinary gynaecological oncology team.

7 Staging system

The TNM classification[5] and the FIGO staging system[6,7] classify vulvar cancer on the basis of the size of the tumour (T), whether the cancer has spread to lymph nodes (N), and whether it has spread to distant sites (M) (**Table 1**). 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 tumour[8]. 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[6,7] 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.

7.1 Summary of available scientific evidence

No studies assessing the performance of the TNM classification have been identified.

Three retrospective studies[9-11] assessing the performance of the revised FIGO staging system have been identified. The new staging system has generally been considered appropriate. This has seen a major downstaging of between 18.3% to 42% of patients. This has mainly involved old patients with stage II disease being downstaged to stage IB. Among the 1,131 patients enrolled in these studies, only 6 patients were upstaged by the new system (< 1%). Nevertheless, Tabbaa *et al.*[10] suggested that tumours > 4 cm in diameter had a less favourable prognosis. A potential limitation with the revised FIGO staging system is that the number of patients with stage II disease will be very low. From the three retrospective studies above[9-11], about 20% of patients were classified as stage II in the old FIGO staging system, whereas it is likely to be less than 5% in the revised system.

LoE 2-

7.2 Previous initiatives

No previous initiative presenting guidelines on the staging system to use was identified.

7.3 Development group comments

The development group recommends using the TNM classification because it more accurately reflects the status of the primary tumour and lymph nodes.

7.4 Guidelines

✓ Vulvar cancer should be staged according to FIGO and/or TNM classification[3].

[3] Throughout these recommendations advanced stage of disease is defined as clinical T3 and/or N3.

Table 1. Staging systems of squamous cell vulvar cancer

PRIMARY TUMOUR (T)		
TNM categories[5]	**FIGO stages[6]**	**Definition**
TX		Primary tumour cannot be assessed
T0		No evidence of primary tumour
Tis*		Carcinoma in situ
T1a	IA	Lesions ≤ 2 cm in size, confined to the vulva or perineum and with stromal invasion ≤ 1.0 mm**, no nodal metastasis
T1b	IB	Lesions > 2 cm in size or with stromal invasion > 1.0 mm*, confined to the vulva or perineum, with negative nodes
T2***	II	Tumour of any size with extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with negative nodes
T3****	IVA	Tumour invades upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone
REGIONAL LYMPH NODES (N)		
TNM categories[5]	**FIGO stages[6]**	**Definition**
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		One or two regional lymph nodes with the following features
N1a	IIIA	One or two node metastasis(es), each 5 mm or less
N1b	IIIA	One lymph node metastasis 5 mm or greater
N2	IIIB	Regional lymp node metastasis with the following features
N2a	IIIB	Three or more lymph node metastases each less than 5 mm
N2b	IIIB	Two or more lymph node metastases 5 mm or greater
N2c	IIIC	Lymph node metastasis with extracapsular spread
N3	IVA	Fixed or ulcerated regional lymph nodes
DISTANT METASTASIS (M)		
TNM categories[5]	**FIGO stages[6]**	**Definition**
M0		No distant metastasis
M1	IVB	Distant metastasis (incluing pelvic lymph node metastasis)

* FIGO no longer includes stage 0 (Tis), ** the depth of invasion is defined as the measurement of the tumour from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion, *** FIGO uses the classification T2/T3. This is defined as T2 in TNM, **** FIGO uses the classification T4. This is defined as T3 in TNM.

8 Preoperative investigations

8.1 Summary of available scientific evidence

Pathology review: two studies enrolling at least 50 pathology reports of vulvar tissues were identified. As part of a retrospective pathology report review, Beugeling *et al.*[12] assessed 1) the impact of pathology review on patient management and 2) the adequacy of the pathology reports, with regard to tumour type, infiltration depth, and, for excision biopsies, resection margins on 121 pathology reports from 112 patients. Two discrepancies have been reported (1.7%) but the huge majority of reviewed reports showed no discrepancy (98.3%). In this study, a report stating histological type and depth of infiltration was considered "adequate". Using this criterion, 56% of the original reports and 83% of the review reports were adequate. In the second identified study[13], 113 pathology reports were reviewed and 4 major discrepancies were reported. **LoE 2+**

Results from the 4 other identified studies[14-17] are limited by the small number of pathology reports taken into account. These studies show a rate between 0% and 15.8% for major discrepancy (**Table 2**). Among the 6 identified studies, it was not possible to estimate how many histology reviews would be necessary to find one major discrepancy. Half of the authors from the 6 identified studies[12,15,16] have expressed doubt concerning the necessity of pathology report review for vulvar cancer.

Accuracy of clinical palpation to assess the lymph nodes status: four studies[18-21] assessing the value of clinical palpation of the groin lymph nodes were identified. But only two studies[18,21] have accrued in excess of 50 patients: **LoE 2+**

- In a series of 258 patients treated with radical vulvectomy and bilateral groin lymphadenectomy, Iversen *et al.*[18] reported metastases to the superficial and/or deep inguinal lymph nodes in 100 cases. Only 64 of which were detected by clinical examination. A false positive rate of 15.5% among the patients with clinically suspicious groin lymph nodes has been reported.

- Podratz *et al.*[21] reported that the preoperative clinical staging efforts were incorrect in 25% of the cases (56/224).

Among the 50 patients enrolled in the study published by Piura *et al.*[19], data with respect to both clinical palpation and histopathologic examination of groin lymph nodes were available in 20 of the 26 patients who had radical vulvectomy and groin lymph node dissection. Authors have noticed that clinical palpation was not very reliable in detecting groin lymph node metastases. Overdiagnosis and underdiagnosis were present in 55.5% and 27.3% of patients (sensitivity: 57.1%, specificity: 61.5%).

Thirty-nine patients out of the 59 patients enrolled in the fourth identified study[20] had inguinofemoral lymphadenectomy and all except one had bilateral groin node excision. Clinical findings were compared with histology result to assess test accuracy for a total of 77 groin nodes. In this study published by Singh *et al.*[20], clinical examination has a sensitivity of 35% and specificity of 94.3%.

Accuracy of MRI to assess the lymph nodes status: as part of a systematic review, Selman *et al.*[22] compared the accuracy of non-invasive tests to assess the groin node status. One prospective[23] and one retrospective[24] studies assessing the value of the MRI have been included in this review for a total of 60 patients. MRI has a pooled sensitivity and specificity of 86% (95% CI = 0.57-0.98) and 87% (95% CI = 0.74-0.95) respectively in predicting the groin node status. **LoE 1-**

Three other original studies[20,25,26] were identified but only one study[25] has accrued in excess of 50 patients. In a retrospective study published by Bipat *et al.* [25], 60 patients underwent MRI examination for preoperative evaluation of lymph nodes. MRI images were read independently and retrospectively by two radiologists, both unaware of physical examination and surgery findings. Both **LoE 2+**

observers detected 12 of the 23 positive groin nodes (sensitivity: 52%). Of the 96 negative nodes, 14 and 11 were scored as positive by the observers (specificity: 85% and 89% respectively). Singh *et al.*[20] (39 patients, 77 groin nodes) reported consistent results with those described by Selman *et al.*[22]. MRI correctly identified metastatic nodal disease in 18 of the 21 positive groins and among the 56 negative groin nodes, 46 nodes were correctly identified on MRI, leading to a sensitivity of 85.7% and a specificity of 82.1%.

It should to be noted that the used MRI criterion for groin lymph node metastasis prediction varied between the studies (short-axis diameter of the node[24,25], short axis/long axis ratio, contour, and signal intensity[20,23]). Kataoka *et al.*[26] used several criteria for evaluation of lymph node metastases of 49 patients (36 primary and 13 recurrent). A short axis/long axis ratio ≥ 0.75 was described as the most relevant criterion for diagnosis of groin lymph node metastasis in groin-by-groin analysis (sensitivity: 86.7% and specificity: 81.3%). The presence of necrosis within a lymph node showed the highest specificity (87.5%), but lower sensitivity (40.0%). Furthermore, MRI accurately classified 31 out of 36 primary cancers (accuracy: 86%). The addition of contrast-enhanced MRI did not change the accuracy of the size category of primary cancers (accuracy: 85%).

<u>*Accuracy of PET to assess the lymph nodes status*</u>: Selman *et al.*[22] pooled results of two prospective studies[27,28] to assess the value of PET in the determination of groin nodes status (75 patients). PET has a pooled sensitivity and specificity of 71% (95% CI = 50-86) and 72% (95% CI = 59-82) respectively. **LoE 1-**

One small original study[29] was also identified (20 patients). Of the 12 positive nodes, 6 were scored as positive (sensitivity: 50%) and all the 8 negative nodes were correctly identified (specificity: 100%). **LoE 3**

<u>*Accuracy of Ultrasound to assess the lymph nodes status*</u>: four prospective studies[30-33] assessing the value of ultrasound have been included in the systematic review published by Selman *et al.*[22]. However, a pooled analysis could not be performed due to the difference between studies in techniques used to discriminate positive and negative groin nodes. Combining the results of another study[34] identified and independently of the test parameters used for ultrasound, the results showed sensitivity and specificity ranging from 45% to 100% and from 58% to 96% respectively (**Table 3**). Moskovic *et al.*[30] combined ultrasound with ultrasound-guided fine-needle aspiration cytology (FNAC) to improve accuracy. This combined technique could accurately predict nodal status in the majority of cases. Falsely negative cytology occurred when the metastatic focus was ≤ 3 mm (two false-negative results out of 40 groins). Hall *et al.*[31], who extended the study of Moskovic *et al.*[30] to 44 patients, reported that the combination of ultrasound and FNAC provides a sensitive and specific tool for preoperative assessment (sensitivity = 93%, specificity = 100%). **LoE 2+**

<u>*Accuracy of CT to assess the lymph nodes status*</u>: no literature is available on the diagnostic value of CT for detection of inguinofemoral lymph node metastases in patients with vulvar cancer. The only experience with CT in patients with vulvar cancer is the measurement of the distance in centimetres between the skin and the underlying inguinofemoral lymph nodes for planning of groin radiation[35,36]. **LoE 4**

8.2 Previous initiatives

Seven previous initiatives[1-4,37-39] presenting guidelines on preoperative investigations were identified.

8.3 Development group comments

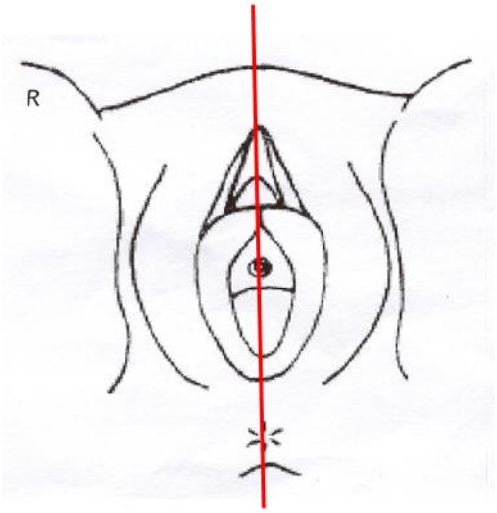
Size of the lesion, distance to the midline and palpation of the lymph nodes all determine the choice for primary treatment. Involvement of clitoris, anus, and/or urethra often means that these structures will need to be radically excised together with the primary tumour. Such information is important 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 <4 cm, inguinofemoral lymphadenectomy can be performed immediately instead of SLN procedure in case when lymph node metastases are diagnosed preoperatively. CT or PET/CT can be performed to rule out involvement of pelvic nodes and to decide whether or not to perform pelvic nodal debulking. Presence of distant metastases should also be evaluated as their presence or absence may influence the radicality of treatment of the primary tumour and the regional lymph nodes.

Treatment policy for melanomas and basal cell cancer for example is different. Depth of invasion is necessary to decide whether groin treatment is indicated, both in squamous cell cancers as well as in melanomas.

8.4 Guidelines

✓ Preoperative work-up should at least include clear documentation of clinical exam (size of lesion, distance to the midline/clitoris/anus/vagina/urethra and palpation of lymph nodes). Picture or clinical drawing is advised (see below).



✓ Evaluation of the cervix/vagina/anus is recommended.

C Prior to sentinel lymph node biopsy, clinical examination and imaging of the groins (either by ultrasound, PET-CT, or MRI) are required to identify potential lymph node metastases.

✓ Suspicious nodes (at palpation and/or imaging) should be analysed by FNA or core biopsy when this would alter primary treatment.

✓ 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.

✓ The pathology report on preoperative biopsy should at least include histological type and depth of invasion.

Table 2. Original studies presenting data on pathology slide review

Author[reference]	Year	N	Major discrepancy	Minor discrepancy
Beugeling *et al.*[12]	2014	121	1.7% (2/121)	0% (0/121)
Santoso *et al.*[13]	1998	113	3.5% (4/113)	10.6% (12/113)
Chafe *et al.*[14]	2000	28	7.1% (2/28)	32.1% (9/28)
Khalifa *et al.*[15]	2003	28	0% (0/28)	10.7% (3/28)
Selman *et al.*[16]	1999	19	15.8% (3/19)	0% (0/19)
Chan *et al.*[17]	1999	13	15.4% (2/13)	15.4% (2/13)

Table 3. Original studies presenting data on the accuracy of imaging to assess the groin node status

Author[reference]	Year	TP	FP	TN	FN	Sensitivity	Specificity
MRI							
Hawnaur *et al.*[23]*	2002	8	1	10	1	89%	91%
Sohaib *et al.*[24]*	2002	4	5	30	1	80%	56%
Bipat *et al.*[25]	2006						
(observer 1)		12	14	80	11	52%	85%
(observer 2)		12	11	90	11	52%	89%
Singh *et al.*[20]	2006	18	10	46	3	85.7%	82.1
Kataoka *et al.*[26]	2010						
(short axis/long axis ratio ≥ 0.75)		26	3	13	4	86.7%	81.3%
(contour)		21	7	8	9	70.0%	53.3%
(necrosis)		12	2	14	18	40.0%	87.5%
(loss of fatty hilum)		24	8	8	6	80.0%	50.0%
(similarity of signal intensity to vulva lesion)		23	8	3	3	88.5%	27.3%
PET							
Cohn *et al.*[27]*	2002	6	2	18	3	67%	90%
de Hullu *et al.*[28]*	1999	9	13	21	3	75%	62%
Kamran *et al.*[29]	2014	6	0	8	6	50%	100%
Ultrasound							
de Gregorio *et al.*[34]	2013	29	6	63	9	76%	91%
Hall *et al.*[31]*	2003	24	2	43	4	86%	96%
Makela *et al.*[32]*	1993	9	5	34	2	81%	87%
Moskovic *et al.*[30]*	1999	11	5	25	2	85%	83%
Abang Mohammed *et al.*[33]*	2000						
(short axis)		5	3	28	6	45%	90%
(long/shot axis ratio)		6	10	14	0	100%	58%
(combined)		5	3	21	1	83%	87%

* studies included in the systematic review published by Selman *et al.*[22], FN: false negative, FP false positive, TN: true negative, TP: true positive.

9 Surgical management

9.1 Summary of available scientific evidence

Radical/wide local excision versus radical vulvectomy : none of the five identified studies[40-44] reported statistically significant differences in overall survival, disease-free survival, local or distant recurrence rates between patients treated by radical/wide local excision and patients treated by radical vulvectomy: **LoE 2+**

- In a retrospective study enrolling 74 patients (T1-2N0-1M0), Farias-Eisner *et al.*[40] compared the effectiveness and safety of a radical local excision (N = 56) versus radical vulvectomy (N = 18). Of women with stage I disease, the 5-year survival was similar for those patients who underwent the more conservative operation (97%) compared with those who underwent a radical vulvectomy (100%). The difference in the overall survival of stage II patients undergoing radical local excision versus radical vulvectomy did not reach statistical significance (90% versus 75%, p > 0.05). Operative morbidity was less in those undergoing a conservative operation. Serious infection, necrosis, or major breakdown of the primary wound occurred in 2 (11%) and 14 (25%) patients undergoing radical local excision and radical vulvectomy, respectively.

- Similar overall survival, local control and 5-year disease-free survival rates were reported by Balat *et al.*[41] between 25 patients treated by wide local excision and 24 patients treated by radical vulvectomy (73% versus 67%, 83% versus 80%, and 75% versus 67%, respectively). In this retrospective study, all patients received irradiation combined with surgery. There were fewer complications (eg lymphedema, wound infection, lymphocyst, vulvar dystrophy) in the patients treated by wide local excision than in those treated with radical vulvectomy. Similar local recurrence rates were reported by de Hullu *et al.*[42] between patients treated by wide local excision and patients treated by radical vulvectomy (11.4% (9/79) versus 7.5% (12/159), p = 0.32). An analysis of the exact tumour free margins among 39 patients treated by wide local excision showed that no patient with histologic tumour free margins measuring > 8 mm developed a local recurrence, whereas 9 of 40 patients with at least one tumour free margin measuring ≤ 8 mm developed local recurrences within 2 years (p = 0.002). As Balat *et al.*[41], there was no difference in overall survival between two groups of patients. Rutledge *et al.*[43] undertook an analysis of 179 stage I and II lesions treated with a curative aim to see if there was a difference in survival or in disease-free interval between those patients treated with radical vulvectomy and those treated with radical wide local excision. No survival advantage from the radical vulvectomy procedure has been reported (data not shown).

- No statistical correlation between the type of primary surgery performed and the frequency of recurrence to any site were described by DeSimone *et al.*[44] in a retrospective study enrolling 122 patients with lateral T1 (N = 61) and T2 (N = 61) vulvar cancer confined to the labium majus and labium minus (local: 13% versus 8%, p = 0.33, groin: 0% versus 3%, p = 0.50, distant (pulmonary): 2% versus 3%, p = 1.0, total: 15% versus 15%, p = 1.0). It should be noted that lymphoedema occurred more commonly in patients undergoing radical vulvectomy than in patients undergoing radical wide excision (26% versus 7.5%, p = 0.007). Likewise, both wound separation (23% versus 7.5%) and lymphocyst formation (6.7% versus 3.2%) were more common in patients undergoing radical vulvectomy.

As part of Cochrane systematic review, van der Velden[45] also assessed the effectiveness and safety of a radical local excision. Two observational studies[46,47] enrolling 94 patients (TIN0M0: N = 51, T2N0M0: N = 43) have been included in this systematic review. No pooled analysis is described and it should be noted that details regarding radiotherapy interventions were not addressed and the grade of complications was not defined in any study. Furthermore, an adequate description of common complications was not stated in one study[47]. Authors reported a recurrence rate of 0%[47] and 12%[46]. **LoE 2-**

None of the patients with a local recurrence died of vulvar cancer after a median follow-up of 38 months.

Three other studies[48-50] documenting recurrence rates after radical/wide local excision were identified (0%[48] (0/18 patients with stage I), 23.1%[49] (28/121 patients with stage I and II), and 10%[50] (5/50 patients with stage I). **LoE 2+**

Only one study comparing quality of life of patients treated by wide local excision versus radical vulvectomy was identified. In this retrospective (57 patients), Gunther *et al.*[51] observed tendencies for a better physical, role, emotional, and cognitive functioning, as well as global health status after surgical treatment with wide local excision. Patients who underwent radical vulvectomy suffered from a significant higher level of pain than those who underwent wide local excision. In addition, these patients suffered from nausea/vomiting, fatigue, insomnia, appetite loss, and diarrhoea to a higher degree ($p > 0.05$). It should be noted that after radical vulvectomy, 89% of patients have sexual complications.

Omission of Inguinofemoral lymphadenectomy: the presence of pelvic node metastases is very rare in the absence of inguinofemoral lymph node metastases. Thirty percent of all patients with vulvar cancer have inguinofemoral metastases and 20% of these patients will have pelvic metastases, too[52,53]. None of the seven identified studies[49,54-59] described positive lymph nodes (or inguinal recurrences after a minimal follow-up of two years) in patients with very early stage vulvar cancer, where the primary lesion measures less than 2 cm in maximum diameter and the depth of invasion is less than 1 mm (FIGO stage IA disease). Among the 30 patients who underwent surgery without lymphadenectomy in the study published by Magrina *et al.*[59], one developed groin, pelvic, and aortic node metastases 7.5 years after initial operation and 3.5 years after experiencing a vulvar recurrence (the primary lesion measured 2 x 1.5 cm, was moderately well differentiated, and was located to the left of the clitoris with only 0.1 mm of invasion). In contrast, with infiltration of 1-2 mm, lymph node metastases or inguinal recurrences were seen from 0 to 17%[54-57]. **LoE 2+**

Several case reports[60-65] of regional lymph node recurrences following treatment for FIGO stage IA vulvar cancer have been published but no pattern of particular risk factors can be defined from this small number of cases. **LoE 3**

Superficial inguinal lymphadenectomy versus total inguinofemoral lymphadenectomy: as part of a retrospective study enrolling 217 patients with stage I disease (5 mm or less invasion, no vascular space involvement, and negative inguinal and femoral nodes), Stehman *et al.*[66] reported a groin recurrence in 7.3% of patients treated with superficial inguinofemoral lymphadenectomy versus 0% recurrences in those treated with radical vulvectomy and bilateral inguinofemoral lymphadectomy (historic controls). The recurrent-free interval was significantly lower for patients treated with superficial inguinal lymphadenectomy compared to historic controls (84.2% (102/121) versus 91.8% (90/98), $p = 0.0028$). For survival time, the difference did not reach statistical significance (87.6% (106/121) versus 82.6% (81/98), $p > 0.05$). **LoE 2-**

Three uncontrolled studies[50,67,68] evaluating outcomes of patients treated with superficial inguinal lymphadenectomy were also identified. Among the 104 patients (stage I or II, depth of invasion greater than 1 mm) treated with radical wide excision (negative margins) and superficial inguinal lymphadenectomy, Gordinier *et al.*[67] reported that nine patients experienced recurrent disease that involved one or both of the groins (8.6%). Berman *et al.*[50] reported outcomes of 50 patients with T1 vulvar cancers < 1 cm diameter with stromal invasion > 5 mm who underwent radical wide excision and superficial inguinal lymphadenectomy. There were no isolated groin recurrences noted during a follow-up period of 36 months. The third study[68] reported that three of the 65 patients with stage I/II vulvar cancer and a pathologically negative superficial inguinal lymphadenectomy recurred in the inguinal region (4.6%). **LoE 2+**

Unilateral inguinofemoral lymphadenectomy versus bilateral inguinofemoral lymphadenectomy: the risk of recurrent disease in a contralateral groin after ipsilateral groin node dissection in patients with T1 or T2 lesions confined to the labium majus or minus is very low. Among the five identified studies[44,46,66,69,70] for a total of 295 patients, only four recurrent diseases in a contralateral groin after ipsilateral groin node dissection have been reported (1.4%). **LoE 2+**

A case report[71] of a contralateral recurrence 2.5 years after wide local excision and unilateral groin node dissection in a patient with a T1 lesion without clinically palpable groin nodes has been also identified. **LoE 3**

As part of a thesis, van der Velden[72] found that 19 out of 489 patients (3.9%) with unilateral vulvar tumours and negative ipsilateral lymph nodes had positive contralateral lymph nodes. In a subgroup analysis taking into account patients with tumours < 2 cm, the incidence of contralateral lymph nodes is only 0.9%. **LoE 2+**

Preservation of the saphenous vein: among the seven identified studies[73-79], Zhang *et al.*[73] showed that preservation of the saphenous vein was associated with a statistically significant decrease in the occurrence of cellulitis, short-term lower extremity lymphoedema, wound breakdown, and chronic edema (18% versus 39%, p = 0.006, 32% versus 70%, p < 0.001, 13% versus 38%, p = 0.001, 32% versus 3%, p = 0.003, respectively) compared to saphenous vein ligation without compromising the local or distant recurrent disease rates (data not shown). Overall, the likelihood of developing no postoperative complications was higher in the saphenous vein preservation group compared with the saphenous vein ligation group (56% versus 23%, p < 0.001). **LoE 2+**

More recently, Zhang *et al.*[74] reported that preservation of the saphenous vein was associated with a statistically significant decrease by about 50% in the occurrence of chronic lower limb lymphoedema, chronic lower extremity pain, chronic cellulitis, and sensory abnormalities (25.0% versus 48.3%, p < 0.01, 23.2% versus 46.6%, p < 0.01, 21.4% versus 41.4%, p < 0.05, and 19.6% versus 36.2%, p < 0.05 respectively) without compromising 5-year survival rate and groin recurrence rate (68% versus 66.7%, p > 0.05 and 8.9% versus 12.1%, p > 0.05, respectively). Short-term lower extremity lymphoedema and short-term lower extremity phlebitis were also less frequent in patients treated by saphenous vein sparing surgery to those treated by lymphadenectomy with saphenous vein ligation (43.5 versus 66.7%, p < 0.01, and 11.3% versus 25.8%, p < 0.05, respectively).

Similarly, Rouzier *et al.*[75] reported that lymphadenectomy with saphenous vein preservation is associated with a significant decrease in the occurrence of wound breakdown, cellulitis and lymphoedema compared to lymphadenectomy with saphenous vein ligation (16.2% versus 36.4%, p < 0.001, 17.7% versus 29.8%, p = 0.01, and 23.1% versus 45.3%, p < 0.001, respectively). A significant differences in the occurrence of cellulitis and wound breakdown were also described by Dardarian *et al.*[76] in favour of saphenous vein sparing surgery (0% versus 45%, p < 0.001, and 0% versus 25%, p ≤ 0.02, respectively). Subsequently, chronic lymphoedema (> 6 months) persisted in 38% of the vein-ligated group compared to 11% in the vein-spared group (p < 0.05) without compromising the incidence of recurrent disease (19.3% versus 22.2%, p > 0.05)[76].

However, preservation of the saphenous vein was not systematically associated with a statistically significant decrease of morbidity. Zhang *et al.*[73] observed that the difference of seroma, phlebitis, deep vein thrombosis, and hematoma in favour of saphenous vein sparing surgery did not reach statistical significance (3% versus 8%, p = 0.29, 0% versus 3%, p = 0.50, 2% versus 5%, p = 0.38, 0% versus 3%, p = 0.50, respectively). More recently, Zhang *et al.*[74] observed also that the difference of acute cellulitis, seroma, lymphocyst formation, chronic lower extremity phlebitis, and deep venous thrombosis with saphenous vein sparing surgery did not reach statistical significance (67.7% versus 72.7%, p > 0.05, 30.6% versus 37.9%, p > 0.05, 25.8% versus 31.8%, p > 0.05, 10.7% versus

15.5%, p > 0.05, 7.1% versus 10.3%, p > 0.05, respectively). Dardarian *et al.*[76] showed that the difference of short-term oedema in favour of saphenous vein ligation did not reach statistical significance (67% versus 72%, p > 0.05). Finally, groin wound breakdown or cellulitis occurred in 18% of patients with saphenous vein preservation, and 24% where the vein was sacrificed in the study published by Paley *et al.*[77].

In contrast, some investigators[73,74,77,78] described an increase of morbidity in patients with saphenous vein sparing compared to patients where it was sacrificed. Paley *et al.*[77] described an increase of the incidence of lymphoedema and lymphocyst formation (36% versus 21%, 27% versus 14%, respectively). Zhang *et al.*[73,74] observed a slight increase of postoperative fever, lymphocyst formation, and pulmonary embolism (96.8% versus 93.9%, 10% versus 4%, 2% versus 0%, respectively) but it should be noted that the differences did not reach statistical significance (p > 0.05, p = 0.19, p = 0.45, respectively). In the study published by Lin *et al.*[78], lymphoedema occurred in 17% of patients who had preservation of the long saphenous vein during the groin dissection versus 13% in whom the long saphenous vein was sacrificed (p = 0.50). It should be noted that the risk of groin recurrence did not change with preservation of the saphenous vein (6% versus 6%).

Finally, Soliman *et al.*[79] did not find significant correlations between saphenous vein ligation and the development of any local complications (data not shown).

<u>*Triple incision technique versus en bloc dissection (the butterfly incision)*</u> : no randomised trials have been performed to evaluate whether the use of the triple incision technique is as safe as the *en bloc* approach, but all the identified studies[42,80-83] that compared these two surgical approaches showed that vulvectomy and inguinofemoral lymphadenectomy via three separate incisions provide similar outcome in terms of survival compared to an en bloc butterfly resection. In multivariate analysis, van der Velden *et al.*[81] reported that surgical technique has no impact on disease-specific survival (after adjustment for tumour diameter, extracapsular lymph node involvement, TNM stage, and number of nodal metastases, HR = 0.99, 95% CI = 0.43-2.30, p = 0.996) and overall survival (data not shown). After correction for tumour dimension, depth of invasion, presence or absence of lymph/vascular invasion, and grade, de Hullu *et al.*[42] observed that wide local excision with inguinofemoral lymphadenectomy through separate incisions was not related independently to an increased risk of death within 4 years related to vulvar carcinoma (OR = 1.98, 95% CI = 0.80-4.80, p > 0.05) even if they described more frequent fatal recurrences in the groin or the skin bridge (6.3% versus 1.3%, p = 0.029).

LoE 2+

Among the seven identified studies[42,80-85], a skin bridge recurrence was observed in only 1.8% of patients (6/336). It should be noted that Hacker *et al.*[84] published 2 skin bridge recurrences, both in patients with lymph node metastases. However, the majority of identified studies[42,81,83] described a lower local recurrence rate among patients treated by an *en bloc* resection. With regard to the risk of vulvar recurrence, van der Velden *et al.*[81] reported that patients treated by an *en bloc* resection showed a significantly lower risk of local recurrence than those treated by the triple incision technique after adjustment for tumour diameter, extracapsular lymph node involvement, TNM stage, and number of nodal metastases (HR = 0.10, 95% CI = 0.02-0.44, p = 0.002). But the type of surgical treatment was not an independent predictor for regional recurrence (HR = 0.39, 95% CI = 0.13-1.17, p > 0.05) or distant recurrence (HR = 0.97, 95% CI = 0.32-2.91, p > 0.05). In multivariate analyses, after correction for tumour dimension, depth of invasion, presence or absence of lymph/vascular invasion, and grade, de Hullu *et al.*[42] mentioned that wide local excision with inguinofemoral lymphadenectomy through separate incisions was associated with a higher risk of developing recurrences 2 and 4 years after primary treatment (OR = 2.29, 95% CI = 1.00-5.28, p < 0.05, and OR = 2.272, 95% CI = 1.11-4.67, p < 0.05, respectively).

LoE 2+

Fambrini *et al.*[86] assessed the feasibility and safety of a modified triple incision total radical vulvectomy and inguinofemoral lymphadenectomy in 57 patients with locally advanced vulvar

cancer (LAVC). In all cases, two teams performed the surgery: one for total radical vulvectomy and the other for inguinofemoral lymphadenectomy. Surgical procedures started at the same time and were performed according to standard triple incision technique. Postoperative complications involving the surgical sites or lymphatic drainage were observed in one third of patients (19/57). None of them required surgical re-intervention. After treatment 29 patients developed local, regional or distant recurrence of disease, with a median progression-free survival of 39.5 ± 20.9 months. Three-year and 5-year overall survival (OS) were of 60.5% and 48.6%, respectively.

9.2 Previous initiatives

Nine previous initiatives[1-4,37-39,87,88] presenting guidelines surgical management were identified.

9.3 Development group comments

Vulvectomy in addition to radical local excision can be considered in tumours 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 tumour 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, since radiotherapy alone will probably not sterilize large nodal pelvic disease.

9.4 Guidelines

Local treatment

C	Radical local excision is recommended.
✓	Consider additional, more superficial resection of d-VIN in addition to radical local excision of invasive tumours.
✓	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 goal of excision is to obtain tumour-free pathological margins. Surgical excision margins of at least 1 cm are advised. It is acceptable to consider less wide margins where the tumour lies close to midline structures (clitoris, urethra, anus) and preservation of their function is desired.
✓	When invasive disease extends to the pathological excision margins of the primary tumour, reexcision is treatment of choice.
✓	Advanced stage patients should be evaluated in a multidisciplinary setting to determine the optimal choice and order of treatment modalities.

Groin treatment

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

Reconstructive surgery

✓	Availability of reconstructive surgical skills as part of the multidisciplinary team is required in early as well as advanced stage disease.

10 Sentinel lymph node procedure

10.1 Summary of available scientific evidence

Diagnostic test accuracy according to the mapping method: three meta-analyses[89-91] assessing the diagnostic accuracy of SLN biopsy were identified. Hassanzade *et al.*[89], Meads *et al.*[90], and Lawrie *et al.*[91] included 47 studies[92-138], 29 studies[97,98,109,110,113-120,124-126,129,135,136,139-148], and 34 studies[92,93,95,97-99,103,104,107,109,110,112,114-119,122-127,129,135,136,140-144,149-169], respectively. It should be noted that studies included in these meta-analyses had methodological limitations, such as lack of an adequate description of population (especially stage of disease), inclusion criteria, assessment procedure, and reference standard used. Data from different reports of the same study were also taken into account. **LoE 1-**

Two meta-analyses[89,90] reported pooled patient basis detection rate of various techniques and provided evidence that a combination of blue dye/99mTc is the most accurate technique (**Table 4**). It should to be noted that many of the studies taken into account by Meads *et al.*[90] were also included in the pooled analysis performed by Hassanzade *et al.*[89], which explains the consistency of results. Only Hassanzade *et al.*[89] published pooled groin basis detection rate data and observed that it was also higher with the use of the combined blue dye and 99mTc testing (**Table 4**).

Two of the three identified meta-analyses[89,91] described per patient and per groin pooled sensitivity of the SLN biopsy and provide evidence that a combination of blue dye/99mTc is also the most sensitive technique (**Table 4**). It should to be noted that many of the studies taken into account by Lawrie *et al.*[91] were also included in the pooled analysis performed by Hassanzade *et al.*[89], which explains the consistency of results.

Diagnostic test accuracy according to the location of the tumour: Hassanzade *et al.*[89] reported that diagnostic test accuracy of the SLN procedure is also related to location of the tumour. For midline lesions (≤ 2 cm of midline), per groin pooled detection rate was 22% lower than per patient pooled detection rate but groin basis pooled sensitivity was 4% higher than patient basis pooled sensitivity (**Table 5**). However, for lateral lesions (> 2 cm from the midline plane), per patient and per groin pooled detection rates and sensitivity were similar. **LoE 1-**

Diagnostic test accuracy according to the tumour size: Hassanzade *et al.*[89] observed that pooled patient basis sensitivity was also related to the size of the primary tumour. Indeed, the pooled sensitivity of SLN mapping in < 4 cm tumours was 7% higher than > 4 cm tumours (< 4 cm: 93% (95% CI = 87-97), > 4 cm: 86% (95% CI = 77-93)). It should be noted that, in the Groningen international study on sentinel nodes in vulvar cancer (GROINSS-V)[170], sentinel-node detection was done in patients with T1-T2 (< 4 cm) squamous-cell vulvar cancer. **LoE 1-**

Diagnostic test accuracy according to the inclusion of patients with palpable or suspicious inguinal nodes in the study population: Hassanzade *et al.*[89] observed that per patient and per groin pooled patient basis detection rate and sensitivy were lower among patients with palpable or suspicious inguinal nodes (**Table 5**). **LoE 1-**

Diagnostic accuracy of intraoperative pathologic analysis of frozen sections: as part of the GROINSS-V[170], frozen sectioning was done in 315 and showed a low sensitivity (48%) but a high specificity (100%). **LoE 2++**

In contrast, two older and smaller studies (52 patients[142] and 42 patients[141]) found sensitivity greater than 90%. It should be noted that these two studies[141,142] reported a specificity for intraoperative analysis of SLN by frozen section greater than 90%. In the fourth identified study[115], 18 positive nodes were detected in 13 of the 43 enrolled women (30.2%). In two cases, although the frozen section was negative, the definitive histopathologic examination revealed a micrometastasis **LoE 2+**

(accuracy: 98%).

Diagnostic test accuracy according to histological methods: only one of the three identified meta-analyses[91] described pooled estimates of sensitivity for the combined technique (blue dye/99mTc) according to histological methods: **LoE 1-**

- Ultrastaging only: 95% (95% CI = 91-97) (per groin data), 95% (95% CI = 89-98) (per patient data)
- Ultrastaging and/or immunohistochemistry (IHC): 94% (95% CI = 88-97) (per groin data), 95% (95% CI = 90-98) (per patient data)

In the GROINSS-V[170], ultrastaging detected a positive SLN in 55 (41%) of 135 patients (66 (40%) of 164 groins). After multiple sectioning, IHC identified micrometastases in 36 (12%) of 304 patients with a negative sentinel node. The risk of metastases in non-SLN was higher when the SLN was found to be positive by traditional pathologic processing than when the SLN was found to be positive only with ultrastaging (23 of 85 groins (27%) versus 3 of 56 groins (5%), p = 0.001). In Gynecologic oncology group (GOG) protocol 173[135], 23% of all positive SLNs were missed by routine H&E staining of SLN tissue cut and were only detected with the addition of immunohistochemical stains. **LoE 2++**

Nine smaller studies[50,54,58,65,67,77,84,112,118] have also reported micrometastases found after ultrastaging and/or IHC among patients that were previously negative with standard H&E. **LoE 2+**

Visualization of the SLN by scintigraphy: in GOG protocol 173, Coleman *et al.*[155] reported a negative correlation between distance of vulvar lesion from midline and the probability of detecting bilateral drainage in preoperative lymphoscintigraphy. Thirty percent of women with tumours invading or crossing the midline had unilateral drainage on lymphoscintigraphy. However, authors observed that more than one in five patients with lateralized primary tumours (> 2 cm from the midline) had bilateral drainage on lymphoscintigraphy. **LoE 2++**

Out of 42 patients with midline tumours enrolled in the retrospective review published by Lindell *et al.*[125], only 18 had bilateral lymphatic drainage at scintigram. The lymphoscintigraphy showed unilateral lymphatic drainage in 40 out of 58 patients, including all 16 patients with lateral lesions. Louis-Sylvestre *et al.*[157] found that of 13 patients with lesions less than 1 cm from the midline in whom lymphoscintigraphy identified only unilateral drainage, 3 patients had metastatic disease in nodes located in the contralateral, lymphoscintigraphy-negative groin. Six identified studies[102,117,118,160,171,172] assessed detection rate of the preoperative visualization of the SLN by scintigraphy and all of them reported a detection rate greater than 90%. **LoE 2+**

De Cicco *et al.*[97] used preoperative and intraoperative lymphoscintigraphy alone to successfully identify at least one sentinel node in each of the 37 patients in their series. There were no false-negative sentinel nodes. Eight patients had positive nodes, and the sentinel node was the only positive node in 5 of these cases. If lymphoscintigraphy did not identify a sentinel node in a groin, no metastases were found at surgery. Using a combination of preoperative lymphoscintigraphy and intraoperative lymphoscintigraphy, de Hullu *et al.*[98] reported that all the 23 patients with lateral lesions or with tumours primarily labial but came within 1 cm of the midline had unilateral SLN detected in the groin on preoperative lymphoscintigraphy and at the time of surgery.

In a very small study enrolling 10 patients, DeCesare *et al.*[93] showed that intraoperative lymphoscintigraphy correctly identified the nodal status as positive in all 4 cases of metastatic disease and negative in all 16 groins negative for metastases.

Impact of training and experience of the surgeon on the diagnostic accuracy: Several authors[118,120,145,173,174] have suggested surgeons should perform at least 10 successful SLN biopsy procedures followed by complete inguinofemoral lymph node dissection without any false-negative results prior to performing SLN biopsy alone. In order to keep the experience at a high level, van der Zee *et al.*[145] proposed that an exposure of at least five to 10 patients per year per surgeon should be regarded as a minimum figure, requiring potentially centralization of early-stage vulvar cancer treatment in oncology centres. **LoE 4**

As part of a prospective study enrolling 52 patients, Levenback *et al.*[142] reported that the number of cases in which the sentinel node is not identified or in which there is a false-negative sentinel node decreases with experience. Indeed, a sentinel node could not be identified in 4 of the 25 (16%) patients and 13 of the 36 (36%) groins dissected, compared with 2 of the 27 (7%) of patients treated and 6 of the 40 (15%) groins dissected during the first two years of the study (p = 0.034). **LoE 2+**

Recurrence and survival rates following SLN procedure: in the GROINSS-V[170], five-year disease-specific survival for patients with positive sentinel nodes was 64.9% when identified by routine pathology versus 92.1% when identified by ultrastaging (p < 0.0001). The update of the GROINSS-V-I[175] (377 patients) highlighted that on the long-term a significant proportion of patients will develop a local recurrence, regardless of sentinel node status and that these local recurrences may occur even a long time after primary treatment. This prospective study also showed that long-term survival is very good for patients with early-stage vulvar cancer and a negative sentinel node. After a median follow-up of 105 months, Te Grootenhuis *et al.*[175] reported an overall local recurrence rate of 24.6% at 5 years and 36.4% at 10 years for sentinel node negative patients, and 33.2% and 46.4% for sentinel node positive patients, respectively (p = 0.03). Disease-specific 10-year survival was 91% for sentinel node negative patients compared to 65% for sentinel node positive patients (p < 0.0001). Overall 5- and 10-year survival was also better for sentinel node negative patients (5y-OS: 81.2% versus 61.3%, 10y-OS: 68.6% versus 43.6%, p < 0.0001). **LoE 2++**

As part of a health technology assessment comparing SLN biopsy and inguinal lymph node dissection (ILND), Reade *et al.*[176] reported from 11 studies[93,96,113,114,117,132,145-147,177,178] enrolling 591 patients a groin recurrence rate after a negative SLN biopsy of 3.6% (range 0 to 22%). It should be noted that follow-up in these studies was variable, but in most was at least two years. A recurrence rate after ILND of 4.3% was also reported (13 studies[46,66-68,179-187] enrolling 1,077 patients). It should be noted that, in general, there was longer follow-up in these studies than in the studies of SLN biopsy.

Multivariate analyses performed from the surveillance, epidemiology, and end results database on 1,094 patients[188] showed that SLN biopsy was not significantly associated with an excess risk of mortality or recurrence after adjustment for age, ethnicity, stage, grade, and lymph node status (data not shown). **LoE 2-**

Complication rates & clinical parameters: Reade *et al.*[176] compared also complication rates between SLN biopsy (6 studies[113,117,120,145,146,178], 532 patients) and ILND (27 studies[46,66,68,73-76,78,82,85,117,120,145,178,179,182,183,186,189-197], 2,135 patients). Wound infection, wound breakdown, lymphocysts, and chronic lymphoedema after SLN biopsy were 4.4%, 9.5%, 3.8%, and 1.5%, respectively. The rate of groin wound infection after ILND across all studies was 30.7%, groin wound breakdown occurred in 23.2%, and lymphocysts occurred in 15.5%. Chronic lymphoedeman occurred in 22.9% accros all studies. **LoE 2++**

In a retrospective study enrolling 128 patients, Brammen *et al.*[171] reported also a higher presence of lymph cysts after ILND compared to SLN biopsy (OR = 3.4 (95% CI = 1.1-10.6), p = 0.02). In addition, three original studies[145,171,178] reported significantly higher operation time, hospital stay or duration of inguinal drainage after ILND (**Table 6**). **LoE 2+**

Quality of life: one study[198] investigated quality of life in 62 patients who participated in the GROINSS-V study. Using the EORTC QLQ-C30 questionnaire, no difference in overall quality of life was observed between the 35 patients who underwent the SLN-procedure alone and the 27 patients who underwent an inguinofemoral lymphadenectomy. The major difference was the increase in complaints of lymphoedema of the legs after inguinofemoral lymphadenectomy (p = 0.01). Patients who underwent inguinofemoral lymphadenectomy also reported more discomfort in groins, vulva and legs (p = 0.03), and more frequent need to wear stockings (p = 0.003). Patients after the SLN procedure only were more content with the treatment they had undergone (p = 0.04). Moreover, no differences in sexual activeness were observed between SLN procedure and inguinofemoral lymphadenectomy. **LoE 2+**

Two smaller studies[199,200] were also identified. As part of a prospective study enrolling 36 patients (12 SLN biopsy procedures and 24 inguinofemoral lymphadenectomies), Novackova *et al.*[199] observed an increased fatigue and impaired lymphoedema in patients after inguinofemoral lymphadenectomy. Among patients who underwent SLN biopsy procedures, none of the quality of life variables worsened postoperatively. In the second small study (5 SLN biopsy procedures and 10 inguinofemoral lymphadenectomies), Former *et al.*[200] found that inguinofemoral lymphadenectomy had a negative impact on sexual function. **LoE 2-**

Preferences of patients/acceptance of the SLN procedure: three identified studies[198,201,202] assessed the preferences of women for SLN procedure versus inguinofemoral lymphadenectomy in the treatment of vulvar cancer. Acceptance of the SLN procedure depended on the false-negative rate: **LoE 2+**

- Oonk *et al.*[198]: when the false-negative rate was stated as 10%, 84% of patients who underwent a SLN procedure would recommend it, whereas only 48% of the patients who required the inguinofemoral lymphadenectomy advised it (p = 0.005). These differences were also observed with a suggested false-negative rate of 1% (97% versus 62%, p = 0.001) and 0.1% (97% versus 71%, p = 0.013).

- de Hullu *et al.*[201]: sixty-six per cent of the patients who had undergone inguinofemoral lymphadenectomy would recommend an inguinofemoral lymphadenectomy if the possibility of missing a lymph node metastasis with the SLN procedure was one out of 80 patients, while this proportion increased to 84% if the estimated risk was 10 out of 80. Their preference was not related to age or the side-effects they had experienced. Investigators also assessed the preferences on the acceptable false-negative rate of the SLN procedure in gynecologists treating patients with vulvar cancer. Sixty per cent of gynecologists were willing to accept a 5-20% false-negative rate of the SLN procedure.

- Farrell *et al.*[202]: if the risk of missing a positive lymph node was higher than 1 in 100, 80% of patients who had undergone inguinofemoral lymphadenectomy chose inguinofemoral lymphadenectomy and 15% of patients chose a SLN procedure (5% of patients were unable to make a decision). An association has been reported between the choice inguinofemoral lymphadenectomy or SLN procedure and the severity of lymphoedema. Of the 48 women choosing inguinofemoral lymphadenectomy, 4 reported moderate or severe lymphoedema, whereas of the 9 women choosing SLN procedure, 3 reported moderate or severe lymphoedema (p = 0.04). But if the risk of missing a positive lymph node was lower than 1 in 100, almost one third of the women would prefer sentinel node biopsy.

10.2 Previous initiatives

Four previous initiatives[2,3,39,88,203] presenting guidelines on SLN procedure were identified.

10.3 Development group comments

In tumours 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.

10.4 Guidelines

B	The sentinel lymph node procedure is recommended in patients with unifocal cancers of < 4 cm, without suspicious groin nodes.
B	Use of radioactive tracer is mandatory, use of blue dye is optional.
C	Lymphoscintigram is advised to enable the preoperative identification, location and number of sentinel lymph nodes.
C	Intraoperative evaluation and/or frozen sectioning of the sentinel lymph node 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.
✓	When a sentinel lymph node is not found (method failure), inguinofemoral lymphadenectomy should be performed.
C	Where metastatic disease is identified in the sentinel lymph node (any size): inguinofemoral lymphadenectomy in the groin with the metastatic sentinel lymph node.
✓	For tumours involving the midline: bilateral sentinel lymph node detection is mandatory. Where only unilateral sentinel lymph node detection is achieved, an inguinofemoral lymphadenectomy in the contralateral groin should be performed.
C	Pathological evaluation of sentinel lymph nodes should include serial sectioning at levels of at least every 200 µm. If the H&E sections are negative, immunohistochemistry should be performed.

Table 4. Pooled data on the test accuracy of various techniques for SLN assessment

Author[reference]	Year	Blue dye	99mTc	Blue dye/99mTc	Fluorescent materials with near infrared imaging
Detection rate *(patient basis)*					
Hassanzade *et al.*[89]	2013	78% (95% CI = 66-86)	94% (95% CI = 89-96)	95% (95% CI = 92-97)	85% (95% CI = 68-94)
Meads *et al.*[90]	2014	68.7% (95% CI = 63.1-74.0)	94.0% (95% CI = 90.5-96.4)	97.7% (95% CI = 96.6-98.5)	NA
Detection rate *(groin basis)*					
Hassanzade *et al.*[89]	2013	72% (95% CI = 62-80)	88% (95% CI = 81-92)	91% (95% CI = 87-94)	85% (95% CI = 64-95)
Sensitivity *(patient basis)*					
Hassanzade *et al.*[89]	2013	89% (95% CI = 65-99)	91% (95% CI = 81-96)	95% (95% CI = 92-98)	NA
Lawrie *et al.*[91]	2014	94% (95% CI = 69-99)	93% (95% CI = 89-96)	95% (95% CI = 89-97)	NA
Sensitivity *(groin basis)*					
Hassanzade *et al.*[89]	2013	86% (95% CI = 65-97)	95% (95% CI = 87-99)	95% (95% CI = 91-97)	NA
Lawrie *et al.*[91]	2014	92% (95% CI = 82-97)	91% (95% CI = 87-94)	94% (95% CI = 88-97)	NA

NA: not available

Table 5. Pooled data pulished by Hassanzade *et al.*[89] on the test accuracy of SLN biopsy according to location of the tumour and inclusion of patients with palpable or suspicious inguinal nodes in the study population)

Test accuracy	Location of the tumour		Inclusion of patients with palpable or suspicious inguinal nodes	
	Lateral tumours	Midline tumours	Yes	No
Detection rate *(patient basis)*	93% (95% CI = 88-96)	95% (95% CI = 92-97)	92% (95% CI = 86-96	95% (95% CI = 92-97)
Detection rate *(groin basis)*	93% (95% CI = 88-96)	73% (95% CI = 67-78)	77% (95% CI = 63-88)	82% (95% CI = 76-87)
Sensitivity *(patient basis)*	92% (95% CI = 79-98)	90% (95% CI = 87-93)	90% (95% CI = 82-96)	92% (95% CI = 88-95)
Sensitivity *(groin basis)*	91% (95% CI = 75-98)	94% (95% CI = 91-97)	90% (95% CI = 78-97)	92% (95% CI = 89-95)

Table 6. Original studies presenting clinical parameters in patients treated by SLNB versus ILND

Author[reference]	Year	N	SLN biopsy	ILND	p-value
Operation time					
Brammen *et al.*[171]	2015	128	76.2 min[1]	103.3 min[1]	< 0.001
Hefler *et al.*[178]	2008	75	85.5 min	120.7 min	0.002
Hospital stay					
Brammen *et al.*[171]	2015	128	13.3 days	18.1 days	0.006
Hefler *et al.*[178]	2008	75	12.6 days	22.9 days	< 0.001
van der Zee *et al.*[145]	2008	403	8.4 days[2]	13.7 days[2]	< 0.0001
Inguinal drainage					
Brammen *et al.*[171]	2015	128	4.1 days	6.9 days	< 0.001
Hefler *et al.*[178]	2008	75	3.3 days	6.9 days	< 0.001

[1] mean value, [2] median value

11 Radiation therapy

11.1 Summary of available scientific evidence

Primary radiotherapy of the groin: as part of Cochrane systematic review, van der Velden *et al.*[204] compared the effectiveness and safety of this therapeutic approach to the inguino-femoral lymph nodes with primary groin surgery. One randomised controlled trial[205], one case-control[206] and two observational[186,207] studies have been included in this review. No pooled analysis is described and it should be noted that two studies also included patients with non-squamous histology[206,207]. The tumour recurrence rate in the groin after primary groin radiation ranged from 0% to 18.5% (**Table 7**). However, only the randomised controlled trial[205] directly compared radiotherapy towards the groin versus surgery. In this trial, there is a difference in groin recurrence, favouring the primary groin surgery (0% versus 18.5%). Overall survival and progression-free survival were significantly lower in the radiation group compared with the surgery group (p = 0.04 and p = 0.03, respectively). But, the patients treated with groin radiation had substantially shorter hospitalizations than those who underwent groin surgery (p = 0.0001). It should be noted that this trial was closed prematurely when interim monitoring revealed an excessive number of groin relapses on the groin radiation regimen. Criticisms could be made of the technique of radiotherapy applied in this trial (potential insufficiency to sterilise subclinical lymph node metastases in the groin). Maximum dose was prescribed at 3 cm in this trial. It is likely, therefore, that the deeper groin nodes were relatively undertreated.

LoE 1-

Neoadjuvant radiotherapy: no studies enrolling at least 50 patients were identified. Interpretation of the results from the 8 identified trials[208-215] are limited notably by the small number of patients evaluated (only 3 trials[208-210] have accrued in excess of 10 patients) and by the heterogeneity in the radiotherapy regimens (external beam radiation and/or intracavitary brachytherapy). Although studies are very small, authors reported low severe complications and high proportions of patients alive with no evidence of disease and no recurrence (**Table 8**). Furthermore, this combined therapeutic approach showed a good probability of bladder and/or rectal preservation.

LoE 3

Adjuvant radiotherapy (close surgical margins or positive margins): Faul *et al.*[216] reported a reduction of local recurrence from 58% to 16% in these patients treated with adjuvant radiation therapy. On multivariate analysis, adjuvant radiation was a significant prognostic predictor for local control (p = 0.009). However, it did not reach statistical significance for overall survival. On subgroup analysis, adjuvant radiation therapy significantly improved actuarial 5-year survival for patients with positive margins (p = 0.001), but not for those with close margins (p = 0.63).

LoE 2+

Adjuvant radiotherapy (no suspicious groin nodes): Stehman *et al.*[205] randomised 58 patients patients with lesions clinically confined to the vulva and no suspicious groin nodes to either radical vulvectomy followed by either groin radiation or inguinal lymphadenectomy (plus groin radiation if nodes were involved) to compare efficacy and morbidity of the two treatment approaches. The groins were treated daily to a dose of 50 Gy over 5 weeks (200 cGy/d). Patients randomised to the groin dissection arm who where found to have metastatic carcinoma in the resected nodes received post-operative radiation therapy to the ipsilateral groin and hemipelvis. A total dose of 50 Gy was administered through anterior portals to the groin and through anterior and posterior portals to the iliac nodes. The study was closed prematurely when interim monitoring revealed an excessive number of groin relapses on the groin radiation regimen (see above).

LoE 1-

Adjuvant radiotherapy (single positive node): the benefit of adjuvant radiation in patients with a single lymph node metastasis and micrometastatic disease to the lymph nodes is controversial. Fons *et al.*[217] could not demonstrate a significant benefit of adjuvant radiotherapy in these patients on both disease-free and disease-specific survival (HR = 0.98, 95% CI = 0.45-2.14, p = 0.97 and HR = 1.02, 95% CI = 0.42-2.47, p = 0.96). Recurrence rates appeared quite similar between the radiotherapy

LoE 2+

and the no-radiotherapy group (39% *versus* 32%). In multivariate subanalysis performed as part of the AGO-CaRE-1 study[218] (163 patients), adjuvant radiotherapy was associated with a not statistically significant better PFS compared to patients without adjuvant treatment (adjustment for age, Eastern cooperative oncology group (ECOG) performance status, Union internationale contre le cancer (UICC) stage, grade, and invasion depth: HR = 0.88, 95% CI = 0.50-1.56, p = 0.67). Similar results were obtained after control for multiple confounding factors by inverse probability of treatment weighting (HR_{IPTW} = 0.93, 95% CI = 0.51-1.67, p = 0.79).

Parthasarathy *et al.*[219] have for their part reported a favourable 5-y disease specific survival (DSS) in patients receiving adjuvant radiation. Controlling for age at diagnosis and extent of lymphadenectomy, their data suggest that adjuvant radiation may improve the survival of these patients although this only reached borderline statistical significance (HR = 0.57, 95% CI = 0.32-1.03, p = 0.06). However, it should be noted that no information about the size and location of tumour is available in this study. Moreover, adjuvant radiation did not significantly benefit women who had more than 12 nodes resected (66.7 versus 77.3%, p = 0.23).

Adjuvant radiotherapy (multiple positive nodes): a randomised trial compared pelvic radiotherapy with pelvic lymphadenectomy in 114 patients with inguinofemoral lymph node metastases after radical vulvectomy and bilateral inguinofemoral lymphadenectomy[220]. The difference in regional (groin) recurrence was significant, favouring the adjunctive radiation therapy group (5.1% versus 23.6%, p = 0.02). Survival proved also to be better in the patients who received postoperative radiotherapy (overall survival (p = 0.03), relative survival (0.004), progression-free interval (0.03)). In this study, the most dramatic survival advantage for radiation therapy was in patients who had either of the two major poor prognostic factors present: 1) clinically suspicious or fixed ulcerated groin nodes, and 2) two or more positive groin nodes. The long time results of this trial revealed a persistent benefit for patients treated with pelvic irradiation[221]. **LoE 1+**

After a median survival follow-up of 74 months, the OS benefit for radiation in patients with clinically suspected or fixed ulcerated groin nodes (p = 0.04) and two or more positive groin nodes (p < 0.001) persisted. The relative risk of progression was significantly reduced in radiation patients (HR = 0.39, 95% CI = 0.17-0.88, p = 0.02) after adjustment for age and adverse tumour characteristics. Moreover, the cancer-related death rate was significantly higher for pelvic node resection compared with radiation (HR = 0.49, 95% CI = 0.28-0.87, p = 0.015). The proportion of patients developing post-operative wound infections, urinary tract infection, and other adverse sequelae were similar between treatment approaches. However, it should be noted that patients with positive groin nodes in the surgery group in this study did not receive adjuvant radiotherapy to the groins.

In multivariate analysis of different nodal subgroups performed as part of the AGO-CaRE-1 study[218] (adjustment for age, ECOG performance status, UICC stage, grade, and invasion depth) adjuvant radiotherapy was associated with statistically significant better progression-free survival (PFS) in patients with two positive nodes (91 patients, HR = 0.31, 95 CI 0.14-0.71, p = 0.005), and in patients with three positive nodes (56 patients, HR = 0.40, 95% CI = 0.16-0.98, p = 0.05) compared to patients without adjuvant treatment. Similar results were obtained after control for multiple confounding factors by inverse probability of treatment weighting (two positive nodes: HR_{IPTW} = 0.24, 95% CI = 0.11-0.56, p < 0.001; three positive nodes: HP_{IPTW} = 0.32, 95% CI = 0.13-0.79, p = 0.009). The benefit of adjuvant radiotherapy among patients with more than three positive nodes did not reach statistical significance (21 patients, HR = 0.52, 95% CI = 0.24-1.10, p = 0.09/HR_{IPTW} = 0.44, 95% CI = 0.17-1.17, p = 0.10). **LoE 2+**

11.2 Previous initiatives

Eight previous initiatives[1-4,37-39,87] presenting guidelines on radiation therapy were identified.

11.3 Development group comments

When possible without damaging structures such as anus, urethra and clitoris, reexcision 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.

11.4 Guidelines

✓ Adjuvant radiotherapy should start as soon as possible, preferably within 6 weeks of surgical treatment.

✓ When invasive disease extends to the pathological excision margins of the primary tumour, and further surgical excision is not possible, postoperative radiotherapy should be performed.

✓ 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.

B Postoperative radiotherapy to the groin is recommended for cases with > 1 metastatic lymph node and/or presence of extracapsular lymph node involvement.

✓ Adjuvant radiotherapy for metastatic groin nodes should include the ipsilateral groin area and where pelvic nodes are non-suspicious on imaging, the distal part of the iliac nodes with an upper limit at the level of the bifurcation of the common iliac artery.

C Based on evidence from other squamous cell cancers such as cervical, head & neck, and anal cancer, the addition of concomitant, radiosensitising chemotherapy to adjuvant radiotherapy should be considered.

Table 7. Original studies presenting data in patients treated with primary groin radiation

Author[reference]	Year	N	Radiotherapy regimen	Groin recurrence	Survival
Stehman *et al.*[205]	1992	52	Dose: 50 Gy at 3 cm Type: 50% electrons	Radiation: 18.5% (5/27) Surgery: 0% (0/25)	Median follow-up: > 36 months OS: 60% versus 86% DSS: 67% versus 92% DFS: 68% versus 92%
Manavi *et al.*[206]	1997	135	Dose: 45 Gy at 5 cm Type: telecobalt	Radiation: 4.6% (6/65) No radiation: 10% (7/70)	Follow-up: NA 5y-OS: 62.4% versus 93.7%
Katz *et al.*[186]	2003	14	Dose: 45 Gy Type: electrons and photons combined	0% (0/14)	Median follow-up: 98 months
Perez *et al.*[207]	1998	19	Dose: 50-70 Gy at 4 cm Type: photons (electron boost)	10.5% (2/19)	Median follow-up: 60 months

5y-OS: 5-year overall survival, DFS: disease-free survival, DSS: disease-specific survival, Gy: Gray, NA: not available, OS: overall survival.

Table 8. Original studies presenting data in patients treated with neoadjuvant radiation

Author[reference]	Year	N	Radiotherapy regimen	Recurrence	Survival/complications
Boronow *et al.*[208]	1987	37	External beam and intracavitary: N = 22 Intracavitary only: N = 12 External beam only: N = 3	Local: N = 5 Pelvic: N = 1	Median follow-up: 38.4 months Status: 59.5% (22/37) alive NED Severe complications: 23%
Balat *et al.*[209]	2000	24	External beam: N = 24	Local: N = 5 Distant: N = 1	Median follow-up: NA Status: 70.8% (17/24) alive NED Severe complications: NA
Rotmensch *et al.*[210]	1990	16	External beam: N = 16	Central: N = 4 Distant: N = 2	Median follow-up: 25 months Status: 56,3% (9/16) alive NED Severe complications: 4%
Hacker *et al.*[211]	1984	8	External beam and intracavitary: N = 1 External beam only: N = 7	NA	Median follow-up: NA Status: 62.5% (5/8) alive NED Severe complications: 12%
Jafari *et al.*[212]	1981	4	External beam: N = 4	Local: N = 0 Distant: N = 0	Median follow-up: NA Status: 100% (4/4) alive NED Severe complications: 0%
Fairey *et al.*[213]	1985	7	External beam: N = 7	Local: N = 1 Distant: N = 1	Median follow-up: NA Status: 85.7% (6/7) alive NED Severe complications: 14%
Carlino *et al.*[214]	1984	6	Intracavitary: N = 6	Local: N = 2	Median follow-up: NA Status: NA Severe complications: NA
Pao *et al.*[215]	1988	2	NA	NA	Median follow-up: NA Status: 100% (2/2) alive NED Severe complications: 0%

NA: not available, NED: no evidence of disease and no recurrence.

12 Chemoradiation

12.1 Summary of available scientific evidence

Primary chemoradiation: as part of Cochrane systematic review, Shylasree *et al.*[222] evaluated the effectiveness and safety of neoadjuvant and primary chemoradiation for women with LAVC. Among the 3 studies included in this review[223-225], only two retrospective studies[224,225] looked at primary chemoradiation versus primary surgery. It should be noted that no pooled analysis is described. The number of cases of tumour recurrence and deaths were too small in one study[225] to allow computing an adjusted hazard ratio (the confidence interval was non-informative for all combinations of covariate adjustment). In the second retrospective study, Landrum *et al.*[224] compared outcomes of 63 patients with LAVC treated by primary surgery (N = 30) of by primary chemoradiation (N = 33). The general schema for chemoradiation involved weekly cisplatin (40 mg/m²) or two cycles of cisplatin (50 mg/m²) plus 5-FU (1,000 mg/m²) concurrent with external beam radiation. The radiation fraction size was generally 160-180 cGy delivered in a once-daily fraction with a median dose of 4,760 cGy (range 3,690-6,300 cGy) to the whole pelvis and primary vulvar site, with additional radiation to the inguinal regions as directed by nodal status. Patients were managed surgically with radical (N = 11) or modified radical vulvectomy (N = 19) when adequate surgical margins could be obtained without urinary or colonic diversion. Adjuvant radiation or chemoradiation was completed in 19 of 25 patients in the primary surgery group with lymph node metastasis. Eight patients had surgical excision of residual disease following primary chemoradiation. **LoE 2+**

At a median follow-up of 31 months, there was no statistically significant difference in the risk of death in patients with LAVC between patients who received primary chemoradiation and those who received primary surgery, after adjustment for age, FIGO stage, size of tumour and nodal status (HR = 1.09, 95% CI = 0.37-3.17, p > 0.05). Recurrence or PFS was not reported in a multivariate analysis in this study. However, the authors reported no statistically significant difference in recurrence rate based on treatment group (5 in the chemoradiation arm versus 7 in the primary surgery arm, p > 0.05). Four patients that were treated with primary chemoradiation only had a partial response to treatment and died of the disease.

An another study enrolling at least 50 patients has been identified. In a GOG phase II study including 58 patients with LAVC not amenable to surgical resection (radical vulvectomy), Moore *et al.*[226] assessed the efficacy and toxicity of radiation therapy and concurrent chemotherapy when used for the primary treatment. Radiation was given daily, five days per week in 1.8 Gy fractions to a total dose of 57.6 Gy. Patients received concurrent cisplatin (40 mg/m² to maximum dose 70 mg) chemotherapy administered weekly throughout radiation therapy. Patients only underwent radical surgical resection after chemoradiation if they had residual disease present on biopsy. After a median follow-up of 24 months, 37 patients (64%) achieved a cCR. Among these patients there were 29 (50%) who underwent surgical biopsy and had a pCR (**Table 9**). Twenty-two of these 29 patients continued to have no evidence of disease, while 7 patients experienced recurrence. Of the 29 patients who had persistent disease after chemoradiation and who underwent surgical resection, 8 (28%) were alive at last follow-up with no evidence of disease recurrence. Although acute toxicity was significant, the protocol was considered tolerable.

Results from the 16 other identified studies[227-242] are limited notably by the small number of patients evaluated (only 2 trials[231,232] have accrued in excess of 20 patients) and by the heterogeneity in the primary chemoradiation regimens. Although studies are small, chemoradiation as a primary therapeutic approach has been reported to produce high response rates (**Table 9**). **LoE 3**

Neoadjuvant chemoradiation: among the 3 studies[223-225] included in the Cochrane systematic review published by Shylasree *et al.*[222], only one study[223] looked at neoadjuvant chemoradiation versus **LoE 1-**

primary surgery. In this randomised controlled trial, 68 women with operable LAVC were randomised to either primary radical surgery followed by radiation if more than one groin lymph node contained metastatic disease, or to neoadjuvant chemoradiation followed by surgery. Chemoradiation comprised 50 Gy neoadjuvant radiotherapy with concurrent infusional 5-FU 750 mg/m² days 1-5 and Mitomycin-C 15 mg/m² IV day 1, with two courses given three weeks apart. In the primary surgery arm, 15 (15/37) patients underwent adjuvant radiation. Surgery was feasible in 24 out of 28 patients in the neoadjuvant arm. At a mean follow-up of 42 months, thirty recurrences have been reported (13 in the neoadjuvant chemoradiation arm and 17 in the primary surgery arm). The authors reported no statistically significant difference in the risk of death at 5 years between the two therapeutic approaches (RR = 1.39, 95% CI = 0.94-2.06, p > 0.05). Furthermore, no statistically significant difference in the risk of overall treatment related morbidity was found (RR = 1.18, 95% CI = 0.71-1.96, p > 0.05). It should be noted that details regarding the extent of primary tumour and the complexity of surgical procedures required in each group are not provided, and quality of life is not reported.

Two other original studies[243,244] enrolling at least 50 patients were identified. In a GOG phase II study including 71 patients with unresectable vulvar disease, or disease requiring exenterations, Moore *et al.*[243] investigated the role of concurrent radiotherapy and cisplatin/infusional 5-FU chemotherapy. A cCR occurred in 47% of patients. Among those patients who had surgery, 70% had a pCR. Two of 71 patients had unresectable disease after chemoradiation, and three patients required exenteration. After a median follow-up of 50 months, 40 patients were alive with no evidence of disease and no recurrence (**Table 10**). Toxicity from chemoradiation was estimated acceptable, although acute cutaneous reactions were almost universal. In the second identified study[244], 58 patients referring for primary or recurrent disease received preoperative radiotherapy to a dose of 54 Gy (divided into two courses with an interval of two weeks). Concurrent preoperative chemotherapy with 5-FU (750 mg/m² daily for 5 days) and Mitomycin-C (15 mg/m² single bolus) were given at the start of each cycle. A cCR of both the vulvar and inguinal disease occurred in 27% of patients. A pCR was confirmed in 13 patients (31%). After a median follow-up of 22 months, 28 patients were alive with no evidence of disease and no recurrence (**Table 10**). Like the GOG phase II study[243], treatment side effects were estimated acceptable.

LoE 2+

As part of a meta-analysis including 7 studies[229,234,237,245-248] for a total of 70 patients, Stuckey *et al.*[249] investigated whether elderly patients are more likely to die of intercurrent disease or of treatment complications. It should be noted that Stuckey *et al.*[249] included patients receiving preoperative or primary chemoradiation treatment with curative intent even if in the majority of cases, this was given with neoadjuvant intent. Radiation doses ranged from 18 to 72 Gy and included the vulvar, inguinal, and the pelvic regions. Chemotherapy included 5-FU with or without cisplatin or Mitomycin-C (**Table 11**). Seventy-eight percent of patients younger than 65 years were without evidence of disease after treatment versus 66% of patients aged 65 years and above. Three percent of patients younger than 65 years of age died of intercurrent disease or treatment-related complications versus 11% of patients aged 65 years and above. But these differences did not reach statistical significance (p = 0.30 and p = 0.37, respectively). It should be noted that 1) the small sample size from included studies and 2) the changes in radiation therapy techniques and chemotherapy could make it difficult to statistically support the trend showing that elderly patients have lower survival and higher intercurrent death.

LoE 1-

Results from the 11 other identified studies[233,242,245-247,250-255] are limited notably by the small number of patients evaluated (only 4 studies[242,250,252,253] have accrued in excess of 20 patients) and by the heterogeneity in the chemotherapy regimens used in the neoadjuvant setting along with radiation therapy (**Table 10**). Although studies are small, chemoradiation as a neoadjuvant therapeutic approach has been reported to produce high response rates and high rates of surgical resectability without exenteration, regardless of chemotherapy regimen used. Overall, authors described high but

LoE 3

manageable rates of vulvar cutaneous toxicity.

Adjuvant chemoradiation: only one study[256] enrolling at least 50 patients was identified. As part of a large population-base analysis, Gill *et al.*[256] evaluated adjuvant chemotherapy for node-positive vulvar cancer patients who received adjuvant radiotherapy. All patients (N = 1,797) received external beam radiotherapy as their radiotherapy treatment modality. Radiation modality was available for 35.7% of patients. For those with modality captured, intensity-modulated radiotherapy was utilized in 6.5%. Median radiotherapy dose was 54 Gy. Median radiation length and time to chemotherapy initiation were 44 days and 76 days, respectively. Of patients receiving chemotherapy, 78.5% started chemotherapy within 7 days of the start of radiotherapy. **LoE 2-**

After a median follow-up of 28.3 months, the unadjusted median survival without (N = 1,324) and with adjuvant chemotherapy (N = 473) was 29.7 months and 44 months (p = 0.001), respectively. On multivariate analysis, delivery of adjuvant chemotherapy resulted in a trend towards reduction in the risk of death among patients who received adjuvant radiotherapy (HR = 0.81, 95% CI = 0.65-1.01, p = 0.059). On regression modeling with an adjustment using propensity score with IPTW, Gill *et al.*[256] reported a statistically significant reduction in the risk of death for patients who received adjuvant chemotherapy (HR_{IPTW} = 0.62, 95% CI = 0.48-0.79, p < 0.001).

Results from the 4 other identified studies[225,230,231,236] are limited notably by the very small number of patients evaluated. No study has accrued in excess of 10 patients (**Table 12**). **LoE 3**

12.2 Previous initiatives

Seven previous initiatives[1,2,4,37-39,87] presenting guidelines on chemoradiation were identified.

12.3 Development group comments

None.

12.4 Guidelines

C Definitive chemoradiation (with radiation dose escalation) is the treatment of choice in patients with unresectable disease.

C In advanced stage disease neoadjuvant chemoradiation should be considered in order to avoid exenterative surgery.

C Radiosensitising chemotherapy, preferably with weekly cisplatin, is recommended.

Table 9. Original studies presenting response and survival data in patients treated with primary chemoradiation

Author[reference]	Year	N	Chemotherapy regimen	Radiotherapy regimen	Response	Survival
Moore *et al.*[a,226]	2012	LAVC: N = 58	Weekly CisP 40 mg/m² IV, up to 7 cycles	57.6 Gy in 1.8 Gy daily fractions	cCR: 64% (37/58) pCR: 50% (29/58)	Median follow-up: 24 months Status: 51% (30/58) alive NED Recurr. 24% (7/29) with pCR
Landrum *et al.*[224]	2008	LAVC: N = 33	Either weekly CisP 40 mg/m² or two cycles of CiSP 50 mg/m² IV d1 + 5-FU 1,000 mg/m² IV d1-4	47.6 Gy in 1.8 Gy daily fractions	CR: 87% (29/33)	Median follow-up: 31 months Status: NA Recurr.: 17% (5/29) with CR
Mak *et al.*[231]	2011	LAVC : N = 24	Either weekly CisP or 3-4 week 5-FU based regimens	50 Gy, timing of fractions varied	CR: 58% (20/34)[b]	Median follow-up: 31.5 months Status: NA Recurr.: NA
Leiserowitz *et al.*[232]	1997	LAVC : N = 23	5-FU 1,000 mg/m² infusion d1-4 + CisP 100 mg/m² IV d2, given 2-3 times during radiotherapy	Vulvar and inguinal region. 54 Gy in 1.8 Gy BID fractions	CR : 78% (18/23)	Mean follow-up: 45 months Status: 60% (14/23) alive NED Recurr.: 17% (4/23)
Tans *et al.*[228]	2011	LAVC : N = 20	5-FU 1,000 mg/m² infusion d1-4 + MMC 10 mg/m² IV d1, given first week of each course of radiotherpay	Split course 40 Gy + 20 Gy in 2 Gy fractions with 2-week break	CR: 70% (14/20)	Median follow-up: NA Status: NA Recurr.: NA
Wahlen *et al.*[234]	1995	LAVC : N = 19	5-FU 1,000 mg/m² infusion d1-4 given weeks 1 + 5 of radiotherapy. Six pts also given MMC 10 mg/m² IV d1	45-50 Gy in 1.8 Gy daily fractions + implant or electron boost to vulva	CR: 52% (10/19) PR : 36% (7/19)	Median follow-up: 34 months Status: 79% (15/19) alive NED Recurr.: 10% (1/10) with CR
Russel *et al.*[229]	1992	LAVC: N = 18	5-FU 750-1,000 mg/m² infusion d1-4 + CisP 100 mg/m² IV d1, 2-3 cycles given	54 Gy for macro and 36 Gy for microscopic disease	CR: 50% (9/18) pCR: 44% (8/18) PR: 6% (1/18)	Median follow-up: 24 months Status: 67% (12/18) alive NED Recurr.: 11% (2/18)
Sebag-Montefiore *et al.*[227]	1994	LAVC: N = 16	5-FU 750 mg/m² infusion d1–5 + MMC 10 mg/m2 IV d1, given first 5 d and last 5 d of radiotherapy	45 Gy in 2-2.5 Gy daily fractions	CR : 44% (7/16) PR : 37% (6/16)	Follow-up: NA Status: NA Recurr.: NA
Koh *et al.*[233]	1993	LAVC: N = 14	5-FU 750-1,000 mg/m² IV infusion d1-4, weekly for 3 cycles	54 Gy in either daily or BID fractions	CR: 57% (8/14) PR: 36% (5/14)	Median follow-up: 27 months Status: 50% (7/14) alive NED Recurr. 7% (1/14)
Cunningham *et al.*[235]	1997	LAVC : N = 14	5-FU 1000 mg/m² infusion d1-4 + CisP 50 mg/m² d1, given on first and last week of radiotherapy	45-50 Gy plus vulvar boost of 9-14 Gy	CR : 64% (9/14) PR : 29% (4/14)	Mean follow-up: 26 months Status: 28% (4/14) alive NED Recurr. : 11% (1/9) with CR
Iversen *et al.*[238]	1982	LAVC: N = 9 Recur.: N =4	Bleo 30 mg IM d 1, 3, 5 repeated after 2 weeks	36-40 Gy in 3 Gy daily fractions	NA	Follow-up: 112 months Status: 30% (4/13) alive NED Recurr. : NA

[a] Radiotherapy given to the vulva, groin and pelvis unless otherwise stated, [b] treatment response among the 34 patients treated with initial chemoradiation (data not available for patients treated by primary chemoradiation specifically), 5-FU: 5-fluorouracil, cCR: clinical complete response, CR: complete response, CisP: cisplatin, Gy: Gray, LAVC: locally advanced vulvar cancer, MMC: mitomycin C, NA: not available, NED: no evidence of disease and no recurrence, pCR: pathologic complete response, PR: partial response, Recurr.: recurrence.

Original studies presenting response and survival data in patients treated with primary chemoradiation *(continued)*

Author[reference]	Year	N	Chemotherapy regimen	Radiotherapy regimen	Response	Survival
Han *et al.*[236]	2000	LAVC : N = 12	5-FU 1,000 mg/m² infusion d1-4 + MMC 10 mg/m² IV d1, given week 1 and 5 of radiotherapy	45 Gy (vulva, pelvic and inguinal lymph nodes), 6-17 Gy to gross disease	CR: 42% (5/12) PR: 58% (7/12)	Follow-up: NA Status: NA Recurr.: NA
Berek *et al.*[a,237]	1991	LAVC: N = 12	5-FU 1,000 mg/m² infusion d1-4 + CisP 100 mg/m² d1 every 28 d for 2 cycles	40-52 Gy in 1.6-1.8 Gy daily fractions, with boost to vulva (up to 74 Gy)	CR: 67% (8/12) PR: 25% (3/12)	Median follow-up: 37 months Status: 83% (10/12) alive NED Recurr. : 17% (2/12)
Akl *et al.*[239]	2000	NA: N = 12	5-FU 1,000 mg/m²/24h as continuous infusion days 1–4 and 29-32 + MMC 15 mg/m² IV day 1	Vulva only (all pts node negative). 30–36 Gy in 2 Gy daily fractions	CR: 100% (12/12)	Mean follow-up: 41 months Status: 66% (8/12) alive NED Recurr.: 16% (2/12)
Thomas *et al.*[230]	1989	LAVC: N = 9	5-FU 1,000 mg/m² infusion d1-4 ± MMC 6 mg/m² (4/6 one injection, and 2/6 two injections 4 weeks apart)	40-64 Gy in 1.6-1.8 Gy twice daily fractions	CR: 67% (6/9)	Median follow-up: 20 months Status: 67% (6/9) alive NED Recurr.: NA
Beriwal *et al.* [242]	2013	LAVC: N = 9	CisP 40 mg/m² d1 (N = 6) and 5-FU 1,000 mg/m² infusion, d1-5 (N = 36). Two cycles, given the first and last week of radiotherapy	IMRT 46 Gy in 1.6 Gy BID fractions for 5d, then 1.8 Gy daily for 7-8d then a break of 10-14 d, then 1.6 Gy BID for 5 d	cCR: 44.4% (4/9)	Follow-up: NA Status: NA Recurr.: NA
Mulayim *et al.*[225]	2004	LAVC : N = 7	5-FU 1,000 mg/m² infusion d1-4 + MMC 10 mg/m² IV d1, given weeks 1 and 4 of radiotherapy	60 Gy for macro and 45 Gy for microscopic disease	CR: 85% (6/7)	Median follow-up: 31 months Status: 42% (3/7) alive NED Recurr.: 28% (2/7)
Evans *et al.*[a,240]	1988	LAVC: N = 4	5-FU 1,000 mg/m² continous infusion d1-4 + MMC 10 mg/m² IV d1	25-50 Gy in 2 Gy daily fractions	CR: 50% (2/4) PR: 50% (2/4)	Mean follow-up: 33 months Status: 50% (2/4) alive NED Recurr.: 0% (0/3)
Kalra *et al.*[a,241]	1985	LAVC: N = 2	MMC 10 mg/m² IV d1 + 5-FU 1,000mg/m² infusion d1-5, given weeks 1 and 4 of radiotherapy	50 Gy in 2 Gy daily fractions	CR: 100% (2/2)	Mean follow-up: 33 months Status: 100% (2/2) alive NED Recurr.: 0% (0/2)

[a] Radiotherapy given to the vulva, groin and pelvis unless otherwise stated, 5-FU: 5-fluorouracil, Bleo: bleomycin, CR: complete response, CisP: cisplatin, Gy: Gray, LAVC: locally advanced vulvar cancer, MMC: mitomycin C, NA: not available, NED: no evidence of disease and no recurrence, PR: partial response, Recurr.: recurrence.

Table 10. Original studies presenting data in patients treated with neoadjuvant chemoradiation

Author[reference]	Year	N	Chemotherapy regimen	Radiotherapy regimen	Response	Survival
Moore *et al.*[a,243]	1998	LAVC: N = 71	5-FU 1,000 mg/m² infusion d1-4 + CisP 50 mg/m² IV d1, given week 1 of each course of radiotherapy	2 courses of 23.8 Gy, given as 1.7 Gy BID for 4 days and daily for 6 days with 2 weeks break	CR: 47% (34/71)	Median follow-up: 50 months Status: 56% (40/71) alive NED Recurr. : 34% (24/69)
Landoni *et al.*[a,244]	1996	LAVC: N = 41 Recurr.: N = 17	5-FU 750 mg/m² infusion d1-5 + MMC 15 mg/m² IV d1 given week 1 of each course of radiotherapy	54 Gy in 2 courses (36 Gy + 18 Gy) with 14 d treatment break	cCR: 27% (14/52) pCR: 31% (13/42)	Median follow-up: 22 months Status: 48% (28/58) alive NED Recurr.: 27% (16/58)
Montana *et al.*[a,250]	2000	LAVC: N = 46	5-FU 1,000 mg/m² infusion d1-4 + CisP 50 mg/m² IV d1, given week 1 of each course of radiotherapy	2 courses of 23.8 Gy, given as 1.7 Gy BID for 4 days and daily for 6 days with planned 2 weeks break	pCR (nodes): 40% (15/37) pCR (vulva): 52% (20/38)	Median follow-up: 78 months Status: 26% (12/46) alive NED Recurr.: 51% (19/37)
Beriwal *et al.*[242]	2013	LAVC: N = 42	CisP 40 mg/m² d1 (N = 6) and 5-FU 1,000 mg/m² infusion, d1-5 (N = 36). Two cycles, given the first and last week of radiotherapy	IMRT 46 Gy in 1.6 Gy BID fractions for 5d, then 1.8 Gy daily for 7-8d then a break of 10-14 d, then 1.6 Gy BID for 5 d	cCR: 51.2% (21/41) pCR: 48.5% (16/33) pCR: 48.8% (20/41)	Median follow-up: 15 months Status: 45.5% (15/33) alive NED Recurr.: 24.2% (8/33)
Lupi *et al.*[a,252]	1996	LAVC: N = 24	5-FU 750 mg/m² infusion d1-5 + MMC 15 mg/m² IV d1, given for 2 cycles	54 Gy in 2 courses with 14 d treatment break	CR: 42% (10/24) PR: 54% (13/24) pCR: 36% (8/22)	Median follow-up: 34 months Status: 65.5% (15/24) alive NED Recurr.: 29% (7/24)
Gaudineau *et al.*[253]	2012	LAVC: N = 22	Carbo AUC 2 weekly during radiotherapy	50 Gy in 2 Gy daily fractions	pCR: 27% (6/22) ORR: 95% (21/22)	Median follow-up: 28 months Status: 54% (12/2) alive NED Recurr.: 32 % (7/22)
Scheistroen *et al.*[251]	1993	LAVC: N = 20	Bleo 30 mg IV d1, 3, 5 during weeks 1 + 3 of radiotherapy	30-45 Gy in 3 Gy daily fractions	CR: 25% (5/20) PR: 50% (10/20)	Follow-up: NA Status: 5% (1/20) alive NED Recurr.: 80% (4/5) of pts with CR
Gerszten *et al.*[254]	2005	LAVC: N = 18	5-FU 1,000 mg/m² infusion d1-4 + CisP 50 mg/m² IV d1, given first and last week of radiotherapy	44.6 Gy in 1.6 Gy BID fractions for 5 d, then 1.8 Gy daily for 7d, with 1-2 weeks break, then 1.6 Gy BID for 5 d	cCR: 72% (13/18) pCR: 39% (7/18)	Mean follow-up: 24 months Status: 83% (15/18) alive NED Recurr.: 17% (3/18)
Eifel *et al.*[245]	1995	LAVC: N = 12	CisP 4 mg/m²/d infusion d1-4 + 5-FU 250 mg/m²/d infusion d1-4, given weekly for 4 weeks	40 Gy in 2 Gy daily fractions	CR: 50% (6/12) PR: 41% (5/12)	Mean follow-up: 18 months Status: 50% (6/12) alive NED Recurr.: 16% (1/6) of pts with CR
Whitaker *et al.*[246]	1990	LAVC: N = 9 Recurr.: N = 3	5-FU 750-1,000 mg/m² infusion d1-4 + MMC 10-12 mg/m² IV d1, week 1 of each course of radiotherapy	25 Gy in 2.5 Gy fractions	CR : 42% (5/12) PR : 58% (7/12)	Follow-up: NA Status: 25% (3/12) alive NED Recurr.: 60% (3/5) of pts with CR

[a] Radiotherapy given to the vulva, groin and pelvis unless otherwise stated, 5-FU: 5-fluorouracil, AUC: area under the curve, BID: twice a day, Carbo: carboplatin, cCR clinical complete response, CisP: cisplatin, cPR clinical partial response, CR: complete response, d: days, Gy: Gray, IMRT: intensity-modulated radiation therapy, LAVC: locally advanced vulvar cancer, MMC: mitomycin C, NA: not available, NED: no evidence of disease and no recurrence, ORR: overall response rate, pCR: pathologic complete response, PR: partial response, pts: patients, Recurr: recurrence.

Original studies presenting data in patients treated with neoadjuvant chemoradiation *(continued)*

Author[reference]	Year	N	Chemotherapy regimen	Radiotherapy regimen	Response	Survival
Carson *et al.*[a,255]	1990	LAVC: N = 6 Recurr.: N = 2	5-FU 750 mg/m² infusion d1-5 + MMC 7.5 mg/m² IVd4 + CisP 0mg/m² IV d1, given weekly during radiotherapy.	45-50 Gy in 1.75 Gy daily fractions	pCR: 75% (6/8)	Mean follow-up: 10 months Status: 25% (2/8) alive NED Recurr. or prog.: 50% (4/8)
Levin *et al.*[247]	1986	LAVC: N = 6	5-FU 1000 mg/m² infusion d1-4 + MMC 10 mg/² IV d1. 1-2 cycles	20-40 Gy in 2 Gy daily fraction	NA	Mean follow-up: 11 months Status: 66% (4/6) alive NED Recurr.: NA
Koh *et al.*[233]	1993	LAVC: N = 4	5-FU 750-1,000 mg/m²/d for 3-4 d	40-44.8 Gy	CR: 25% (1/4) PR: 50% (2/4)	Mean follow-up: 29.8 months Status: 25% (1/4) alive NED Recurr.: 0% (0/4)

[a] Radiotherapy given to the vulva, groin and pelvis unless otherwise stated, 5-FU: 5-fluorouracil, CisP: cisplatin, CR: complete response, d: days, Gy: Gray, LAVC: locally advanced vulvar cancer, MMC: mitomycin C, NA: not available, NED: no evidence of disease and no recurrence, pCR: pathologic complete response, PR: partial response, prog.: progression, Recurr: recurrence.

Table 11. Original studies included in the meta-analysis published by Stuckey *et al.*[249]

Author[reference]	Year	N	Median age (years)	Chemotherapy regimen	Radiotherapy regimen	Median follow-up (months)	DOD (%)	DOT (%)	DICD (%)	NED (%)
Eifel *et al.*[245]	1995	11	55 (37-85)	5-FU/CisP	40-50 Gy	21	27.3	0.0	9.1	63.6
Wahlen *et al.*[234]	1995	15	64 (37-89)	5-FU± MMC	45-50.4 Gy	36	13.3	0.0	13.1	73.3
Berek *et al.*[237]	1991	12	69 (52-76)	5-FU/CisP	46.64 Gy	34	16.7	0.0	0.0	83.3
Whitaker *et al.*[246]	1990	7	73 (65-87)	5-FU/MMC	25-50 Gy	7	57.1	14.3	0.0	28.8
Levin *et al.*[247]	1986	5	60 (44-66)	5-FU/MMC	18-60 Gy	5	0.0	0.0	0.0	80.0
Beriwal *et al.*[248]	2006	4	66.5 (54-84)	5-FU/CisP	43-49 Gy	19.5	0.0	0.0	0.0	100.0
Russel et al.[229]	1992	16	71 (13-90)	5-FU ± CisP	46-72 Gy	17 months	6.3%	6.3	0.0	75.0

5-FU: 5-fluorouracil, CisP: cisplatin, DICD: dead of intercurrent disease, DOD: dead of disease, DOT: dead of treatment, Gy: Gray, MMC: mitomycin C, NED: no evidence of disease and no recurrence.

Table 12. Original studies presenting response and survival data in patients treated with adjuvant chemoradiation

Author[reference]	Year	N	Chemotherapy regimen	Radiotherapy regimen	Survival
Mak *et al.*[231]	2011	LAVC : N = 10	Either weekly CisP or 3-4 week 5-FU based regimens	50 Gy, timing of fractions varied	Median follow-up: 31.5 months Status: NA Recurr.: NA
Thomas *et al.*[230]	1989	LAVC: N = 9	5-FU 1,000 mg/m² infusion d1-4 ± MMC 6 mg/m² (4/6 one injection, and 2/6 two injections 4 weeks apart)	40-64 Gy in 1.6-1.8 Gy twice daily fractions	Median follow-up: 21 months Status: 78% (7/9) alives NED Recurr.: 22% (2/7)
Mulayim *et al.*[225]	2004	LAVC: N = 6	5-FU 1,000 mg/m² infusion d1-4 and 21-24 of radiotherapy + MMC 10 mg/m² IV d1 and d21 of radiotherapy	60 Gy for macro and 45 Gy for microscopic disease	Median follow-up: 20 months Status: 0% (0/6) Recurr.: 33% (2/6)
Han *et al.*[236]	2000	LAVC: N = 6	5-FU 1,000 mg/m² infusion d1-4 + MMC 10 mg/m² IV d1, given week 1 and 5 of radiotherapy	40-62 Gy	Median follow-up: 17 months Status: 83% (5/6) alive NED Recurr.: 17% (1/6)

5-FU: 5-fluorouracil, CisP: cisplatin, Gy: Gray, LAVC: locally advanced vulvar cancer, MMC: mitomycin C, NA: not available, NED: no evidence of disease and no recurrence, Recurr.: recurrence.

13 Systemic treatment

13.1 Summary of available scientific evidence

Neoadjuvant chemotherapy: no studies enrolling at least 50 patients were identified. Results from the 8 identified studies[257-264] are limited notably by the heterogeneity and the number of patients evaluated (only 3 studies[258,262,263] have accrued in excess of 20 patients), and by the heterogeneity in the chemotherapy regimens. Although studies are very small, agents showing response include bleomycin, cisplatin, and most notably infusional 5-FU (**Table 13**). It should be noted that response rates differ quite extensively among the studies. But, the identified trials have not shown significant evidence of improved survival. Additionally, some effective agents produce high toxicity, such as Bleomycin, that is a significant issue.

LoE 3

Adjuvant chemotherapy: only one very small study[265] was identified. To assess the use of chemotherapy alone in the adjuvant setting, Bellaty *et al.*[265] included 14 patients with inguinal node metastases after radical surgery. Cisplatin (100 mg/m²) was administered every 21 days for 4 cycles. Four of 14 patients recurred (29%) at a median of 57 months of follow-up, including two recurrences in the groin. Three-year OS and PFS were 86% and 71%, respectively.

LoE 3

Targeted therapy: only one small study was identified. Horowitz *et al.*[266] evaluated the efficacy and toxicity of erlotinib (150 mg daily), a selective epidermal growth factor receptor tyrosine kinase inhibitor, among 41 patients with locally advanced, primary, recurrent or metastatic vulvar squamous cell carcinoma. In this first phase II trial, overall clinical benefit rate was 67.5% including partial response (27.5%) and stable disease (40%). No complete response has been observed. It should to be noted that 1) responses were of relatively short duration and toxities were significant, and 2) quality of life evaluation was not assessed in this study.

LoE 3

13.2 Previous initiatives

Three previous initiatives[1,3,39] presenting guidelines on systemic treatment were identified.

13.3 Development group comments

None.

13.4 Guidelines

D Data in vulvar cancer are insufficient to recommend a preferred schedule in a palliative setting.

Table 13. Original studies presenting data in patients treated with neoadjuvant chemotherapy

Author[reference]	Year	N	Chemotherapy regimen	Nb of cycles	Response	Survival
Aragona *et al.*[263]	2012	LAVC: N = 35	CisP + 5-FU (n = 12) or CisP + Tax (n = 6) or CisP + 5-FU + Tax (n = 6) or VinC + Bleo + CisP (n = 6) or Bleo alone (n = 5)	3	PR: 86% (30/35)	Median follow-up: 49 months Status: 68% (24/35) alive NED Recurr. : 14% (4/29) of pts undergoing surgery
Domingues *et al.*[262]	2010	LAVC: N = 25 A) N = 10 B) N = 5 C) N = 10	A) Bleo 20 mg/m² IV d1-10 continuous infusion B) Tax 100 mg/m² IV weekly C) 5-FU 750 mg/m² d1-4 continuous infusion + CisP 60–80 mg/m² IV d1, weekly	3	A) CR: 10% (1/10), PR: 50% (5/10) B) PR: 40% (2/5) C) PR: 20% (2/10)	Mean follow-up: 22 months Status: A) 30% (3/10) alive NED, B) 20% (1/5) alive NED, C) 10% (1/10) alive NED Recurr.: NA
Benedetti-Panici *et al.*[258]	1993	LAVC: N = 21	CisP 100 mg/m² day 1 + Bleo 15 mg days 1 and 8 + MTX 300 mg/m² day 8 every 21 days	Up to 3	PR in 14% (3/21) SD in 81% (17/21)	Median follow-up: 33 months Status : NA Recurr. : NA
Durrant *et al.*[257]	1990	LAVC: N = 18	Bleo 5 mg IM d1–5 + MTX 15 mg PO d1 and 4 + CCNU 40 mg PO d5-7 week 1, then Bleo 5 mg IM d1 and 4 + MTX 15 mg PO d1 and 4 weeks 2-5	Up to 4	ORR: 67% (12/18)	Follow-up: NA Status: NA Recur.: NA
Geisler *et al.*[261]	2006	LAVC: N = 13 A) N = 10 B) N = 3	A) 5-FU 1,000 mg/m²/24 h infusion d1-5 + CisP 50 mg/m² IV d1, q3 weeks B) CisP 50 mg/m² IV q3 weeks	3-4	A) PR: 60% (6/10), pCR: 40% (4/10) B) 0% response	Median follow-up: 49 months Status: A) 90% (9/10) alive NED, B) 0% alive NED Recur.: NA
Wagenaar *et al.*[259]	2001	LAVC: N = 12	Week 1: Bleo 5 mg IM d1-5 + CCNU 40 mg PO d5-7 + MTX 10 mg PO d1+4 Weeks 2-6: Bleo 5 mg IM d1 + 4 + MTX 15 mg PO d1.	Up to 3	ORR: 58% (7/12)	Median follow-up: 8 months Status: NA Recurr.: NA
Bafna *et al.*[260]	2004	LAVC: N = 9	Cyclo 500 mg + MTX 50 mg + 5-FU 500 mg days 1, 8 every 14 d	3	pCR: 11% (1/9) PR: 89% (8/9)	Follow-up: NA Status: NA Recur.: NA
Han *et al.*[264]	2012	LAVC: N = 4	Tax 60 mg/m² IV + Carbo AUC 2.7 IV weekly	Up to 9	ORR = 0%	Mean follow-up: 12 months Status: 50% (2/4) alive NED Recurr. : -

5-FU: 5-fluorouracil, Bleo: bleomycin, Carbo: carboplatin, CisP: cisplatin, CCNU: lomustine, CR: complete response, Cyclo: cyclophosphamide, LAVC: locally-advanced vulvar cancer, MTX: methotrexate, NA: not available, NED: no evidence of disease and no recurrence, ORR: overall response rate, pCR: pathologic complete response, PR: partial response, Recurr. : recurrence, Tax: paclitaxel, VinC: vincristine.

14 Treatment of recurrent disease

14.1 Summary of available scientific evidence

Chemoradiation: no studies enrolling at least 50 patients were identified. Results from the 8 identified studies[227-230,241,244,251,252] are limited notably by the small number of patients evaluated (only one study[251] has accrued in excess of 20 patients) and by the heterogeneity in the chemoradiation regimens (**Table 14**). **LoE 3**

Chemotherapy: no studies enrolling at least 50 patients were identified. Results from the 7 identified trials[257,259,264,267-270] are limited notably by the small number of patients evaluated (only 2 trials[267,268] have accrued in excess of 20 patients) and by the heterogeneity in the chemotherapy regimens (**Table 15**). **LoE 3**

14.2 Previous initiatives

Four previous initiatives[1-3,39] presenting guidelines on treatment of recurrent disease were identified.

14.3 Development group comments

Local recurrences should be treated as primary tumours with wide local excision and inguinofemoral lymphadenectomy in case of depth of invasion >1 mm and not performed previously.

CT 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.

14.4 Guidelines

Treatment of vulvar recurrence

- ✓ Radical local excision is recommended.
- ✓ For vulvar recurrence with a depth of invasion > 1 mm and previous sentinel lymph node removal only, inguinofemoral lymphadenectomy should be performed.
- ✓ The indications for postoperative radiotherapy are comparable to those for the treatment of primary disease.

Treatment of groin recurrence

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

Treatment of distant metastases

- ✓ Systemic (palliative) therapy may be considered in individual patients (see systemic treatment).

Table 14. Original studies presenting response and survival data in recurrent patients treated with chemoradiation

Author[reference]	Year		Chemotherapy regimen	Radiotherapy regimen	Response	Survival
Scheistroen *et al.*[251]	1993	22	Bleo 30 mg IV d1, 3, 5 during weeks 1 + 3 of radiotherapy	30-45 Gy in 3 Gy daily fractions	CR: 9% (2/22) PR: 50% (11/22)	Follow-up: NA Status: NA Recurr.: NA
Landoni *et al.*[a,244]	1996	17	5-FU 750 mg/m² infusion d1-5 + MMC 15 mg/m² IV d1 given week 1 of each course of radiotherapy	54 Gy in 2 courses (36 Gy + 18 Gy) with 14 d treatment break	pCR: 18% (3/17) pPR: 35% (6/17)	Follow-up: NA Status: 29% (5/17) alive NED Recurr.: NA
Sebag-Montefiore *et al.*[227]	1994	16	5-FU 750 mg/m² infusion d1–5 + MMC 10 mg/m2 IV d1, given first 5 d and last 5 d of radiotherapy	45 Gy in 2-2.5 Gy daily fractions	CR : 50% (8/16) PR : 31% (5/16)	Follow-up: NA Status: NA Recurr.: NA
Thomas *et al.*[230]	1989	15	5-FU 1,000 mg/m² infusion d1-4 ± MMC 6 mg/m² (4/6 one injection, and 2/6 two injections 4 weeks apart)	40-64 Gy in 1.6-1.8 Gy twice daily fractions	CR: 53% (8/15)	Follow-up: 5-45 months Status: 47% (7/15) alive NED Recurr.: NA
Tans *et al.*[228]	2011	8	5-FU 1,000 mg/m² infusion d1-4 + MMC 10 mg/m² IV d1, given first week of each course of radiotherpay	Split course 40 Gy + 20 Gy in 2 Gy fractions with 2-week break	CR: 75% (6/8)	Median follow-up: NA Status: NA Recurr.: NA
Russel *et al.*[229]	1992	7	5-FU 750-1,000 mg/m² infusion d1-4 + CisP 100 mg/m² IV d1, 2-3 cycles given	54 Gy for macro and 36 Gy for microscopic disease	CR: 57% (4/7)	Mean follow-up: 17.9 months Status: 29% (2/7) alive NED Recurr.: 14% (1/7) in pts with pCR
Lupi *et al.*[a,252]	1996	7	5-FU 750 mg/m² infusion d1-5 + MMC 15 mg/m² IV d1, given for 2 cycles	54 Gy in 2 courses with 14 d treatment break	CR: 71% (5/7) PR: 29% (2/7)	Median follow-up: 38 months Status: 57% (4/7) alive NED Recurr.: NA
Kalra *et al.*[a,241]	1985	1	MMC 10 mg/m² IV d1 + 5-FU 1000mg/m² infusion d1-5, given weeks 1 and 4 of radiotherapy	50 Gy in 2 Gy daily fractions	CR: 100% (1/1)	Follow-up: NA Status: 100% (1/1) alive NED Recurr. : 0% (0/1)

[a] Radiotherapy given to the vulva, groin and pelvis unless otherwise stated, 5-FU: 5-fluorouracil, Bleo: bleomycin, CR: complete response, CisP: cisplatin, Gy: Gray, MMC: mitomycin C, NA: not available, NED: no evidence of disease and no recurrence, pCR: pathologic complete response, pPR pathologic partial response, PR: partial response, Recurr. recurrence.

Table 15. Original studies presenting data in recurrent patients treated with chemotherapy alone

Author[reference]	Year	N	Chemotherapy regimen	Response	Survival
Witteveen *et al.*[267]	2009	29	Tax 175 mg/m² IV q3 weeks; up to 9 cycles	ORR: 13.8% (4/29) CR: 6% (2/29) PR: 6% (2/29)	Median PFS: 2.6 months Median OS: 6.8 months
Thigpen *et al.*[268]	1986	22	CisP 50 mg/m² IV q3 weeks	ORR: 0% CR: 0% PR: 0%	NA
Cormio *et al.*[269]	2009	15	CisP 80 mg/m2 IV d1 + Vinorelbine 25 mg/m² IV d1 and d8, q21 d for up to 6 cycles	ORR: 40% (6/15) CR: 27% (4/15) PR: 13% (2/15)	Median PFS: 10 months Median OS: 19 months
Thigpen *et al.*[268]	1986	13	Piperazinedione 9 mg/m² IV q3 weeks	ORR: 0% CR: 0% PR: 0%	PFS: NA OS: NA
Wagenaar *et al.*[259]	2001	13	Week 1: Bleo 5 mg IM d1-5 + CCNU 40 mg PO d5-7 + MTX 10 mg PO d1+4 Weeks 2-6: Bleo 5 mg IM d1 + 4 + MTX 15 mg PO d1.	ORR: 54% (7/13)	Median follow-up: 8 months Median PFS: 4.8 months[a] Median OS: 7.8 months[a]
Muss *et al.*[270]	1989	11	Mitoxantrone 12 mg/m² IV q3 weeks	ORR: 0% CR: 0% PR: 0%	Median PFS: 1.3 months Median OS: 3.2 months
Durrant *et al.*[257]	1990	11	Bleo 5 mg IM d1–5 + MTX 15 mg PO d1 and 4 + CCNU 40 mg PO d5-7 week 1, then Bleo 5 mg IM d1 and 4 + MTX 15 mg PO d1 and 4 weeks 2-5	ORR: 60% (6/10) CR : NA PR : NA	PFS: NA OS: NA
Han *et al.*[264]	2012	2	Tax 60 mg/m² IV + Carbo AUC 2.7 IV weekly	ORR = 0%	Mean follow-up: 3.5 months PFS: - OS: NA

[a] median survival among 12 patients with primary locally advanced disease and 13 with locoregional recurrence (data not available for patients with locoregional recurrence specifically), Bleo bleomycin, Carbo: carboplatin, CCNU: lomustine, CisP: cisplatin, CR: complete response, LAVC: locally advanced vulvar cancer, NA: not available, ORR: overall response rate, OS: overall survival, PR: partial response, PFS: progression-free survival, MTX: methotrexate, Tax: paclitaxel.

15 Follow-up

15.1 Summary of available scientific evidence

No directly applicable clinical studies have been identified.

15.2 Previous initiatives

Six previous initiatives[1-3,38,39,271] presenting guidelines on follow-up were identified.

15.3 Development group comments

There is no evidene for best follow-up schedule. Since local recurrences may occur many years after primary treatment, lifelong follow-up is advised.

Since patients with associated vulvar intraepithelial neoplasia or lichen sclerosus/planus have a higher risk on local recurrence, more intensive follow-up may be indicated.

15.4 Guidelines

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

✓ After primary surgical treatment the following follow-up schedule is suggested:

- First follow-up 6-8 weeks postoperative
- First two years every three-four 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 vulva and groins.[4]

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

- First follow-up visit 10-12 weeks post completion of definitive (chemo)radiation.
- First two years every three-four months
- Third and fourth year biannually
- Afterward, long-term follow-up, especially in case of predisposing vulvar disease.

At first follow-up visit 10-12 weeks post definitive (chemo)radiation CT or PET-CT is recommended to document complete remission.

[4] Despite the well-recognized low sensitivity of palpation to identify groin recurrences, currently available data do not support routine use of imaging of the groins in follow-up.

16 Acronyms and abbreviations

5-FU 5-fluorouracil

99mTc technectium-99m

ACPG Alberta clinical practice guidelines

AGDH Australian government department of health

AHRQ agency for healthcare research and quality

AquAS agència de qualitat i avaluació sanitàries de Catalunya

ASCO American society of clinical oncology

AUC area under the curve

BCCA British Columbia cancer agency

BID twice a day

Bleo bleomycin

CADTH Canadian agency for drugs and technologies in health

Carbo carboplatin

CCO cancer care Ontario

CCNU lomustine

cCR clinical complete response

CEPO comité de l'évolution des pratiques en oncologie

CI confidence interval

CisP cisplatin

CoCanCPG coordination of cancer clinical practice guidelines in Europe

COMPAQ-HPST coordination pour la mesure de la performance et l'amélioration de la qualité, hôpital, patient, sécurité, territoire

CR complete response

CT computed tomography

Cyclo cyclophosphamide

DICD dead of intercurrent disease

DOD dead of disease

DOT dead of treatment

DSS disease specific survival

ECOG Eastern cooperative oncology group

ESGO European society of gynaecological oncology

ESMO European society of medical Oncology

FIGO international federation of gynecology and obstetrics

FN false negative

FNA fine-needle aspiration

FNAC fine-needle aspiration cytology

FP false positive

GIN guidelines international network

GOC gynaecological oncology centre

GOG gynecologic oncology group

GROINSS-V Groningen international study on sentinel nodes in vulvar cancer

H&E haematoxylin and eosin

HAS haute autorité de santé

HR hazard ratio

IHC immunohistochemistry

ILND inguinal lymph node dissection

IMRT intensity-modulated radiation therapy

INAHTA international network of agencies for health technology assessment

INCa institut national du cancer

INESSS institut national d'excellence en santé et en services sociaux

IPTW inverse probability of treatment weighting

KCE centre fédéral d'expertise des soins de santé

LAVC locally advanced vulvar cancer

MMC mitomycin C

MRI magnetic resonance imaging

MSAC medical services advisory committee

MTX methotrexate

NA not available

NCCN national comprehensive cancer network

NED no evidece of disease and no recurrence

NHMRC national health and medical research council

NHS national health service

NICE national institute for health and care excellence

NZGG New Zealand guidelines group

OR odd ratio

ORR overall response rate

OS overall survival

pCR pathologic complete response

PET positron emission tomography

PET-CT positron emission tomography-computed tomography

PFS progression-free survival

PR partial response

Recurr recurrence

RCT randomised controlled trial

SIGN Scottish intercollegiate guidelines network

SLN sentinel lymph node

Tax paclitaxel

TN true negative

TP true positive

UICC union internationale contre le cancer

VinC vincristine

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18 Appendices

18.1 Appendix 1 - People involved in the development of the guidelines

18.1.1 Appendix 1.1 - List of the international development group

Name	Specialty	Affiliation
Ate van der Zee	Gynecologic Oncologist (chair)	University Medical Center, Groningen (Netherlands)
Maaike Oonk	Gynecologic Oncologist (co-chair)	University Medical Center, Groningen (Netherlands)
François Planchamp	Methodologist	Institut Bergonié, Bordeaux (France)
Peter Baldwin	Gynecologic Oncologist	Addenbrooke's Hospital, Cambridge (United Kingdom)
Mariusz Bidzinski	Gynecologic Oncologist	Hollycross Oncology Center, Kielce (Poland)
Mats Brännström	Gynecologic Oncologist	University of Göteborg, Göteborg (Sweden)
Fabio Landoni	Gynecologic Oncologist	European Institute of Oncology, Milano (Italy)
Sven Mahner	Gynecologic Oncologist	University of Munich, Munich (Germany)
Sergio Martinez	Gynecologic Oncologist	Hospital Clinic, Barcelona (Spain)
Umesh Mahantshetty	Radiation Oncologist	Tata Memorial Hospital, Mumbai (India)
Mansoor Mirza	Medical Oncologist	Finsen Centre, Rigshospitalet, Copenhagen (Denmark)
Cordula Petersen	Radiation Oncologist	University Medical Center, Hambourg (Germany)
Sigrid Regauer	Pathologist	Medical University, Graz (Austria)
Lukas Rob	Gynecologic Oncologist	Charles University , Prague (Czech Republic)
Roman Rouzier	Surgeon	Pierre and Marie Curie University, Paris (France)
Elena Ulrikh	Gynecologic Oncologist	St. Petersburg N.N Petrov Research Institut, St. Petersburg (Russia)
Jacobus van der Velden	Gynecologic Oncologist	Academic Medical Center, Amsterdam (Netherlands)
Ignace Vergote	Gynecologic Oncologist	University Hospital, Leuven (Belgium)
Linn Woelber	Gynecologic Oncologist	University Clinic, Hamburg (Germany)

18.1.2 Appendix 1.2 - List of external panel of physicians and patients (international reviewers)

Name	Physician/Patient	Country
Anonymous	patient	Germany
Reem Abdallah	gynaecological oncology	Lebanon
Ieera Aggarwal	gynaecology	Singapore
Diogo Alpuim Costa	medical oncology	Portugal
Roberto Altamirano	gynaecological oncology	Chile
Georgios Angelopoulos	gynaecological oncology	United Kingdom
Pérez Benavente Assumpcio	gynaecological oncology	Spain
Beyhan Ataseven	gynaecological oncology	Germany
Annika Auranen	gynaecological oncology	Finland
Gabriela Baiocchi	obstetric & gynaecology	Italy
Marc Barahona	gynaecological oncology	Spain
Manel Barahona Orpinell	gynaecological oncology	Spain
Lisa Barbera	radiation oncology	Canada
Jana Barinoff	gynaecological oncology	Germany
Margarida Barros	gynaecological oncology	Portugal
Ali Ergin Bengisu	gynaecological oncology	Turkey
Virginia Benito	gynaecological oncology	Spain
Farouk Benna	radiation oncology	Tunisia
Jonathan Berek	gynaecological oncology	United States of America
Margarida Bernadino	gynaecological oncology	Portugal
David Bernshaw	radiation oncology	Australia
Ruben Betoret	obstetric & gynaecology	Spain
Claudia Bessa Pereira Chaves	gynaecological oncology	Brazil
Line Bjorge	gynaecology	Norway
Pawel Blecharz	gynaecological oncology	Poland
Michaela Bossart	gynaecological oncology	Germany
Jacky Botterman	clinical oncology	Belgium
Jiri Bouda	obstetric & gynaecology	Czech Republic
Katharina Buser	medical oncology	Switzerland
Silvia Cabrera Diaz	gynaecology	Spain

Name *(continued)*	**Physician/Patient**	**Country**
Sonia Carballo Rastrilla	obstetric & gynaecology	Spain
Carmine Carriero	obstetric & gynaecology	Italy
Ghee Kheng Chew	gynaecological oncology	Singapore
Vesna Colakovic-Popovic	gynaecological oncology	Montenegro
Lucia Correia	gynaecological oncology	Portugal
Margaret Cummings	pathology	Australia
Maite Cusido	gynaecological oncology	Spain
Caetano da Silva Cardial	gynaecological oncology	Brazil
Grisaru Dan	gynaecological oncology	Israel
Elsie Rodriguez Dancel	gynaecological oncology	Philippines
Horanyi Daniel	obstetric & gynaecology	Hungary
Nagindra Das	gynaecological oncology	United Kingdom
Joanne de Hullu	gynaecological oncology	Netherlands
Philippe de Sutter	gynaecological oncology	Belgium
Grigorios Derdelis	gynaecology	Greece
Begona Diaz de la Noval	obstetric & gynaecology	Spain
Violante Di Donato	gynaecological oncology	Italy
Santiago Domingo	gynaecological oncology	Spain
Jelena Dotlic	obstetric & gynaecology	Serbia
Geanina Elena Dragnea	obstetric & gynaecology	Romania
Paula Ambrosio Duarte	gynaecological oncology	Portugal
Sally Sayed El-Tawab	gynaecological surgery	Egypt
Nour El-Etreby	gynaecological oncology	Egypt
Henrik Falconer	gynaecological oncology	Sweden
Farah Farzaneh	obstetric & gynaecology	Iran
Ani Mihaljevic Ferari	radiation oncology	Croatia
José Alberto Fonseca-Moutinho	gynaecological oncology	Portugal
Dirk Michael Forner	gynaecological oncology	Germany
Christina Fotopoulou	gynaecological oncology	United Kingdom
Ligita Froding	gynaecological oncology	Denmark

Name *(continued)*	Physician/Patient	Country
Katrine Fuglsang	gynaecological oncology	Denmark
Ketan Gajjar	gynaecological oncology	United Kingdom
Prafull Ghatage	gynaecological oncology	Canada
Nidal Ghaoui Dit Ebef	gynaecology	United Kingdom
Ronny Goethals	obstetric & gynaecology	Belgium
Andreja Gornjec	gynaecological oncology	Slovenia
Mikel Gorostidi	gynaecological oncology	Spain
Andreas Gunthert	gynaecological oncology	Switzerland
Wolfgang Hamm	gynaecological oncology	Germany
Philipp Harter	gynaecological oncology	Germany
Adnan Hassan	gynaecological oncology	Jordan
Thomas Hebert	gynaecological oncology	France
Reda Hemida	obstetric & gynaecology	Egypt
Cathrine Holland	gynaecological oncology	United Kingdom
Christoph Honegger	gynaecological oncology	Switzerland
Brigitte Honhon	medical oncology	Belgium
Sara Iacoponi	gynaecology	Spain
Christos Iavazzo	gynaecological oncology	United Kingdom
Ibon Jaunarena	gynaecological oncology	Spain
Marcin Jedryka	gynaecological oncology	Poland
Silke Johann	gynaecological oncology	Switzerland
Matias Jurado	gynaecological oncology	Spain
Preben Kjolhede	obstetric & gynaecology	Sweden
Malgorzata Klimek	radiation oncology	Poland
Pawel Knapp	gynaecological oncology	Poland
Petra Kohlberger	gynaecological oncology	Austria
Jan Kotarski	gynaecological oncology	Poland
Kalpana Kothari	gynaecological oncology	India
Antonio Augusto Carvalho Lagoa	gynaecological oncology	Portugal
Ignacio Lobo	gynaecological oncology	Spain

Name *(continued)*	Physician/Patient	Country
Alberto Lopes	gynaecological oncology	United Kingdom
Domenica Lorusso	gynaecological oncology	Italy
Lene Lundvall	gynaecological oncology	Denmark
Mathieu Luyckx	gynaecological oncology	Belgium
José Claudio Maanon	obstetric & gynaecology	Spain
Beata Mackowiak-Matejczyk	gynaecological oncology	Poland
Aljosa Mandic	gynaecological oncology	Serbia
Slobodan Maricic	gynaecological oncology	Serbia
Nuno Nogueira Martins	gynaecology	Portugal
Ladislav Masak	gynaecological oncology	Slovakia
Jane McMeilage	gynaecological oncology	Australia
Sebastjan Merlo	gynaecological oncology	Slovenia
Manfred Miehe	gynaecology	Germany
Swarupa Mitra	radiation oncology	India
Milos Mlyncek	gynaecological oncology	Slovakia
Michael Mueller	gynaecological oncology	Switzerland
Seoud Muhieddine	gynaecological oncology	Lebanon
Eva Myriokefalitaki	gynaecological oncology	United Kingdom
Purushothaman Natarajan	gynaecological oncology	United Kingdom
Krassimir Nedialkov	gynaecological oncology	Bulgaria
Andy Nordin	gynaecological oncology	United Kingdom
Reita Nyberg	gynaecological oncology	Finland
Felipe Ojeda	gynaecology	Spain
Gitte Ortoft	obstetric & gynaecology	Denmark
Borja Otero	gynaecological oncology	Spain
Pablo Padilla Iserte	gynaecological oncology	Spain
Dimitrios Papatheodorou	gynaecological oncology	Greece
Eduardo Paulino	medical oncology	Brazil
Tamar Perri	gynaecological oncology	Israel
Suzana Pessini	gynaecological oncology	Brazil

Name *(continued)*	Physician/Patient	Country
Imre Pete	gynaecological oncology	Hungary
Stamatios Petousis	obstetric & gynaecology	Greece
Maria Cristina Petrella	gynaecological oncology	Italy
Jurgen Piek	gynaecological oncology	Netherlands
Evelin Pinto	gynaecology	Portugal
Robert Poka	obstetric & gynaecology	Hungary
Stephan Polterauer	gynaecological oncology	Austria
Jordi Ponce	gynaecological oncology	Spain
Sonia Prader	gynaecological oncology	Germany
Denis Querleu	gynaecological oncology	France
Rajeev Ramanah	gynaecological surgery	France
Isabelle Ray Coquard	medical oncology	France
Daniel Reimer	gynaecological oncology	Austria
Enzo Ricciardi	obstetric & gynaecology	Italy
Isabel Rodriguez	radiation oncology	Spain
Philip Rolland	gynaecological oncology	United Kingdom
Ingo Runnebaum	gynaecological oncology	Germany
Azmat Sadozye	clinical oncology	United Kingdom
Alfonso Lenin Salinas Miranda	gynaecological oncology	Nicaragua
Angel Sanchez del Rio	obstetric & gynaecology	Spain
Fernanda Santos	gynaecology	Portugal
Marcia Schmidt	gynaecological oncology	United States of America
Tine Schnack	gynaecological oncology	Denmark
Stephanie Schneider	gynaecological oncology	Germany
Henk Schreuder	gynaecological oncology	Netherlands
Alejandro Soderini	gynaecological oncology	Brazil
Amr Soliman	gynaecological oncology	Germany
Rita Mafalda Sousa	gynaecological oncology	Portugal
Bogdan Ioan Stefanescu	gynaecological oncology	Romania
Regina Strueber	gynaecology	Germany

Name *(continued)*	Physician/Patient	Country
Sudha Sundar	gynaecological oncology	United Kingdom
Grzegorz Szewczyk	obstetric & gynaecology	Poland
Karl Tamussino	gynaecological oncology	Austria
Ai Ling Tan	gynaecological oncology	New Zealand
Ingrid Thranov	gynaecological oncology	Denmark
John Tidy	surgery	United Kingdom
Tayfun Toptas	gynaecological oncology	Turkey
Anna Torrent	gynaecological oncology	Spain
Nicholas Trip Reed	clinical oncology	United Kingdom
Irina Tripac	gynaecological oncology	Moldova
Elisa Tripodi	obstetric & gynaecology	Italy
Nataliya Tsip	gynaecological oncology	Ukraine
Dimitrios Tsolakidis	gynaecological oncology	Greece
Arno Uppin	gynaecological oncology	Estonia
Giorgio Valabrega	medical oncology	Italy
Ales Vakselj	gynaecological oncology	Slovenia
Helena van Doorn	gynaecology	Netherlands
Johan van Ginderachter	gynaecology	Belgium
Katrien Vandecasteele	radiation oncology	Belgium
Dogan Vatansever	obstetric & gynaecology	Turkey
Ingvild Vistad	gynaecology	Norway
Khadija Mohamed Warfa	gynaecological oncology	Kenya
Anne Westermann	medical oncology	Netherlands
Peter Widschwendter	gynaecology	Germany
Edward Wight	gynaecological oncology	Switzerland
Pauline Wimberger	gynaecological oncology	Germany
Diana Zach	gynaecological oncology	Sweden
Vanna Zanagnolo	gynaecological oncology	Italy
Giuliano Carlo Zanni	gynaecological oncology	Italy
Ignacio Zapardiel	gynaecological oncology	Spain
Vibeke Zobbe	gynaecological oncology	Denmark

18.2 Appendix 2 - List of evidence-based medicine websites consulted

Organism/agency	Website
ACPG	http://www.topalbertadoctors.org/home/
AGDH	http://www.health.gov.au/
AHRQ	http://www.guideline.gov/
AQuAS	http://aquas.gencat.cat/ca/
ASCO	http://www.asco.org/
BCCA	http://www.bccancer.bc.ca/default.htm
CADTH	http://www.cadth.ca/
CCO	https://www.cancercare.on.ca/
CEPO	http://www.msss.gouv.qc.ca/index.php
CoCanCPG	http://www.cocancpg.eu/
COMPAQ-HPST	http://www.compaqhpst.fr/fr/
ESMO	http://www.esmo.org/
GIN	http://www.g-i-n.net/
HAS	http://www.has-sante.fr/portail/jcms/fc_1249588/fr/accueil
INAHTA	http://www.inahta.org/
INCa	http://www.e-cancer.fr/
INESSS	http://www.inesss.qc.ca/
KCE	https://kce.fgov.be/fr
MSAC	http://www.msac.gov.au/
NCCN	http://www.nccn.org/
NHMRC	http://www.nhmrc.gov.au/
NHS	http://www.nhs.uk/Pages/HomePage.aspx
NICE	http://www.nice.org.uk/
NZGG	http://www.health.govt.nz/
SIGN	http://www.sign.ac.uk/

ACPG Alberta Clinical Practice Guidelines, AGDH Australian Government Department of Health, AHRQ Agency for Healthcare Research and Quality, AQuAS Agència de Qualitat i Avaluació Sanitàries de Catalunya, ASCO American Society of Clinical Oncology BCCA British Columbia Cancer Agency, CADTH Canadian Agency for Drugs and Technologies in Health, CCO Cancer Care Ontario, CEPO Comité de l'Evolution des Pratiques en Oncologie, CoCanCPG Coordination of Cancer Clinical Practice Guidelines in Europe, COMPAQ-HPST Coordination pour la Mesure de la Performance et l'Amélioration de la Qualité, Hôpital, Patient, Sécurité, Territoire, ESMO European Society of Medical Oncology, GIN Guidelines International Network, HAS Haute Autorité de santé, INAHTA International Network of Agencies for Health Technology Assessment, INCa Institut National du Cancer, INESSS Institut National d'Excellence en Santé et en Services Sociaux, KCE Centre fédéral d'expertise des soins de santé, MSAC Medical Services Advisory Committee, NCCN National Comprehensive Cancer Network, NHMRC National Health and Medical Research Council, NHS National Health Service, NICE National Institute for Health and Care Excellence, NZGG New Zealand Guidelines Group, SIGN Scottish Intercollegiate Guidelines Network.

18.3 Appendix 3 - Key to evidence statements and grades of recommendations[5]

LEVELS OF EVIDENCE	
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
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies 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
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

GRADES OF RECOMMENDATIONS	
A	At least one 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+

GOOD PRACTICE POINTS	
✓	Recommended best practice based on the clinical experience of the guideline development group

[5] http://www.sign.ac.uk/guidelines/fulltext/50/annexoldb.html

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