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Clinical Studies

Incidence of inguinofemoral lymph node metastases at the first local recurrence of vulvar cancer: a Dutch nationwide study

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BACKGROUND: Up to 40% of vulvar cancer patients present with local recurrence within 10 years of follow-up. An inguinofemoral lymphadenectomy (IFL) is indicated if not performed at primary treatment. The incidence and risk factors for lymph node metastases (LNM) at first local recurrence, however, are unclear. Our aim was to determine the incidence of LNM at first local recurrence, in relation to previous groin treatment and clinicopathological factors.

METHODS: A multicenter cohort study including vulvar cancer patients with a first macroinvasive local recurrence after primary surgical treatment between 2000 and 2015 was conducted in the Netherlands. Groin status at local recurrence was defined as *positive (N+)*, *negative (N−)* or *unknown (N?)* and based on histology, imaging and follow-up. Patient-, tumour- and treatment characteristics of primary and recurrent disease were analysed.

RESULTS: Overall, 16.3% (66/404) had a *N+ groin status* at first local recurrence, 66.4% (268/404) *N−* and 17.3% (70/404) *N? groin status*. The incidence of a *N+ groin status* was comparable after previous SLN and IFL, 11.5% and 13.8%, respectively. A *N+* groin status was related to tumour size (25 vs.12 mm; $P < 0.001$), depth of invasion (5 vs. 3 mm; $P < 0.001$) and poorly differentiated tumours (22.9 vs. 11.9%; $P = 0.050$) at local recurrence.

CONCLUSIONS: The incidence of LNM at first local recurrence in vulvar cancer patients was 16.3%, and independent of previous type of groin surgery. In accordance with primary diagnosis, tumour size, depth of invasion, and tumour grade were significantly associated with a positive groin status.

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INTRODUCTION

Vulvar cancer is a rare disease with an incidence of 2.6 per 100.000 women per year, accounting for 5% of gynaecological malignancies [1, 2]. The most common histological subtype is squamous cell carcinoma (SCC) [3]. Prognosis is strongly dependent on the presence, number, and size of inguinofemoral lymph node metastases (LNM) [4, 5]. A meta-analysis of the prognostic significance of FIGO stage showed a 5-year survival rate of 84% for Stage I, and 75%, 48% and 9% for Stage II, III and IV, respectively [6].

Surgery is the cornerstone of treatment for primary vulvar cancer. Throughout the years, the extent of surgical resection has been reduced, which has limited surgically related morbidity [7–9]. Currently, radical local excision (RLE) of the primary tumour with either a sentinel lymph node (SLN) procedure or inguinofemoral lymphadenectomy (IFL) is performed, depending on the depth of invasion (>1 mm), tumour size, multifocality and the presence of LNM [10]. In up to 85% of patients, significant short- and long-term complications are reported after IFL, such as wound breakdown and infection, lymphoceles, lymphedema and erysipelas [11, 12].

Despite treatment consistent with current guidelines, local recurrences are reported in 40% of patients with early-stage disease in the first 10 years of follow-up, a second recurrence in around half of these patients [13, 14]. In patients with a first local recurrence, disease-specific survival (DSS) decreases from 90 to 70%, and even further after subsequent recurrences [13, 14].

Treatment of macroinvasive local recurrences consists of a RLE, combined with a IFL if a SLN was performed previously [10].

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Consequently, patients who previously underwent a SLN will currently suffer from significant short- and long-term morbidity caused by subsequent IFL [8, 15]. A repeat SLN procedure in these patients has been found feasible, yet the oncological safety is currently studied (clinical trial number NL8467) [16]. Thus far the incidence of inguinofemoral LNM at the time of first local recurrence is unknown, nor the impact of previous groin surgery.

Therefore the aim of our study is to determine the incidence of LNM in patients with a first local recurrence of vulvar cancer, in relation to previous groin treatment and clinicopathological factors.

METHODS

Design and participants

A multicenter retrospective cohort study of patients with recurrent vulvar cancer was performed among all gynaecological oncology referral centres ($n = 8$) in the Netherlands; the Amsterdam University Medical Centers, location AMC, Amsterdam; Antoni van Leeuwenhoek, Amsterdam; Erasmus MC Cancer Institute, Rotterdam; Leiden University Medical Center, Leiden; Maastricht University Medical Center, Maastricht; Radboud University Medical Center, Nijmegen; University Medical Center Groningen, Groningen and the University Medical Center Utrecht, Utrecht. All consecutive patients diagnosed with a first local recurrence of vulvar cancer were identified between 2000–2018. Inclusion criteria were (1) primary surgical treatment for macroinvasive vulvar SCC; (2) first macroinvasive local recurrence between 2000–2018. Exclusion criteria were (1) FIGO Stage IV disease at primary diagnosis and (2) isolated inguinofemoral first recurrence.

Data collection

Patient, tumour and treatment characteristics at diagnosis and recurrence, were collected from medical and pathology files at the participating centres with minimal follow-up of 1 year. Data collection was performed using Castor EDC and records were anonymized, with traceable patient data only available to the principal investigator at each participating centre. The study was approved by the Medical Ethics Committee at the Radboud University Medical Center (case file number 2017–3475) and all local ethics committees.

Variables

Patient and tumour characteristics. Patient characteristics included age at primary and recurrent treatment, body mass index (BMI), presence of diabetes mellitus, use of immunosuppressive medication and smoking.

Tumour characteristics involved uni-or multifocality, location (clitoral, central—not clitoral, lateral or perineal), tumour diameter, depth of invasion, differentiation grade, resection margin, groin status and FIGO-2009 stage [15]. Regarding primary treatment performance of vulvar surgery, type of groin surgery and application of adjuvant radiotherapy (RT) were collected. In case a uni- or bilateral SLN procedure was followed by IFL, these were displayed in the IFL group in order to calculate the baseline characteristics and part of the primary outcome measure. In case of unilateral groin surgery, the groin at which the treatment took place was referred to as the 'treated' groin, the contralateral groin as the 'untreated' groin.

Follow-up was documented by date of last visit at the outpatient clinic, health status and if applicable, date and cause of death.

First local recurrence. For the first local recurrence, the abovementioned variables were collected accordingly. In addition, data concerning evaluation of groin status at first local recurrence using physical examination and imaging (ultrasound with/without fine-needle aspiration cytology (FNAC), computer tomography (CT), positron emission tomography (PET)-CT, magnetic resonance imaging (MRI)), as well as the presence of distant metastases, was registered.

Groin status at first local recurrence. The status of the groins at first local recurrence was classified as positive *(N+)*, negative *(N−)* or unknown *(N?)* and based on histology, imaging and follow-up (Fig. 1). Suspicious nodes on imaging were defined as a short-axis diameter ≥1 cm, combined with other features such as irregular contour and presence of necrosis [17, 18]). The follow-up period of 18 months was based on previous research showing all groin recurrences will be diagnosed within 18 months after only local treatment [14]. The establishment of LNM in this period was based on physical examination or imaging. Groin status was considered *unknown (N?)* if neither histology nor imaging of the groins was performed and follow-up was <18 months after the first local recurrence.

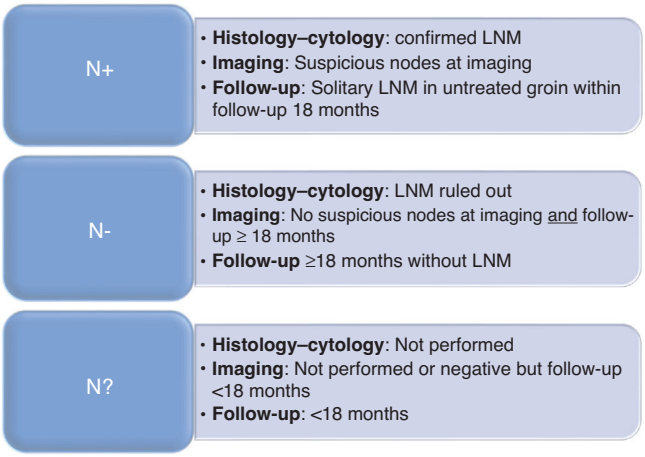

Fig. 1 Classification of groin status at first local recurrence, according to prioritised information; criteria used for patients with positive (N+), negative (N-) or unknown (N?) groin status regarding histology, imaging and follow-up.

Outcome

The primary outcome was defined as the incidence of a *positive (N+) groin* status at first local recurrence. The secondary outcome was defined as the *N+ groin* status in relation to previous groin treatment. In addition, other prognostic factors related to patient- and tumour characteristics were analysed.

Statistical analysis. Analyses were performed using IBM Statistical Package for Social Sciences (SPSS) version 25. Descriptive statistics were used to calculate baseline characteristics and incidence of a *N+ groin status* at first local recurrence. The correlation between tumour size and depth of invasion at primary treatment and first local recurrence was analysed using the Wilcoxon S-R test. To analyse the influence of primary surgical treatment on groin status and identify prognostic factors for a *N+ groin* status, only data from patients with a *known groin status* (*N+ or N−*) was used for analysis. The Chi-Square test was applied at non-parametric nominal variables; a Mann–Whitney *U* test for non-parametric continuous and ordinal variables and an independent *T* test for the parametric continuous variables. Variables significantly correlated at univariate analysis ($P \leq 0.05$), were further analysed using a multivariate analysis.

Previous groin surgery was analysed through a per-patient analysis, then further explored in a per-groin analysis. Follow-up time was calculated in months from the date of primary treatment until the date of the last follow-up. Kaplan–Meier curves were used to analyse the interval time to first local recurrence for the several FIGO stages (*N+* or *N−*) at primary diagnosis of vulvar cancer. A *P* value of <0.05 was considered statistically significant.

RESULTS

In total 404 patients with a first macroinvasive local recurrence of vulvar cancer were eligible for inclusion. Baseline characteristics are shown in Table 1. The median age at primary diagnosis was 71 years, and the majority presented with FIGO stage IB disease. At primary diagnosis, all patients underwent a RLE, only 3.7% without surgical treatment of the groin(s).

At first local recurrence, nearly all patients underwent a RLE, in 41.3% combined with surgical groin treatment. Patients presented with a smaller tumour size ($P < 0.001$) and lesser depth of invasion ($P < 0.001$) compared to their primary tumours.

The localisation of the primary tumour in relation to the first local recurrence was known in 338 patients. In 40.8% (138/338) of

Table 1. Baseline characteristics and treatment at diagnosis of primary vulvar cancer, and treatment of first local recurrence ($n = 404$)

Baseline characteristics		
	Primary tumour	**First local recurrence**
Age at diagnosis (years) (median (range))	71 (26–98)	75 (26–99)
BMI (kg/m^2) (mean (SD)) ($n = 131$)	27.5 (5.4)	–
Diabetes mellitus ($n = 324$)	67 (20.7%)	–
Immunosuppressive medication ($n = 311$)	10 (3.2%)	–
FIGO stage		
IB	252 (62.4%)	–
II	28 (6.9%)	–
IIIA/B/C	124 (30.7%)	–
Tumour size (mm)(median (range))	22 (2–110)	15 (1–135)
Depth of invasion (mm) (median (range))	5 (1–35)	3 (1–45)
Surgical treatment vulva (RLE)		
Yes	404 (100%)	383 (94.8%)
No	–	21 (5.2%)
Surgical treatment groins	389 (96.3%)	167 (41.3%)
SLN procedure	209 (51.8%)	47 (11.6%)
IFL	180 (44.5%)	120 (29.7%)
None	15 (3.7%)	237 (58.7%)
Adjuvant radiotherapy		
None	293 (72.6%)	350 (86.7%)
Vulva	26 (6.4%)	22 (5.4%)
Groins	74 (18.3%)	9 (2.2%)
Vulva and groins	11 (2.7%)	23 (5.7%)
Adjuvant chemoradiation	0 (0.0%)	3 (0.7%)

patients, tumours were located in the same region, compared to 59.2% (200/338) located at a different area of the vulva (Supplement 1).

Groin status at first local recurrence

Of the 404 included patients, 16.3% (66/404) had a *positive (N+) groin status* at first local recurrence, 66.4% (268/404) a *negative (N−) groin status* and in 17.3% of patients (70/404) the groin status was *unknown (N?)* (Fig. 2).

The *N+ groin status* was histologically confirmed in 50.0% (33/66) of patients, based on imaging in 15.1% (10/66), and in 34.9% (23/66) LNM were found during follow-up. Detailed information on patients with positive imaging without histology is provided in Supplementary Fig. 2. Of the 268 patients with a *N− groin status*, this was histologically confirmed in 65.3% (175/268), based on imaging and follow-up in 26.5% (71/268), and LNM-free follow-up in 8.2% (22/268). Among the 70 patients in which the groin status was *unknown*, in 74.3% (52/70) the follow-up time was <18 months. In 25.7% (18/70) a second recurrence developed within 18 months after first local recurrence or at an unknown location. At the end of their follow-up period, 67.2% (47/70) were deceased, in 47.1% (33/70) due to vulvar carcinoma (but without details concerning groin status). Another 25.7% (18/70) was alive but lost to follow-up, and in 7.1% (5/70) the health status was unknown.

Groin status at first local recurrence in relation to previous groin treatment

Groin outcome related to previous surgical treatment. Of the 66 patients with a *N+ groin status* at local recurrence, 50% (33/66) underwent a SLN procedure at primary treatment (Fig. 2); 63.6% (21/33) bilateral and 36.4% (12/33) unilateral. Amongst the patients with a unilateral SLN, the LNM at recurrence was located at the 'treated' groin in 5/12. Of the patients with a N+ groin status at local recurrence undergoing a IFL at primary treatment, 66.7% (18/27) was bilateral and 33.3% (9/27) unilateral in which the LNM was located at the IFL 'treated' groin in 2/9. Six patients with a *N+ groin status* (9.1% (6/66)) did not undergo any previous treatment of the groins based on personal preference, and had a median age of 84 years (range 51–93) at primary diagnosis. Resulting in 78.8% (52/66) of patients with *N+ groin status*, in a previous surgically treated groin. Among the 268 patients with a *N− groin status* at recurrence, 57.5% (154/268) primarily underwent a SLN procedure, 40.7% (109/268) a IFL and 1.9% (5/268) had no previous groin treatment.

At 'per patient analysis' of all 334 patients with a *known groin status*, a *N+ groin status* was present in 17.6% of patients that underwent a SLN procedure and 19.9% for IFL at primary treatment, compared to 54.5% in patients without groin treatment (Fig. 3). When analysed 'per treated groin', this was 11.5% (SLN) and 13.8% (IFL), respectively (Figs. 4 and 5). The incidence of a *N+ groin status* at local recurrence does therefore not appear to be related to previous groin treatment.

Previous groin treatment and risk of N+ groin status *at first local recurrence*. As illustrated in Fig. 3, 56.0% of patients (187/334) underwent a SLN procedure at primary treatment, 40.7% (136/334) a IFL and in 3.3% (11/334) no groin treatment was applied.

Previous SLN procedure. Of the 187 patients undergoing a SLN procedure at primary treatment, 84.0% (157/187) did not undergo adjuvant RT to the groins of which 14.0% (22/157) had a N+ groin status at first local recurrence, nearly all at the previously treated groin (18/22). Resulting in an incidence rate of 11.5% (18/157) at the treated groin (Fig. 4). In total 16.0% (30/187) received adjuvant RT to the groins of which 36.7% (11/30) presented with a N+ groin status at recurrence; 7/11 at the previously treated groin (surgery and radiotherapy), 3/11 at the surgically treated and 1/11 at the radiated groin. The incidence of a N+ groin status after SLN and adjuvant RT is therefore 23.4% (7/30), at the previously treated groin.

Previous IFL procedure. Of the 136 patients undergoing a IFL at primary treatment, 69.2% (94/136) did not receive adjuvant RT to the groins, of which 19.2% (18/94) presented with a *N+ groin status* at first local recurrence (Fig. 5). In 13.8% (13/18) these LNM were located at the previously treated groin. In total 30.1% (41/136) received adjuvant RT to the groins, of which 19.5% (8/41) had a *N+ groin status* at recurrence; 1/8 at the treated groin (surgery and radiotherapy), 6/8 at the surgically treated and 1/8 at the untreated groin. The incidence of a *N+ groin status* after IFL and adjuvant RT is therefore 2.4% (1/41) at the previously treated groin.

No previous groin treatment. In the group of eleven patients in whom surgical treatment of the groins was omitted by patient preference, none received adjuvant RT to the groins either. In total 54.5% (6/11) presented with a *N+ groin status* at recurrence.

Additional prognostic factors related to patient- and tumour characteristics. There were no statistically significant differences in age, BMI, FIGO stage or other patient characteristics for patients with a *N+* or *N− groin status* at first local recurrence (Table 2). Yet, patients with *a N+ groin status* presented with significantly larger tumours, greater depth of invasion, and more frequently poorly

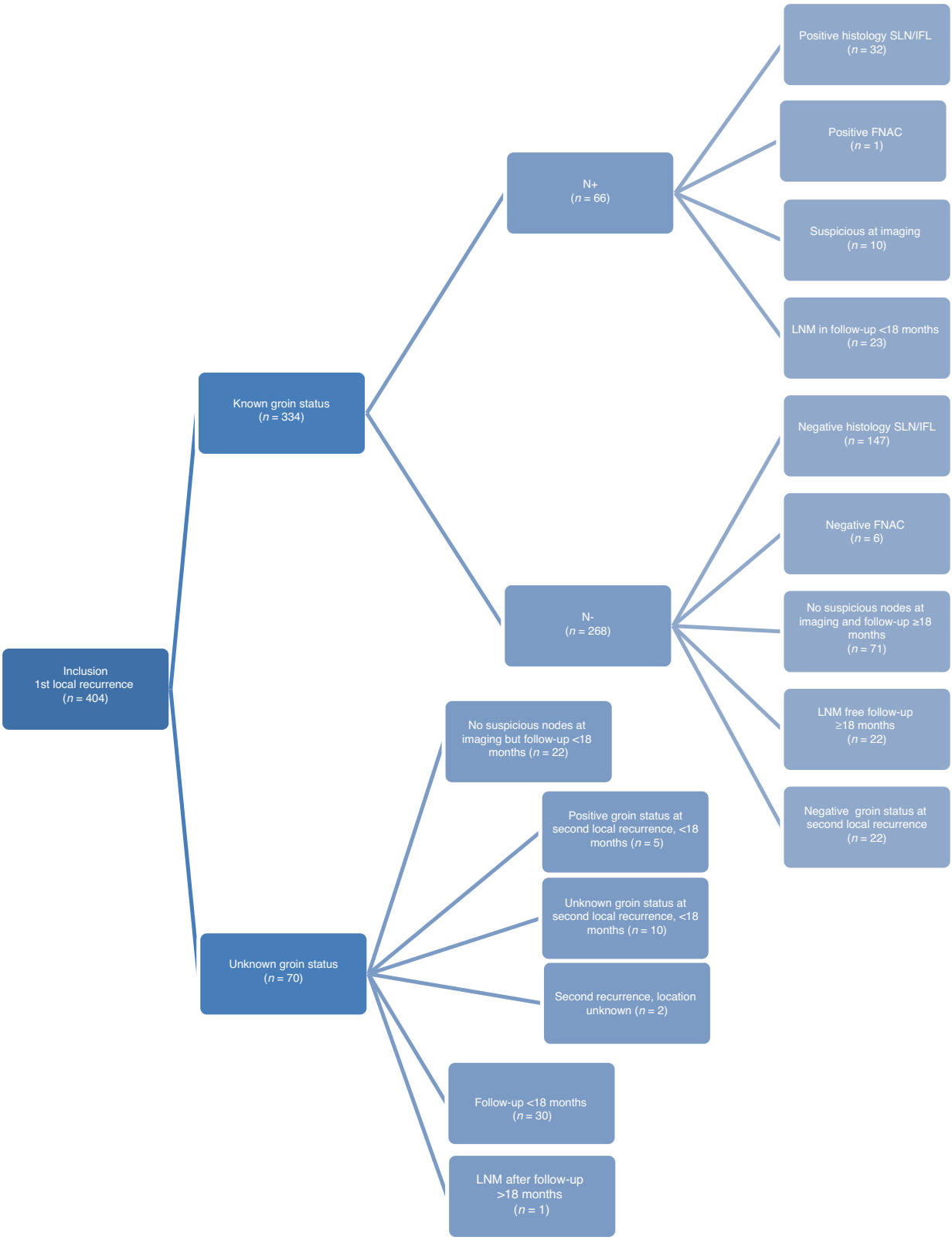

Fig. 2 Groin status at first local recurrence of vulvar cancer ($N = 404$). Overview of distribution of patients according to groin status and the criteria used for classification.

differentiated tumours at first local recurrence, compared to those with a *N− groin status*. At multivariate analysis, only a larger tumour size (≥20 mm) was an independent risk factor for the development of a *N+ groin status* ($P < 0.001$).

Surgical treatment of the first local recurrence

Of all 404 included patients, nearly all underwent a RLE at first local recurrence. Surgical groin treatment was applied in 41.3% (167/404), predominantly IFL (120/167) (Table 1).

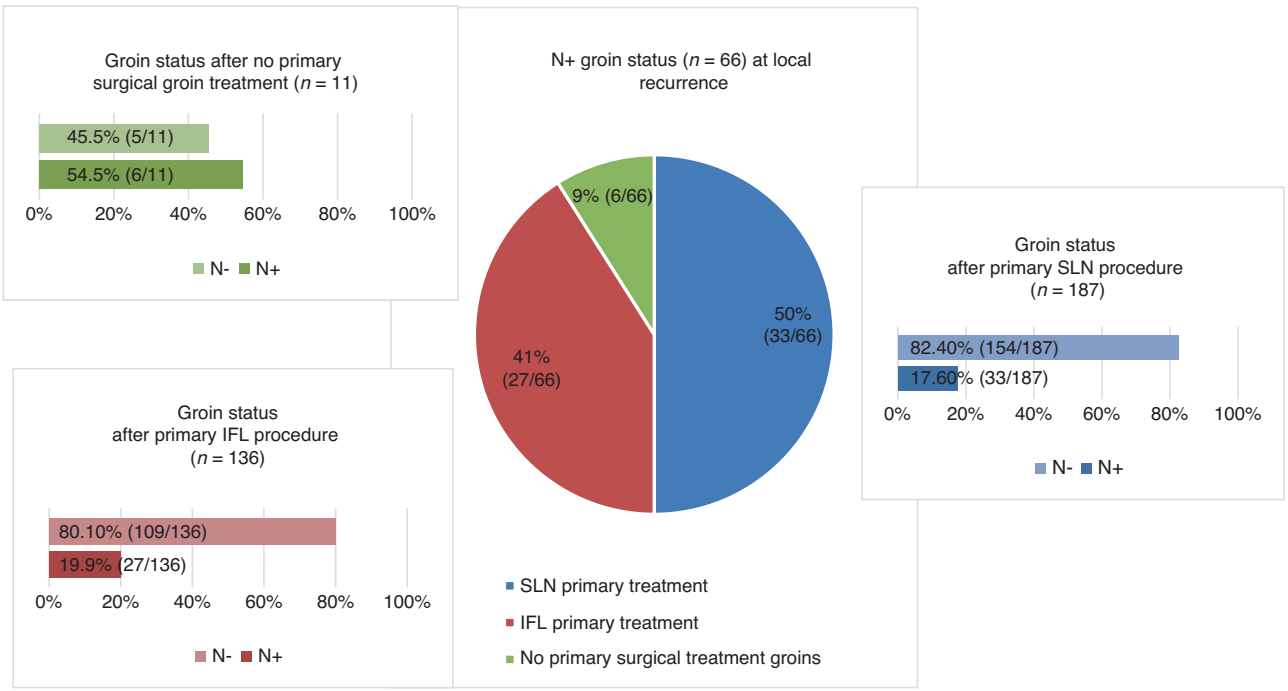

Fig. 3 Positive groin status at local recurrence in relation to type of groin surgery at primary treatment ($n = 66$). Subdivisions by groin status at recurrence per type of groin surgery at primary treatment, in patients with a known groin status ($n = 334$).

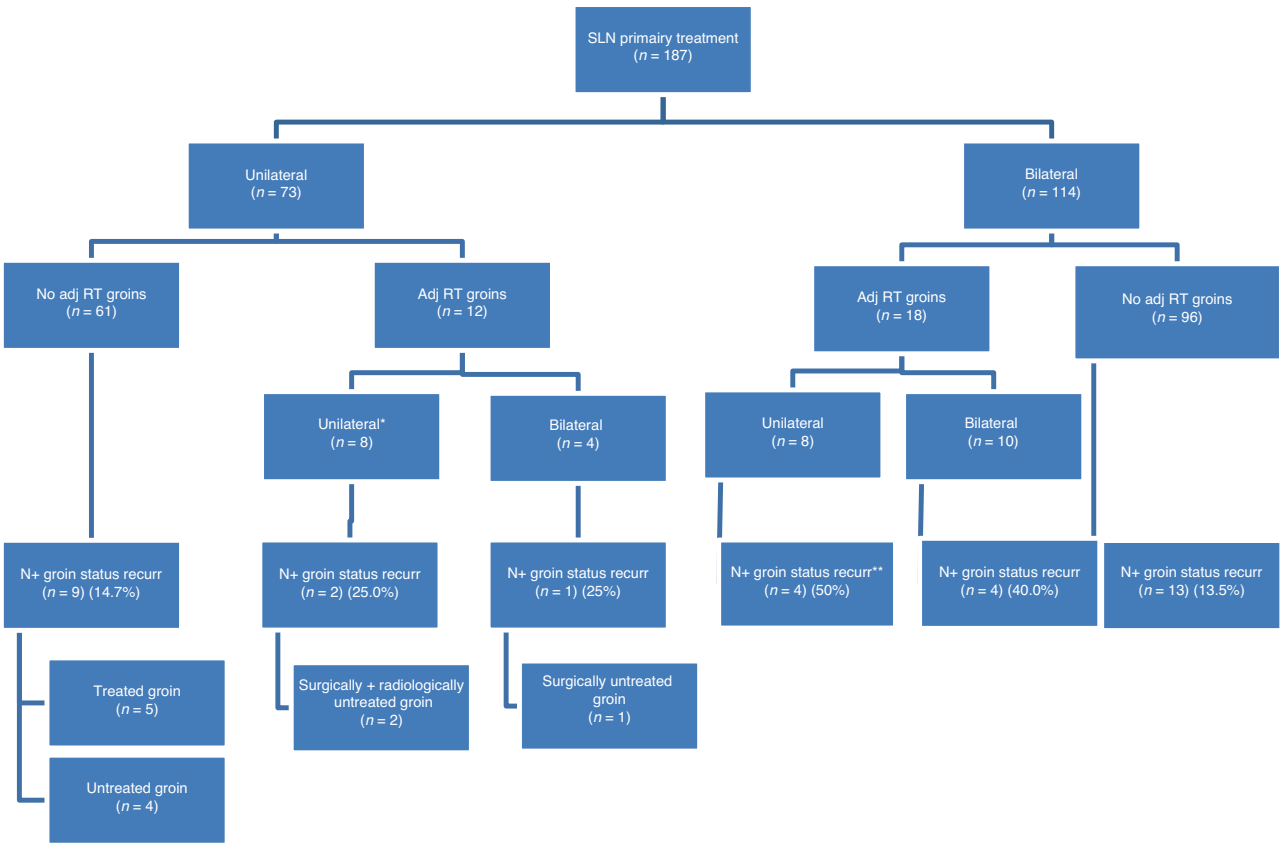

Fig. 4 Positive groin status at local recurrence in patients with SLN procedure at primary treatment ($n = 187$). *Adjuvant radiotherapy applied at corresponding groin SLN procedure in 8/8. **Positive groin status at treated groin adjuvant radiotherapy (RT) prim treatment in 1/4—in 3/4 at radiotherapeutically untreated groin.

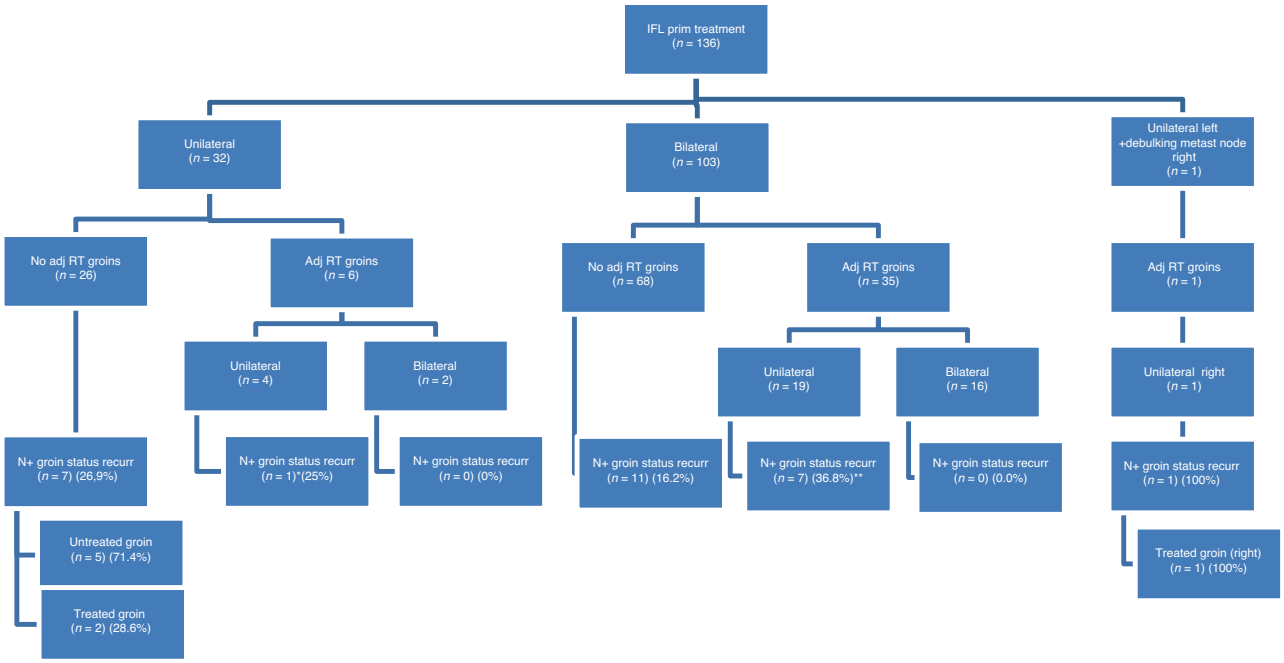

Fig. 5 Positive groin status at recurrence in patients with previous IFL ($n = 136$). *Positive groin status at untreated groin/without adj RT at prim treatment. **Positive groin status at corresponding/treated groin adj RT prim treatment in 1/7—in 4/7 at untreated groin—in 2/7 side unknown.

Table 2. Prognostic factors for positive and negative groin status at first local recurrence, in patients with known groin status ($n = 334$)

	N+ groin status ($n = 66$)	N− groin status ($n = 268$)	*P* value
Age at first local recurrence (years) (mean (SD))	71.4 (13.7)	71.8 (11.2)	0.80[a]
BMI (kg/m^2) (mean (SD)) ($n = 116$)	28.9 (5.7)	27.7 (5.1)	0.33[a]
Diabetes mellitus ($n = 263$)	8 (12.1%)	42 (15.8%)	0.26[b]
Immunosuppressive medication ($n = 256$)	2 (3.0%)	7 (2.6%)	0.78[b]
Smoking ($n = 216$)	8 (12.3%)	26 (9.8%)	0.84[b]
FIGO stage primary vulvar SCC ($n = 334$)			
IB/II ($n = 237$)	42 (63.6%)	195 (72.8%)	0.14[b]
IIIA/B/C ($n = 97$)	24 (36.4%%)	73 (27.2%)	
Surgical treatment groins at primary diagnosis ($n = 334$)			
SLN procedure	33 (55.0%)	154 (57.5%)	0.97[b]
IFL	27 (45.0%)	109 (40.7%)	
Adjuvant radiotherapy groins primary treatment ($n = 72$)	20 (30.3%)	52 (19.4%)	0.05[b]
Tumour size first local recurrence (mm) (median)	25 (4–80)	12 (1–135)	**0.0001**[c]
Focality first local recurrence ($n = 334$)			
Unifocal	53 (80.3%)	238 (88.8%)	0.06[b]
Multifocal	13 (19.7%)	30 (11.2%)	
Depth of invasion first local recurrence (mm) (median)	5 (1–45)	3 (1–37)	**0.0001**[c]
Differentiation grade first local recurrence ($n = 241$)			
Good	6 (12.5%)	68 (35.2%)	**0.002**[b]
Moderate	31 (64.6%)	102 (52.8%)	0.14[b]
Poor	11 (22.9%)	23 (11.9%)	**0.05**[b]

Statistically significant *p*-values are in bold.
[a]Independent *T* test.
[b]Pearson Chi-square.
[c]Mann–Whitney *U* test.

A SLN procedure was performed in 11.6% (47/404) of patients at local recurrence after shared decision-making with the individual patient. In three of them no surgical groin treatment had been performed previously, 38/47 previously underwent a SLN at the same/ipsilateral groin (repeat SLN procedure), and 6/47 a IFL (all but one at the other/contralateral groin).

Of those 58.2% (235/404) without surgical groin treatment at local recurrence, in 11 groin surgery had not been performed at primary treatment either. A majority of 64.2% (151/235) previously underwent a IFL, and 31.1% (73/235) a SLN procedure.

Follow-up

The median follow-up time from date of primary treatment to last check-up or death of all 404 patients, was 79 months (range 4–229). The median follow-up time from date of first local recurrence to last check-up or death was 33 months (range 1–192) and 42 months (range 1–192) in only patients with a *known groin status*.

The median interval time to first local recurrence was 31 months (range 2–202), and was not different for the several FIGO stages at primary diagnosis ($P = 0.406$) (Fig. 6).

DISCUSSION

In our large multicenter nationwide cohort study, including 404 patients with a first local recurrence of vulvar cancer, 16.3% of patients had LNM, independent of the previous type of groin surgery. In line with previously established prognostic factors at primary diagnosis, tumour size, depth of invasion, and tumour grade were associated with LNM at first local recurrence.

The incidence of LNM at first local recurrence and its relation to previous groin treatment has not been reported so far. At primary diagnosis, the incidence of LNM is described to be 25–35% [19] and is mainly related to tumour size and depth of invasion. We observed an incidence rate of 30.7% at primary diagnosis in accordance to existing data in the literature [19]. At first local recurrence this was substantially lower with approximately 16%, likely explained by the life-long follow-up of vulvar cancer patients leading to early detection of (pre)malignancies. This is supported by our findings of significantly smaller tumours, with less depth of invasion at local recurrence.

With respect to previous surgical groin treatment, the incidence of a *N+ groin status* at local recurrence was comparable for patients with a previous SLN and IFL. While tumour diameter and depth of invasion were greater at first diagnosis in patients undergoing primary IFL compared to SLN, at first local recurrence the tumour diameter and depth of invasion were comparable for both groups, and so are thus the incidence rates of a N+ groin status (data not shown). These incidence rates, combined with the comparable prognostic factors for LNM to the primary setting, support the hypothesis that most local recurrences are 'de novo' tumours rather than 'true' recurrences [20–22]. The fact that the majority of local recurrences were located at a different vulvar region than the primary tumour, further strengthens this theory. However, in further prospective studies digital photo's should be considered to know the exact localisation of the tumours. The ongoing cumulative local recurrence rate of vulvar SCC of 4% every year (up to 10 years) as described by te Grootenhuis et al., reinforces the 'de novo' suggestion [23]. In order to further distinct between 'de novo' primary tumours and 'true' recurrences genetic and molecular profiling could be valuable.

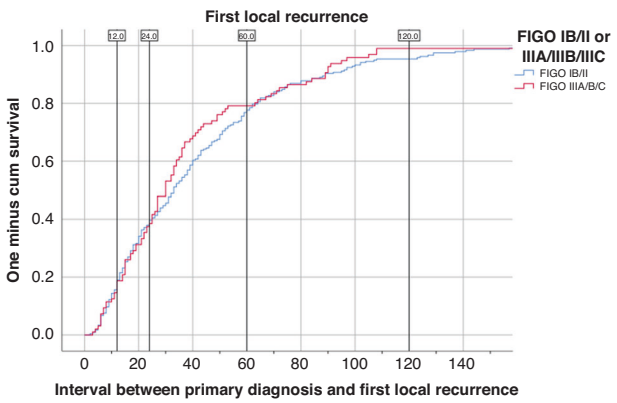

Fig. 6 Time to first local recurrence of vulvar cancer. Interval between primary and first local recurrence by FIGO stage (N+ versus N-) at primary diagnosis, in months ($n = 334$) ($P = 0.406$, log rank).

The very high incidence rate of a *N+ groin status* at local recurrence in patients without previous groin treatment highlight the importance of primary groin surgery if treatment is focused on curative intent.

Current international guidelines recommend a IFL in patients with a first local recurrence, if not performed at primary treatment [10, 24]. Therefore patients that previously underwent a SLN procedure, will yet be exposed to significant morbidity, such as lymphedema. The clinical consequence of 'missing' inguinofemoral LNM on the other hand, is tremendous and nearly always results in palliative treatment. In several other fields of medicine this dilemma has been attended to by exploring the safety of repeat SLN-procedures; in breast cancer patients the repeat SLN procedure has been found feasible and optimises treatment strategies [25], as well as in recurrent melanoma [26]. As described by van Doorn et al. [27], the repeat SLN procedure is feasible in vulvar cancer patients. The procedure is however technically more challenging due to local fibrosis and aberrant lymph drainage patterns, resulting in a lower SLN identification rate of 77% when compared to over 95% at initial SLN procedure. The safety of the procedure is therefore yet unclear but the aim of the ongoing V2SLN study (clinical trial number NL8467) [16].

In our study a small group of patients (9.4% (38/404)) already underwent a repeat SLN procedure after shared decision-making. In line with the hypothesis that most local recurrences are 'de novo' tumours, the performance of a repeat SLN procedure at local recurrence theoretically seems a valid treatment option, when all safety criteria are met and preferably executed within the context of a clinical trial.

In addition, for patients with a previous IFL the probability of LNM at local recurrence should be taken into account, considering the comparable incidence rates of LNM after previous SLN procedure and IFL. In these patients, more elaborate diagnostic screening of the groins (using CT, ultrasound or PET-CT), as well as adjuvant RT to the groins, should be considered at local recurrence.

With respect to previous adjuvant RT to the groins, after primary IFL the incidence of a *N+ groin status* at recurrence was only 2.4%. This questions whether surgical groin treatment at recurrence in these patients can be safely omitted. The incidence of LNM at recurrence after SLN with previous adjuvant RT to the groins was higher (23%) than previously reported in the GROINSS-VII study by Oonk et al. [28], however in a different studied population (patients with primary vulvar SCC compared to patients with already a first local recurrence in our study). In addition, when those cases were closely reviewed, 81.8% of these patients (received their primary treatment (SLN and RT) before 2010 and might therefore have been part of the GROINSS-VII trial (before activation of the stopping rule that excluded patients with SLN macrometastases (>2 mm) and amendment of the study protocol). Long-term results of the GROINS VII study show that RT is a safe alternative for IFL in case of micrometastases (≤2 mm), but not when macrometastases are present. The effectiveness of chemoradiation in these patients with macrometastases will be explored in the GROINSS-V III trial (clinical trial number NCT05076942).

The strength of the study is the nationwide coverage and large number of patients. The study cohort reflects current clinical practice, and is therefore relevant for patient counselling. The challenge was to accurately define the groin status. As mentioned in detail, we incorporated imaging results combined with follow-up, additional to histological and cytological diagnosis of LNM. We realise that solely negative imaging does not rule out micrometastases [29]), but the combination with a recurrence-free follow-up of at least 18 months makes the presence of a LNM highly unlikely. Narrowing down to merely histologically proven LNM would have strengthened reliability of the data, but might result in a distorted reflection/underestimation of the number of patients with a *N+*, as well as *N− groin status* at recurrence and not in line with everyday practice.

By combining imaging and follow-up however, a considerable number of patients with negative imaging but a short follow-up was referred to the 'unknown' group. This might have underrepresented the group of patients with a *N− groin status*. In the remaining patients with *N? groin status* no imaging was performed for unknown/undocumented reasons, which could have introduced bias.

Another difficulty in defining the groin status, was distinguishing the 'treated' from the 'untreated' groin. Basically, all patients were treated according to the current guideline and 'untreated' groins were rightfully untreated based on very low risk on metastases. Exceptions made to the guideline however, can never be ruled out with certainty. Finally, inherent to the retrospective character of the study, some data (such as premalignancies, presence of lymphangitis cutis after previous IFL) could not be consistently retrieved from the patient files.

In conclusion, our study shows an incidence of 16.3% of LNM at first local recurrence of vulvar cancer, independent of previous groin surgery. Tumour size, depth of invasion, and tumour grade were associated with a LNM at recurrence, similar to the prognostic factors at primary diagnosis. These data support the hypothesis that local recurrent vulvar cancer behaves more like ‘de novo’ primary tumours. Combined with future prospective studies on the accuracy and safety of a repeat SLN procedure with digital photos of primary and recurrent tumours, this study can already provide a basis for counselling of patients resulting in more personalised groin treatment. Furthermore, for future research, genetic and molecular profiling could contribute to the distinction between ‘de novo’ primary tumours and ‘true’ recurrences.

DATA AVAILABILITY

All data generated or analysed during this study are included in this published article (and its supplementary information files).

REFERENCES

1. Institute NC SEER cancer statistics factsheets: vulvar cancer. 2020. https://seer.cancer.gov/statfacts/html/vulva.html.
2. Schuurman M, van den Einden L, Massuger L, Kiemeney L, van der Aa M, de Hullu J. Trends in incidence and survival of Dutch women with vulvar squamous cell carcinoma. Eur J Cancer. 2013;49:3872–80.
3. Pleunis N, Schuurman MS, Van Rossum MM, Bulten J, Massuger LF, De Hullu JA, et al. Rare vulvar malignancies; incidence, treatment and survival in the Netherlands. Gynecol Oncol. 2016;142:440–5.
4. van der Steen S, de Nieuwenhof HP, Massuger L, Bulten J, de Hullu JA. New FIGO staging system of vulvar cancer indeed provides a better reflection of prognosis. Gynecol Oncol. 2010;119:520–5.
5. Oonk MH, Hemel BMV, Hollema H, Hullu JAD, Ansink AC, Vergote I, et al. Size of sentinel-node metastasis and chances of non-sentinel-node involvement and survival in early stage vulvar cancer: results from GROINSS-V, a multicentre observational study. Lancet Oncol. 2010;11:646–52.
6. Zhou J, Shan G. The prognostic role of FIGO stage in patients with vulvar cancer: a systematic review and meta-analysis. Curr Med Res Opin. 2016;32:1121–30.
7. De Hullu JA, Hollema H, Lolkema S, Boezen M, Boonstra H, Burger MP, et al. Vulvar carcinoma. The price of less radical surgery. Cancer. 2002;95:2331–8.
8. Van der Zee AG, Oonk MH, De Hullu JA, Ansink AC, Vergote I, Verheijen RH, et al. Sentinel node dissection is safe in the treatment of early-stage vulvar cancer. J Clin Oncol. 2008;26:884–9.
9. Hacker NF, Leuchter RS, Berek JS, Castaldo TW, Lagasse LD. Radical vulvectomy and bilateral inguinal lymphadenectomy through separate groin incisions. Obstet Gynecol. 1981;58:574–9.
10. Oonk M, Planchamp F, Baldwin P, Bidzinski M, Brännström M, Landoni F, et al. European Society of Gynaecological Oncology Guidelines for the management of patients with vulvar cancer. Int J Gynecol Cancer. 2017;27:832–7.
11. Gaarenstroom KN, Kenter GG, Trimbos JB, Agous I, Amant F, Peters AA, et al. Postoperative complications after vulvectomy and inguinofemoral lymphadenectomy using separate groin incisions. Int J Gynecol Cancer. 2003;13:522–7.
12. Leermakers ME, Pleunis N, Boll D, Hermans RH, Ezendam NP, Pijnenborg JM. High incidence of erysipelas after surgical treatment for vulvar carcinoma: an observational study. Int J Gynecol Cancer. 2016;26:582–7.
13. Woolderink JM, de Bock GH, de Hullu JA, Davy MJ, van der Zee AG, Mourits MJ. Patterns and frequency of recurrences of squamous cell carcinoma of the vulva. Gynecol Oncol. 2006;103:293–9.
14. Te Grootenhuis NC, van der Zee AG, van Doorn HC, van der Velden J, Vergote I, Zanagnolo V, et al. Sentinel nodes in vulvar cancer: long-term follow-up of the GROningen INternational Study on Sentinel nodes in Vulvar cancer (GROINSS-V) I. Gynecol Oncol. 2016;140:8–14.
15. Pouwer AW, Arts HJ, van der Velden J, de Hullu JA. Limiting the morbidity of inguinofemoral lymphadenectomy in vulvar cancer patients; a review. Expert Rev Anticancer Ther. 2017;17:615–24.
16. van Doorn HC, Oonk MHM, Fons G, Gaarenstroom KN, de Hullu J, van Rosmalen J, et al. Sentinel lymph node procedure in patients with recurrent vulvar squamous cell carcinoma: a proposed protocol for a multicentre observational study. BMC Cancer. 2022;22:445.
17. Nikolić O, Sousa FAE, Cunha TM, Nikolić MB, Otero-García MM, Gui B, et al. Vulvar cancer staging: guidelines of the European Society of Urogenital Radiology (ESUR). Insights Imaging. 2021;12:131.
18. Land RHJ, Moskovic E, King M, Sohaib SA, Trott P, et al. Routine computerized tomography scanning, groin ultrasound with or without fine needle aspiration cytology in the surgical management of primary squamous cell carcinoma of the vulva. Int J Gynecol Cancer. 2006;16:312–7.
19. Woelber L, Eulenburg C, Kosse J, Neuser P, Heiss C, Hantschmann P, et al. Predicting the course of disease in recurrent vulvar cancer—a subset analysis of the AGO-CaRE-1 study. Gynecol Oncol. 2019;154:571–6.
20. Nooij LS, van der Slot MA, Dekkers OM, Stijnen T, Gaarenstroom KN, Creutzberg CL, et al. Tumour-free margins in vulvar squamous cell carcinoma: Does distance really matter? Eur J Cancer. 2016;65:139–49.
21. Yap JK, Fox R, Leonard S, Ganesan R, Kehoe ST, Dawson CW, et al. Adjacent lichen sclerosis predicts local recurrence and second field tumour in women with vulvar squamous cell carcinoma. Gynecol Oncol. 2016;142:420–6.
22. Tantipalakorn C, Robertson G, Marsden DE, Gebski V, Hacker NF. Outcome and patterns of recurrence for International Federation of Gynecology and Obstetrics (FIGO) stages I and II squamous cell vulvar cancer. Obstet Gynecol. 2009;113:895–901.
23. Te Grootenhuis NC, Pouwer AW, de Bock GH, Hollema H, Bulten J, van der Zee AGJ, et al. Prognostic factors for local recurrence of squamous cell carcinoma of the vulva: a systematic review. Gynecol Oncol. 2018;148:622–31.
24. (WOG) WOG. National Guideline vulvar carcinoma. 2018. https://www.oncoline.nl/vulvacarcinoom2011.
25. Maaskant-Braat AJ, Voogd AC, Roumen RM, Nieuwenhuijzen GA. Repeat sentinel node biopsy in patients with locally recurrent breast cancer: a systematic review and meta-analysis of the literature. Breast Cancer Res Treat. 2013;138:13–20.
26. Beasley GM, Speicher P, Sharma K, Seigler H, Salama A, Mosca P, et al. Efficacy of repeat sentinel lymph node biopsy in patients who develop recurrent melanoma. J Am Coll Surg. 2014;218:686–92.
27. van Doorn HC, van Beekhuizen HJ, Gaarenstroom KN, van der Velden J, van der Zee AG, Oonk MH, et al. Repeat sentinel lymph node procedure in patients with recurrent vulvar squamous cell carcinoma is feasible. Gynecol Oncol. 2016;140:415–9.
28. Oonk MHM, Slomovitz B, Baldwin PJW, van Doorn HC, van der Velden J, de Hullu JA, et al. Radiotherapy versus inguinofemoral lymphadenectomy as treatment for vulvar cancer patients with micrometastases in the sentinel node: results of GROINSS-V II. J Clin Oncol. 2021;39:3623–32.
29. Pounds R, O'Neill D, Subba K, Garg A, Scerif M, Leong E, et al. The role of preoperative computerized tomography (CT) scan of the pelvis and groin in the management of clinically early staged vulva squamous cell carcinoma. Gynecol Oncol. 2020;157:444–9.
30. Pleunis N, Pouwer A, van Heertum A, te Grootenhuis N, Massuger L, Tjiong M, et al. EP1180 Incidence and prognostic factors for inguinofemoral lymph node metastasis in patients with a first local recurrence of vulvar squamous cell carcinoma. Int J Gynecol Cancer. 2019;29:A609.

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AUTHOR CONTRIBUTIONS

Conceptualisation: JdH, HP, NP and AFP. Data curation: NP, AFP, MO, HvD, MT, JvdV, HZ, MvP, EvD and BS. Formal Analysis: NP, JdH and HP. Methodology: NP, AFP, JdH and HP. Supervision: JdH and HP. Writing—original draft: NP. Writing—review and editing: NP, AFP, MO, HvD, MT, JvdV, HZ, MvP, EvD, BS and CV.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the medical ethics committee at the Radboud University Medical Center (case file number 2017–3475) and all local ethics committees. All required data had been previously registered during medical treatment and records were anonymized. The study was performed in accordance with the Declaration of Helsinki.

CONSENT FOR PUBLICATION

Not applicable.

ADDITIONAL INFORMATION

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