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Radiotherapy is not indicated in patients with vulvar squamous cell carcinoma and only one occult intracapsular groin node metastasis

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HIGHLIGHTS

- Omission of adjuvant radiotherapy in patients with one intracapsular groin metastasis results in 1% isolated groin recurrence
- Neither size of the metastasis nor lymph node ratio had a significant impact on the risk of groin recurrence.
- Adjuvant radiotherapy is not recommended in patients with a single occult intracapsular lymph node metastasis.

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ABSTRACT

Objective. Most guidelines advise no adjuvant radiotherapy in vulvar squamous cell carcinoma and a single occult intracapsular lymph node metastasis. However, several recent studies have questioned the validity of this recommendation. The aim of this study was to analyze the groin recurrence rate in patients with a single intracapsular positive lymph node treated without adjuvant radiotherapy.

Methods. Patients with a single clinically occult intracapsular lymph node metastasis, treated without adjuvant radiotherapy, formed the basis for this study. Groin recurrences, and the risk of death, were analyzed in relation to the size of the metastasis in the lymph node and the lymph node ratio. Data were analyzed using SPSS, version 26.0 for Windows.

Results. After a median follow-up of 64 months, one of 96 patients (1%) was diagnosed with an isolated groin recurrence and another two (2.1%) were diagnosed with a combination of a local and a groin recurrence. The only isolated groin recurrence occurred in a contralateral lymph node negative groin. Size of the metastasis and lymph node ratio had no impact on the groin recurrence risk, nor on survival. The 5-year actuarial disease-specific and overall survivals were 79% and 62.5% respectively. The 5-year actuarial groin recurrence-free survival was 97%.

Conclusion. Because of the low risk of groin recurrence and the excellent groin recurrence-free survival, we recommend that adjuvant radiotherapy to the groin in patients with vulvar squamous cell carcinoma and a single occult intracapsular lymph node metastasis can be safely omitted to prevent unnecessary toxicity and morbidity.

1. Introduction

Vulvar cancer is a rare disease and mainly affects older women. A steep increase is seen in the yearly incidence in the Netherlands, from 1-2/100.000 in women aged 50 to 60 years to 14 per 100.000 in women over 80 years [1]. Regional metastases in the inguinal femoral lymph nodes occur frequently and are related to pathological variables such as depth of invasion, lymph vascular space invasion and tumor size [2]. Only stage T1A tumors with a diameter 2 cm or less and a depth of invasion 1 mm or less have a negligible risk of lymph node metastases [3]. Standard treatment for all other squamous cell cancers (SCC) of the vulva consists of a radical local excision of the primary tumor and either lymph node evaluation by sentinel lymph node (SLN) biopsy or primary inguinal femoral lymphadenectomy (IFL) [4].

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When positive lymph node(s) are identified following IFL, there is debate about the issue of when and how to give adjuvant radiotherapy. A randomized Gynecologic Oncology Group (GOG) study showed a benefit for adjuvant radiotherapy, both in terms of inguinal recurrence rate and survival, in patients who had adjuvant radiotherapy to the groins and pelvis as compared to patients who had a pelvic node dissection without radiotherapy [5]. In a subgroup analysis of this study, patients with a single clinically occult positive lymph node displayed no benefit from radiotherapy. A subsequent study from our institution confirmed that patients with a single clinically occult intracapsular lymph node metastasis had a low risk of groin recurrence [6].

The current ESGO guidelines [4] and most, but not all [7] other guidelines, recommend adjuvant radiotherapy, except for patients with one clinically occult and pathologically intracapsular lymph node metastasis [8–11]. However, some recent publications have questioned these recommendations and have recommended adjuvant radiotherapy for all patients with lymph node metastases, irrespective of the number and/or pathological characteristics of these metastases [12–15].

The objective of this study was to analyze recurrence patterns and survival of patients with a single intracapsular lymph node metastasis who were treated without adjuvant radiotherapy.

2. Patients and methods

2.1. Patients

The files of consecutive patients with SCC of the vulva and positive lymph nodes treated from 1987 till 2018, by a radical local excision of the primary tumor and either a unilateral or bilateral IFL, were retrospectively reviewed. Patients were treated in three referral hospitals in the Netherlands and one in Sydney, Australia (Amsterdam UMC, The Netherlands Cancer Institute/Antoni van Leeuwenhoek hospital, Radboud UMC and the Royal Hospital for Women (RHW), Sydney). Patients with a single, clinically occult, positive lymph node without capsule breakthrough who were treated without adjuvant radiotherapy were included in this study. Clinically occult was defined as no palpably suspicious lymph nodes. In these hospitals, it was standard policy not to recommend adjuvant radiotherapy to the inguinal region, nor other adjuvant treatments in patients with the above-mentioned lymph node characteristics. Surgery was performed by experienced gynecologic oncologists who each treated more than 10 patients with invasive vulvar cancer each year. The following clinical and pathological data were retrieved from the files: age of the patient, FIGO 2009 stage, clinical diameter of the primary tumor (mm), total number of removed lymph nodes, lymph node ratio ≤ 10 versus > 10 (percentage of positive nodes in relation to the total number of resected nodes (per groin)), extra-capsular spread and size of the metastasis in the lymph node (< 5mm versus ≥ 5 mm). The data on pathological variables were retrieved from the pathology reports. In cases where data were missing, the original slides were reviewed by an experienced gynecologic pathologist. All patients had a radical local excision of the primary vulvar tumor and a bilateral or unilateral IFL, either primarily or after detection of a single positive sentinel node. A unilateral tumor was defined as a tumor with a medial margin positioned > 1 cm from an imaginary line drawn between the clitoris and anus. In one participating center (RHW, Sydney) it was standard policy not to perform a contralateral inguinal femoral dissection if a single, clinically occult, intracapsular lymph node metastasis was found in the ipsilateral groin in a strictly unilateral vulvar tumor. In the other centers a bilateral groin dissection was standard policy, but this was individualized in selected cases after counseling of the patient. The study was approved by the appropriate Institutional Review Board (IRB), and written informed consent was waived by the IRB, because according to Dutch law, this is not obligated if de-identified patient data are used, keeping in mind the rules of good clinical practice. Approval was obtained from the relevant RHW Ethics Committee for inclusion of their de-identified data in this study.

2.2. Follow-up

All patients were followed-up at regular intervals of at least 3 months in the first two years and 6 monthly thereafter. Recurrences were subdivided into local, groin or distant (including pelvic recurrences). Groin recurrences were analyzed both per patient and per groin.

2.3. Statistics

Standard descriptive statistics were applied: absolute and relative frequencies for categorical variables and median and range for continuous variables. Fisher's exact test was employed to evaluate associations between categorical variables. Estimates of overall survival (OS), and disease-specific survival (DSS) were performed based on the Kaplan-Meier product limit method. OS was defined as the time from primary diagnosis to death from any cause. Survivors were censored on the last day they were known to be alive. DSS was defined as the time from primary diagnosis to death from vulvar cancer. Survivors were censored on the last day they were known without disease. The survival curves were compared using the log-rank test. A p value of < 0.05 was considered statistically significant for all analyses. Statistical analyses were performed in SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA).

3. Results

From the four hospital databases, 96 patients with vulvar cancer and a single clinically occult intracapsular lymph node metastasis were identified. A bilateral (n=76) or unilateral (n=20) inguinal femoral lymph node dissection, either primarily (n=64) or after a single positive sentinel node (n=32) was performed. The characteristics of the patients are shown in Table 1. In four patients, it was not possible to retrieve the tumor diameter in the lymph node.

Of the 57 patients with a lymph node metastasis < 5mm, 26 metastases had a diameter ≤ 2mm and three lymph nodes had only isolated tumor cells. The median follow-up of censored patients was 64 months (range 7-248). First recurrences occurred in 40 of 96 patients (41.7%) after a median recurrence-free interval of 14 months (range 1-152).

One patient (1%) developed an isolated groin recurrence, and 2 patients (2.1%) developed a local and a groin recurrence. The only patient with an isolated groin recurrence developed the groin recurrence in the contralateral (right) groin nine months after a bilateral IFL with one positive node out of 11 resected lymph nodes in the left groin and 0/9 in the right groin. Of the two patients with a combined local and groin recurrence, one patient had a large local recurrence and a lymphangitis carcinomatosa of the skin in the groin. The other patient had a local recurrence and a groin nodal recurrence in the undissected left groin. This patient initially had a single positive lymph node in the right groin (1 out of 6) and a negative sentinel node in the left groin.

Three patients developed an isolated pelvic recurrence. One patient (33 years old) with a 10 mm vulvar tumor and a 3 mm nodal metastasis in the left groin had a 9 mm pelvic node in the left pelvis on a preoperative CT scan. It was decided not to remove the pelvic node but 4 months postoperatively, the node had increased in size and was confirmed to be tumor positive by fine needle aspiration. Another patient (77 years old) was treated for a 7 cm vulvar tumor by a radical local excision and a bilateral IFL. A single intracapsular nodal metastasis was found, while pathology of the vulvar tumor showed tumor positive margins. This patient refused further radiotherapy and three months later she was diagnosed with a left pelvic nodal recurrence. The third patient (52 years old), with a 50 mm vulvar tumor and a 4 mm metastasis in a

Table 1
Characteristics of clinical and pathological variables in 96 patients with a single positive lymph node after complete IFL without RT. (* = percentage of positive nodes to the total number of resected nodes per groin)

Variable	
Age (median and range)	69 (33-96)
Clinical tumor size in mm (median and range)	30 (24-120)
SLN before IFL (%)	32/96 (33.3%)
Unilateral IFL (%)	20/96 (20.8%)
Bilateral IFL (%)	76/96 (79.2%)
Number of resected lymph nodes in affected groin	
• Right (median/range)	10 (4-20)
• Left (median/range)	11 (2-16)
Lymph node ratio*: mean ± SD	11,51 ± 5.68
• ≤ 10	54 (56.3%)
• > 10	42 (43.8%)
Size of nodal metastases in mm: mean ± SD	4.1 ± 2.8
• < 5 mm	57 (59.3%)
• ≥ 5 mm	35 (36.5%)
• missing	4 (4.2%)
FIGO 2009 stage	
• IIIA	89 (92.7%)
• IVA	7 (7.3%)
Recurrence localization	
• None	56 (58.3%)
• Isolated local	27 (28.1%)
• Isolated groin	1 (1%)
• Isolated pelvis	3 (3.1%)
• Isolated distant	3 (3.1%)
• Local plus groin	2 (2.1%)
• Local plus distant	4 (4.2%)

left groin node, showed an isolated left pelvic recurrence 15 months after the treatment of the primary tumor (Table 2).

The diameter of the metastasis in the node (< 5 mm vs ≥ 5 mm) was not significantly associated with any groin recurrence (isolated or combined): 1/57 (1.7%) vs 2/35 (5.7%) respectively (p = 0.322) (S1). When a subdivision was made in diameter of the metastasis ≤ 2 mm, 2-5 mm and ≥ 5 mm, again no significant difference in groin recurrence rate was found (S2). Risk of groin recurrence (isolated groin and combined groin) was not significantly different in the group with a lymph node ratio ≤ 10 versus > 10: 2/54 (3.7%) versus 1/42 (2.4%) respectively (p = 0.594) (S3). The 5-year actuarial disease-specific and overall survivals were 79% and 62.5% respectively (Fig 1a/b). The 5-year actuarial groin recurrence-free survival (including combined groin recurrences) was 97%. There was no significant difference between the DSS or OS in the groups of patients with size of the metastasis in the node < 5 mm versus ≥ 5 mm (S4). The same was found for DSS and OS in the groups of patients with a lymph node ratio ≤ 10 versus > 10 (S5).

4. Discussion

This study demonstrated a very low risk of an isolated groin recurrence in patients with squamous cell cancer of the vulva and a single clinically occult intracapsular positive lymph node after IFL without adjuvant radiotherapy. Only one patient showed an isolated groin recurrence (on the contralateral side). Neither the size of the metastasis in the lymph node (< 5 vs ≥ 5 mm) nor the lymph node ratio had any impact on the groin recurrence rate and/or survival in this group of patients.

Homesley and co-workers showed that there was no benefit of adjuvant radiotherapy in patients with one clinically occult positive lymph node [5]. Although this was a subgroup analysis of a randomized controlled trial and should have been hypothesis generating, many gynecologic oncologists subsequently did not recommend adjuvant radiotherapy for this specific group of patients. In a retrospective study from the National Cancer Database, published in 1997, Creasman and co-workers were also unable to demonstrate any benefit from adjuvant radiotherapy in patients with a single positive lymph node. Neither the size of the metastasis nor the presence of extra-capsular spread was considered in this analysis [16].

As shown in Table 3, the policy of abandoning adjuvant radiotherapy in patients with a single positive lymph node is recommended in most published national guidelines [4,7–11]. Most of the national guidelines take the number of nodes, presence of extra-capsular spread and the size of the metastasis into consideration when recommending adjuvant radiotherapy. Only the NCCN guidelines do not take extra-capsular spread into account, recommending adjuvant radiotherapy in any patient with positive inguinal femoral lymph nodes [7]. In the latter guidelines, the number of positive nodes and the size of the metastasis are used to consider adding chemotherapy to the radiotherapy.

Despite these national recommendations, several recent studies have questioned this policy [12–15,17–19]. A summary of the literature on this subject is shown in Table 4. Six out of 10 published studies recommend adjuvant radiotherapy in all patients, irrespective of the number of positive lymph nodes [12–15,17,19]. Three other studies do not recommend adjuvant radiotherapy [5,6,16], while the large AGO study could not show a significant difference in recurrence free survival with or without adjuvant radiotherapy and was therefore considered inconclusive [18]. The main flaws in the studies are that the previously mentioned nodal characteristics are not always considered. Clinically suspicious nodes, large diameter nodal metastases and especially extra-capsular spread are well known poor prognostic variables [2,20,21]. Comparing adjuvant radiotherapy with no further treatment in patients with a single positive node will only be scientifically valid when the frequencies of these poor nodal characteristics are reported and well balanced.

Two studies, expressing a preference for adjuvant radiotherapy for all patients with positive lymph nodes take into account extra-capsular spread [12,15]. In one of these studies, there is no specific information on extra-capsular spread or recurrence pattern in the six reported patients with a single nodal metastasis who did not get adjuvant radiotherapy [12]. In the other study, Serre and co-workers

Table 2
Characteristics of the three patients with a groin recurrence and three patients with a pelvic recurrence

Age	Initial treatment groin(s)	Diameter of lymph node metastasis (laterality)	Recurrence	Time to recurrence (months)	Outcome
58	Bilateral IFL	9 mm (left)	Isolated node right groin	10	DOD
82	Unilateral IFL right	5 mm (right)	Local and skin right groin	6	DOD
81	Unilateral IFL right/SLN left	4 mm (right)	Local and node left groin	4	DOD
77	Bilateral IFL	Unknown (left)	Isolated node left pelvis	3	DOD
52	Unilateral IFL left	4 mm (left)	Isolated node left pelvis	15	DOD
33	Bilateral IFL	3 mm (left)	Isolated node left pelvis	4	DOD

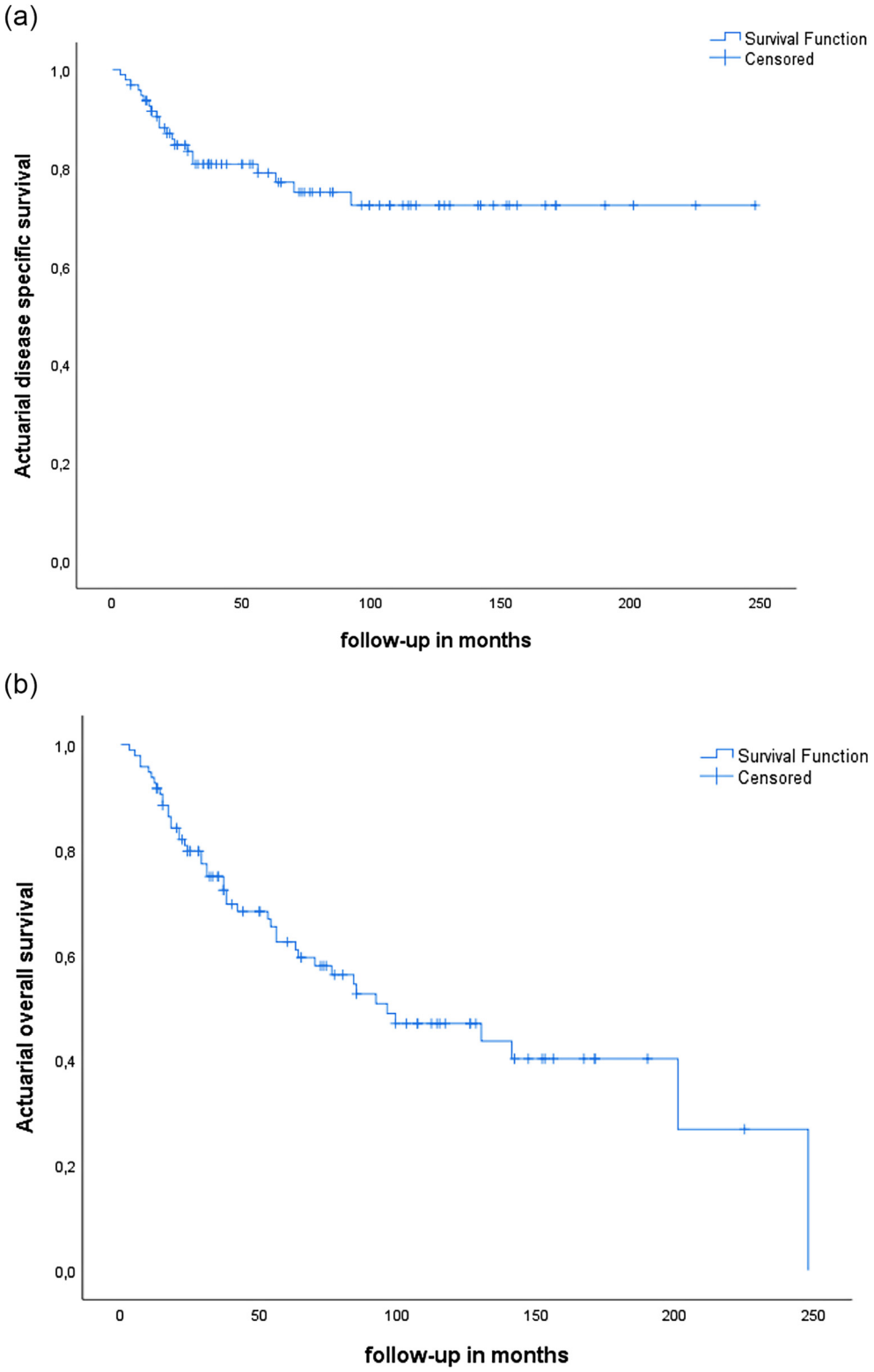

Fig. 1. a/b. Disease specific survival (a) and overall survival (b) of patients with vulvar cancer and a single occult intracapsular metastasis without adjuvant radiotherapy

report on 65 patients with a single intracapsular metastasis [15]. It is not clear what the indications were for adjuvant radiotherapy in 22 patients or for omitting adjuvant radiotherapy in the other 43 patients. In a univariate analysis, adjuvant radiotherapy did not impact on recurrence-free or overall survival, while in a multivariate analysis, adjuvant radiotherapy was an independent favorable prognostic variable for recurrence-free but not overall survival. Unfortunately, no information on the groin recurrence rate or groin recurrence-free survival was available for patients with a single intracapsular metastasis who either had adjuvant radiotherapy or observation. Hence, it is impossible to determine the impact of radiotherapy on the tumor control in the groin in this study.

Table 3
Recommendations on adjuvant radiotherapy in patients with vulvar cancer and positive groin lymph nodes in national guidelines. (*also radiotherapy in case fixed or ulcerated lymph node RT=radiotherapy, CRT= chemo-radiotherapy, n.m.= not mentioned; RCOG: Royal College of Obstetricians and Gynaecologists; DGGG/DKG:Deutsche Gesellschaft fur Gynakologie und Geburtshilfe/Deutsche Krebsgesellschaft; ESGO: European Society of Gynecologic Oncology; NCCN: National Comprehensive Cancer Network; JSGO: Japanese Society of Gynecologic Oncology; GOC/SOGC: Society of Gynaecologic Oncology of Canada /Society of Obstetricians and Gynaecologists of Canada).

	Number of nodes	Size of metastasis	Extra-capsular
RCOG 2014 [8]	>1	RT if complete replacement	If yes: RT
DGGG/DKG 2015 [9] *	>1	RT if any node ≥ 5 mm	If yes: RT
ESGO 2017 [4]	>1	n.m.	If yes: RT
NCCN 2017 [7]	Any (CRT if ≥2)	CRT if any node > 2 mm	n.m.
JSGO 2018 [10]	>1	n.m.	If yes: RT
GOC/SOGC 2019 [11]	>1	RT if any node ≥5 mm	If yes: RT

Table 4
Collated literature data on the impact of adjuvant radiotherapy in patients with squamous cell cancer of the vulva and a single positive lymph node in the groin. ([1] Nodal characteristics such as clinical nodal status (cN) and extra-capsular spread [2]NCDB years 1988-1989 and 1993-1994; [3] SEER data 1988-2001; [4] SEER data 1991-2009; [5] NCDB years 2004-2014; [6] SEER data 2004-2013).

	Source	RT	no RT	Nodal characteristics[1]	RT benefit
Homesley [5]	Hospital	19	17	Only info on cN status	No
Creasman [16]	NCDB[2]	212		no	No
Parthasaraty [17]	SEER[3]	106	102	no	Yes
Fons [6]	Hospital	31	44	yes	No
Woelber [12]	Hospital	14	6	yes	Yes
Mahner [18]	Hospital	77	86	No info on capsule	Inconclusive
Swanick [19]	SEER[4]	94	76	No info on capsule	Yes
Rydzewski [14]	NCDB[5]	816	620	no	Yes
Xanthopoulos [13]	SEER[6]	209	124	no	Yes
Serre [15]	Hospital	22	43	No info on cN status	Yes

Other than the one isolated groin recurrence in our series, it could be argued that the three isolated pelvic nodal recurrences could have been prevented if adjuvant groin and pelvic radiotherapy had been given. A pelvic node metastasis in patients with a single positive groin node is very uncommon. Both Curry et al and Hacker et al reported no pelvic nodal metastases in 16 patients with a single positive groin node [22,23]. In contrast, and in line with our findings, one study reported pelvic metastases in 2 of 14 such patients (14.3%) [5] and another in 1 of 44 (2.3%) [6]. This would give an overall incidence of 3.3% (3/90).

Whether adjuvant radiotherapy could have prevented these recurrences remains unproven, but it does suggest that preoperative imaging (PET/CT scan) should be considered to try to exclude pelvic lymph node metastases. Adjuvant groin and pelvic radiotherapy, even in patients with a single occult groin metastasis, does not always prevent pelvic recurrences [5,6,24] and it increases the risk of lower limb lymphedema after IFL [25,26]. Short term grade 1 and 2 morbidity will also increase, even after intensity modulated radiation therapy [27].

The main flaw of the current study is its retrospective nature, which could theoretically result in a selection bias. A possible selection of prognostically favorable patients is unlikely, however, because the local guidelines of the participating institutes advocate omitting adjuvant radiotherapy in patients with a single occult intracapsular metastasis. The strength of the study is the large number of patients from institutes that perform a high volume of surgical procedures for vulvar cancer. Additionally, all known relevant prognostic clinical and pathological variables with respect to the lymph node metastases were taken into account, such as clinical node status, the size of the metastasis and extra-capsular spread.

In conclusion, among 96 patients with vulvar SCC and a single occult intracapsular lymph node metastasis treated with IFL without adjuvant radiotherapy, a 1% risk of isolated groin recurrence was seen. Therefore, we suggest that adjuvant radiotherapy to the groin and pelvis should not be recommended in these patients.

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CRediT authorship contribution statement

Jacobus van der Velden: Conceptualization, Formal analysis, Investigation, Resources, Writing - original draft. **Noortje Pleunis:** Investigation, Resources, Writing - review & editing. **Ellen Barlow:** Investigation, Resources, Writing - review & editing. **Henry Zijlmans:** Investigation, Resources, Writing - review & editing. **Joanne de Hullu:** Investigation, Resources, Writing - review & editing. **Neville F. Hacker:** Investigation, Resources, Writing - review & editing. **Guus Fons:** Investigation, Resources, Writing - review & editing.

Declaration of Competing Interest

Authors do not declare any conflict of interest related to this paper.

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