



Surgical treatment of vulvar cancer: Impact of tumor-free margin distance on recurrence and survival. A multicentre cohort analysis from the francogyn study group



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ARTICLE INFO

Article history:

Received 24 March 2019

Received in revised form

24 June 2019

Accepted 2 July 2019

Available online 3 July 2019

Keywords:

Vulvar cancer

Tumor-free margin

Recurrence

Survival

ABSTRACT

Objective: In vulvar cancer, it is admitted that tumor-free margin distance is one of the most important element for locoregional control. It is currently recommended to surgically remove the tumor with at least an 8 mm tumor-free margin. The aim of this study was to evaluate the impact of tumor-free margin distance on recurrence and survival in vulvar cancer.

Material and methods: From 2005 to 2016, 112 patients surgically treated for a vulvar squamous cell cancer were included in a retrospective multicenter study. Overall, disease-free and metastasis-free survivals were analyzed according to tumor-free margin distance.

Results: Patients were divided into three groups: group 1 (margin <3 mm, n = 47); group 2 (margin ≥3 mm to <8 mm, n = 48) and group 3 (margin ≥8 mm, n = 17). During the study, 26,8% patients developed recurrence (n = 30) after a median of 8 months (1-69). Analysis of 5-year overall survival, as well as disease-free and metastasis-free survivals, did not reveal a difference between groups. We performed a subgroup analysis in patients with a tumor-free margin <8 mm (group 1 and 2). It showed that histological lesions observed closest to the edge of the specimen were more often invasive or in situ carcinoma lesions in group 1 than in group 2, in which VIN lesions were mainly observed at this location. After re-excision, no patients in group 1 and 50% (n = 2) patients in group 2 developed recurrence.

Conclusion: This study did not reveal a significant impact of tumor-free margin distance on recurrence and survival in vulvar cancer. Moreover, the benefit of re-excision seems stronger when tumor-free margins are positive or very close (<3 mm), cases in which invasive or in situ lesions are often present closest to the edge of the specimen.

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Introduction

Vulvar cancer is a rare disease that represents 1% of women cancers and 3–5% of all gynecological cancers. Its incidence, estimated at 3 to 4 for 100 000 women in the United States, has increased over the last years in the United States and in Europe

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[1,2]. It mainly affects elderly women, even though cases between 40 and 60 years-old are more and more often observed. 90% of these cancers are squamous cell carcinoma. There are precancerous lesions represented by vulvar intra-epithelial neoplasia (VIN), that may occur on a lichen sclerosus field or are caused by an oncogenic Human Papilloma (HPV) infection. Immunosuppression and smoking are other medical conditions at risk of developing vulvar cancer. Symptoms and circumstances leading to diagnosis are not specific.

Disease progression is first locoregional groin lymph node metastases and occur early. Thus, first intention treatment is surgery, including complete tumor resection and lymph node staging. Over the last decades, surgical management has evolved towards wide local excision and uni or bilateral lymph node staging, carried out with a sentinel lymph node procedure or an inguinofemoral lymphadenectomy [3–6]. Nowadays, the sentinel node procedure has shown to be feasible in a very wide range of vulvar tumors, without impairing the oncologic radicality, but dramatically reducing the treatment related morbidity [7]. It is currently recommended to remove the tumor with a histological tumor-free margin of at least 8 mm, which corresponds to a surgical margin of 1–2 cm [8–13]. This wide margin may be difficult to achieve, especially for tumors located close to the urethra or the anus. Although the use of flap can achieve these margins, this does not prevent infectious complication and dehiscence [14,15]. These complications causing a delay in adjuvant treatment. Flaps can also reduce post inguinofemoral lymphadenectomy [16]. In case of a tumor-free margin <8 mm, reexcision is recommended to prevent local recurrence [17]. However, in many cases, reexcision is not possible. Furthermore, strict application of recommendations is sometimes difficult in very old patients presenting with locally advanced disease.

The prognostic value of the 8 mm cut off is currently discussed and due to its impact on therapeutic management, it constitutes an important issue.

The aim of this study was to evaluate the impact of tumor-free margin distance on survival in patients surgically treated for a vulvar squamous cell carcinoma.

Material and method

Patients

A retrospective multicenter study using a database pooling all patients with a squamous cell vulvar cancer diagnosed between 2005 and 2016 and treated in 4 French University hospitals (Reims University Hospital, TENON Hospital (Paris), Tours University Hospital, Marseille University Hospital) was conducted.

Inclusion criteria were: a histologically proven vulvar cancer, primary surgically treated. Patients were more than 18 year-old, affiliated to social security, able to read and speak french.

Exclusion criteria were: neoadjuvant therapy, other histological types than squamous cell.

Study protocol was approved by the Institutional Review Board of the College National des Gynécologues et Obstétriciens Français (CEROG).

Procedures

In agreement with french recommendations, surgical treatment consisted in a total or partial vulvectomy, according to the tumor size and location. Lymph node staging was not performed in case of a small tumor <2 cm with a stromal invasion <1 mm (stage IA) and no lymphovascular space invasion. Otherwise, this staging consisted in a sentinel lymph node procedure for unifocal tumor <4 cm, with no evidence of lymph node metastasis. For tumors located close to the median line (<1 cm), this procedure was done

bilaterally. An inguinofemoral lymphadenectomy was done in case of tumor >4 cm or multifocal, in case of evidence of lymph node metastasis or after a positive sentinel lymph node procedure and before validation of the sentinel lymph node in vulvar cancers [17].

Surgical specimens were sent, oriented, to the histology Department. Surgical margin distances were measured under microscope and were defined as the smallest distance between the edge of the tumor and the edge of the specimen, deeply and laterally. We separated patients into three groups according to the smallest lateral tumor-free margin distance: group 1 with a margin <3 mm, group 2 with a margin ≥ 3 mm to <8 mm and group 3 with a margin ≥ 8 mm. Those threshold were chosen to individualize patients with a positive or very close margin from patients with a negative margin but <8 mm or >8 mm, as it was done in previous studies [18,19]. To define this tumor-free margin and determine if the 8 mm cut off was reached or not, only invasive or in situ carcinoma lesions were taken into account. Presence of VIN or lichen sclerosus lesions surrounding the tumor was also mentioned. All cases were reviewed by a local referent pathologist. In case on close margin, the criteria for re-excision versus radiotherapy was the technical feasibility of re-excision. In the contrary cases, the patients had systematically radiotherapy. If the re-excision allowed in sano margins, the patient had the appropriate adjuvant treatment at the stage of the disease. After histological examination, tumors were classified according to the International Federation of Gynaecology and Obstetrics (FIGO) classification of 2009 [20].

During follow-up, a local recurrence was defined as a recurrence located at the vulva, a regional recurrence as a lymph node metastasis located in the groin. Pelvic lymph node metastases were considered as a distant recurrence, as well as pulmonary, hepatic or bone metastases.

Statistical analysis

The aim of this study was to evaluate the impact of tumor-free margin distance on survival in patients with a squamous vulvar cancer surgically treated. Our first objective was to determine the tumor-free margin distances after surgery. Our second objective was to compare Overall survival, disease-free survival and metastasis-free survival between the three groups of patients. Our third objective was to compare the type of adjuvant treatment received in patients who developed a recurrence.

A univariate analysis was performed to compare patients and tumor characteristics, type of surgical procedure and adjuvant treatment received between the three groups. To compare, categorical variables, we used a Chi² test or a Fisher test when conditions for a Chi² test were not met. To compare a continuous variable with a categorical variable, we used a Student test or a Wilcoxon test if necessary. A Kruskal-Wallis test was performed to compare several means (>2).

Survival curves were calculated using Kaplan-Meier method and compared using a log rank test. We defined global survival as the time period between surgery and death of the patient (any cause) or last follow-up. Disease-free survival and metastasis-free survival were defined as the time period between surgery and locoregional recurrence; and the time period between surgery and distant metastasis recurrence, respectively. A Cox model was used to analyse survival and calculate the Hazard Ratio with a 95% CI. Thus, we compared global, disease-free and metastasis-free survival at 5 years between the three groups. Results were considered significant when $p < 0.05$.

Data were managed with an Excel database (Microsoft, Redmond, WA, USA) and analyzed using the R 3.0.2 software, available online.

Results

Between 2005 and 2016, 124 patients were surgically treated for a squamous cell carcinoma of the vulva in 4 french centers: Department of Gynaecology of Reims University Hospital (Reims, France) (16.1%, n = 20), Department of Gynaecology of Tenon Hospital (Paris, France) (37.9%, n = 47), Department of Gynaecology of Tours University Hospital (Tours, France) (31.4%, n = 39), Department of Gynaecology of Marseille University Hospital (Marseille, France) (14.5%, n = 18). Twelve patients were excluded of the study because of neoadjuvant treatment (n = 2), missing data (n = 9) and palliative care (n = 1). A total of 112 patients primary surgically treated for a squamous cell carcinoma of the vulva were included.

Regarding patients' characteristics, mean age at the time of diagnosis was 70 years-old (range 29–96). A medical history of lichen sclerosus concerned 29.5% of cases (n = 33), of VIN in 8% of cases (n = 9) and of a HPV-induced cancer in 9.8% of cases (n = 11), mostly cervix cancer (90% of cases (n = 10)). Other risk factors as smoking or immunodeficiency were present in 21.4% (n = 24) and 6.2% of cases (n = 7), respectively (Table 1).

FIGO stage was known for 106 patients with mostly stages IB (n = 43) and stages III (n = 36). Mean tumor size was 3.3 cm (0.2–11). Tumor affected adjacent organs in 35.7% of cases (n = 40). It was an invasion of the urethra, the vagina or the clitoris in 8.9% (n = 10), 17% (n = 19) and 15.2% of cases (n = 17), respectively. All these lesions were accessible to immediate surgical treatment. 26.8% of patients (n = 30) underwent total vulvectomy and 69.6% of patients (n = 78) partial vulvectomy. Lymph node staging was performed with a sentinel lymph node procedure in 53.6% (n = 60) of cases and with a uni or bilateral inguinofemoral lymphadenectomy in 49.1% of cases (n = 55). 34.8% patients (n = 39) underwent adjuvant radiotherapy and 16.1% (n = 18) patients received both radiotherapy and chemotherapy (Table II).

A total of 42% of patients (n = 47) had tumor-free margins < 3 mm and were in group 1; 42.8% of patients (n = 48) had margins between 3 mm and 8 mm and were in group 2 and 15.2% of patients (n = 17) had margins ≥ 8 mm and were in group 3. Patient's age was similar between groups. There were no differences regarding FIGO stage, tumor size, histologic grade, lymphovascular space invasion, between groups. However, a stromal invasion > 5 mm was more frequent in group 3: 58.8% of cases (n = 10) versus 12.8% (n = 6) and 14.6% (n = 7) of cases in groups 1 et 2, respectively (p < 0.05). Proportion of patients presenting with inguinofemoral lymph node metastasis was not different between groups. Surgical management of the tumor was similar between groups, except for sentinel lymph node procedure which was more often performed in group 3: 76.5% (n = 13) of patients versus 38.3% (n = 18) and 60.4% (n = 29) of patients in groups 1 et 2, respectively (p < 0.05). In group 1, 12.8% of patients (n = 6) and in group 2, 8.3% of patients (n = 4) underwent re-excision (p = 0.51). 40.4% (n = 19), 27.1% (n = 13) and 41.2% (n = 7) of patients received adjuvant radiotherapy in groups 1, 2 and 3, respectively (p = 0.2).

Mean follow-up was 25 months (1–137). A total of 26.8% patients (n = 30) developed recurrence within a median time of 8 months (1–69). Recurrence occurred at the vulva in 23.2% of patients (n = 26), at the groin in 7.1% of patients (n = 8). Distant metastasis occurred in 5.4% of patients (n = 6).

Analysis of recurrence rates according to tumor-free margin distance did not show a difference between groups. Recurrence rate was 29.8% (n = 14) in group 1, 20.8% (n = 10) in group 2 and 35.3% (n = 6) in group 3 (p = 0.48). Local recurrence rate was not different between groups: 23.4% (n = 11) in group 1, 18.8% (n = 9) in group 2 and 35.3% (n = 6) in group 3, (p = 0.43); as well as regional recurrence rate: 8.5% (n = 4), 6.3% (n = 3) and 5.9% (n = 1) in groups 1, 2 and 3, respectively (p = 0.85). No distant recurrence was observed

Table 1
Patient's characteristics.

	n (%)
Age at diagnosis	
Mean (years)	70.2 (29–96)
≤ 60	26 (23.2%)
> 60	86 (76.8%)
WHO score	
0	25 (22.3%)
1	36 (32.1%)
2	5 (4.5%)
3	1 (0.9%)
Body Mass Index	
Mean (kg/m ²)	26.8 (15.2–43)
Vulvar cancer risk factors	
<i>Tabacco</i>	24 (21.4%)
<i>Immunodeficiency</i>	7 (6.2%)
<i>HIV</i>	1 (0.9%)
<i>HPV induced cancer</i>	11 (9.8%)
Cervix	10 (90.9%)
Anus	2 (18.2%)
<i>Condyloma</i>	3 (2.7%)
<i>Lichen sclerosus</i>	33 (29.5%)
<i>VIN</i>	9 (8%)
<i>Bowen disease</i>	2 (1.8%)
Diagnosis period	
2005–2008	22 (19.6%)
2009–2012	56 (50%)
2013–2016	33 (29.5%)

Data: mean (minimum - maximum), number (%). WHO: World Health Organization.

HIV: Human Immunodeficiency Virus. HPV: Human Papilloma Virus.

VIN: Vulvar Intra-epithelial Neoplasia.

in group 3. Distant recurrence rates were 6.4% (n = 3) in group 1 and 6.3% (n = 3) in group 2 (p = 0.87). It was mostly pelvic lymph node metastases, centro-pelvic area recurrences and pulmonary metastases. (Table II).

There were also no differences in overall survival, disease-free survival and metastasis-free survival at five years between groups (uni or multivariate). (Fig. 1).

When examining the type of histological lesion located closest to the edge of surgical specimen in patients of groups 1 and 2, we observed that there were more often in situ and invasive carcinoma lesions in group 1 than in group 2 (21.3% in situ (n = 10) and 27.7% invasive carcinoma lesions (n = 13) versus 2.1% in situ (n = 1) and 6.3% invasive carcinoma lesions (n = 3)). Whereas in group 2, it was mainly VIN lesions that were observed at this site in 18.8% of cases (n = 9), especially VIN3 lesions in 77.8% of cases (n = 7).

In group 1, recurrence rate was 29.8% (n = 14). No recurrence occurred after re-excision alone, as well as after re-excision and adjuvant radiotherapy. Yet, 21.4% of patients (n = 3) developed recurrence after adjuvant radiotherapy alone and 35% (n = 7) after no adjuvant treatment. In group 2, recurrence rate was 20.8% (n = 10). It was 50% (n = 1) after re-excision alone; 50% (n = 1) after re-excision and adjuvant radiotherapy and 13.8% (n = 4) after no adjuvant treatment. Statistical analysis was not possible because of the small number of patients in this subgroup analysis.

Discussion

This study did not reveal a significant impact of tumor-free margin distance on recurrence and survival in vulvar cancer. In particular, we did not confirm the 8 mm cut off. This last is based on studies that have observed a better local control when margins are beyond this threshold. In these studies, local recurrence rates were between 23% and 48% in groups with margins < 8 mm and no local recurrences were observed in groups with margins ≥ 8 mm [11–13].

Table 2
General features of tumor and per group of resection margin.

	n = 112	group 1	group 2	group 3	p
		<3 mm (n = 47)	≥3 mm et < 8 mm (n = 48)	≥8 mm (n = 17)	
Age (years)	70.2 (29–96)	69.9 (38–88)	70.2 (29–96)	70.9 (45–84)	1
Margin distance (median, mm)	3 (1–5)	0 (0–2.5)	4 (3–7)	10 (8–20)	<0.05
FIGO stage★					0.78
I	54 (48.2%)	18 (38.3%)	27 (56.2%)	9 (52.9%)	
Ia	7 (6.2%)	5 (27.8%)	1 (3.7%)	1 (11.1%)	
Ib	43 (38.4%)	11 (61.1%)	25 (92.6%)	7 (77.8%)	
unspecified	4 (3.6%)	2 (11.1%)	1 (3.7%)	1 (11.1%)	
II	12 (10.7%)	3 (6.4%)	8 (16.7%)	1 (5.9%)	
III	36 (32.1%)	19 (40.4%)	10 (20.8%)	7 (41.2%)	
IIIa	16 (14.3%)	7 (36.8%)	4 (40%)	5 (71.4%)	
IIIb	10 (8.3%)	4 (21.1%)	5 (50%)	1 (14.3%)	
IIIc	7 (6.2%)	7 (6.2%)	1 (10%)	1 (14.3%)	
unspecified	3 (2.7%)	3 (15.8%)	0	0	
IV	4 (3.6%)	1 (2.1%)	3 (6.2%)	0	
IVa	1 (0.9%)	1 (100%)	0	0	
IVb	1 (0.9%)	0	1 (33.3%)	0	
unspecified	2 (1.8%)	0	2 (66.6%)	0	
unknown	6 (12.8%)	6 (12.8%)	0	0	
Tumor size (cm) *					
Mean	3.3 (0.2–11)	3.2 (0.3–11)	3.2 (0.2–8.4)	3.8 (0.6–8.2)	0.53
≤ 4 cm	79 (70.5%)	35 (74.5%)	34 (70.8%)	10 (58.8%)	
> 4 cm	27 (24.1%)	8 (17%)	13 (27.1%)	6 (35.3%)	
Stromal invasion (mm) ✧					
Median	7 (0–40)	7 (0–40)	5 (0–7)	6.5 (2–15)	<0.05
≤ 5 mm	49 (43.7%)	21 (44.7%)	26 (54.2%)	2 (11.8%)	
> 5 mm	23 (20.5%)	6 (12.8%)	7 (14.6%)	10 (58.8%)	
Lymphovascular space invasion ✧	32 (28.6%)	14 (29.8%)	12 (25%)	6 (35.3%)	0.61
Histologic grade					0.96
1	57 (50.9%)	22 (46.8%)	26 (54.2%)	9 (52.9%)	
2	29 (25.9%)	13 (27.6%)	13 (27.1%)	3 (17.6%)	
3	7 (6.2%)	3 (6.4%)	3 (6.2%)	1 (5.9%)	
Type of surgery					
Total vulvectomy					
Radical	29 (96.7%)	13 (27.6%)	13 (27.1%)	3 (17.6%)	0.7
Superficial	1 (3.3%)	0	1 (2.1%)	0	0.51
Partial vulvectomy					
Radical	61 (6.8%)	24 (51.1%)	26 (54.2%)	11 (64.7%)	0.62
Superficial	17 (15.2%)	8 (17.0%)	7 (14.6%)	2 (11.8%)	0.9
Lymph node staging					
Sentinel node procedure	60 (53.6%)	18 (38.3%)	29 (60.4%)	13 (76.5%)	<0.05
positive lymph node(s)	13 (11.6%)	6 (33.3%)	5 (17.2%)	2 (15.4%)	0.89
Inguinofemoral lymphadenectomy	55 (49.1%)	25 (53.2%)	20 (41.7%)	10 (58.8%)	0.33
positive lymph node(s)	28 (25%)	14 (56%)	8 (40%)	6 (60%)	0.32
Adjuvant radiotherapy ✧	35 (31.2%)	19 (40.4%)	13 (27.1%)	7 (41.2%)	0.2
Re-excision ✧	12 (10.7%)	6 (12.8%)	4 (8.3%)	2 (11.8%)	0.51
Follow-up (median, months)	25.5 (0–137)	18 (0–99)	13.5 (0–137)	18 (1–71)	0.57
Recurrence ✧	30 (26.8%)	14 (29.8%)	10 (20.8%)	6 (35.3%)	0.48
Local	26 (23.2%)	11 (78.6%)	9 (90%)	6 (100%)	0.43
Regional	8 (7.1%)	4 (28.6%)	3 (30%)	1 (16.7%)	0.87
Distant	6 (5.3%)	3 (21.4%)	3 (30%)	0	0.85
Pelvic lymph nodes	3 (2.7%)	1 (33.3%)	2 (66.7%)	0	0.58
Centro-pelvic area	4 (3.6%)	2 (66.7%)	2 (66.7%)	0	0.72
Bone	1 (0.9%)	1 (33.3%)	0	0	0.57
Lung	4 (3.6%)	3 (100%)	1 (33.3%)	0	0.49
Liver	1 (0.9%)	1 (33.3%)	0	0	0.57

Data: Mean (minimum - maximum), number (%), ★ *data available on only 106 cases, ✧ data available on only 85 cases, ✧ data available on only 110 cases.

✧ data available on only 110 cases, ✧ data available on only 99 cases, ✧ data available on only 109 cases.

Viswanathan et al. and Rouzier et al. showed, in their studies of 205 and 215 patients, that local recurrence risk was increased three times when margins were <10 mm, with statistical significance [8,9]. Nooij et al. meta-analysis, about ten studies carried out between 1990 and 2015, involving 1278 patients, indicated a relative risk of local recurrence multiplied by 1.99 (IC95% [1.13–3.51], $p=0.02$) when margins are <8 mm [21]. Our study, with 112 patients included and a recurrence rate of 26.8% ($n=30$), did not confirm this increased risk for recurrence, neither for survival (Overall, disease-free and metastasis-free) according to margin

distance. However, in patients with margins >8 mm, recurrences were foremost local recurrences (with one case of regional recurrence associated and any case with distant recurrence) which occurred with a delay of more than 24 months after surgery for half of them. Thus, we cannot exclude that some of these recurrences were actually new cancers and that we overestimated the number of real recurrences in that group. According to Nooij et al., 80% of local recurrences occur within two years after initial treatment and even if this delay depends also on the tumor's characteristics in particular its growth potential, it is likely that most of the tumors

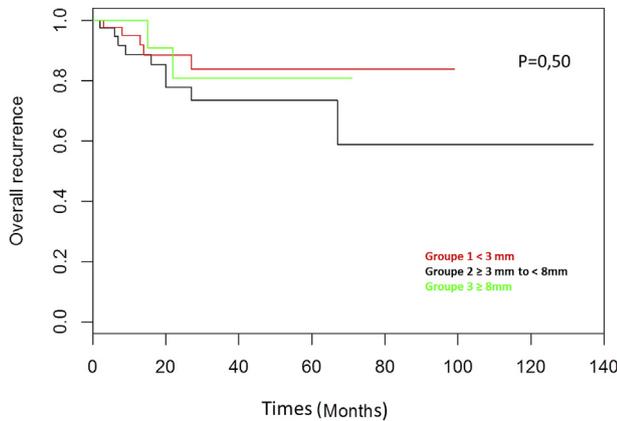


Fig. 1. Overall recurrence according to size margins resection.

occurring after this period are new primitive tumors, arising from a persistent precancerous local condition [21].

Another part of literature did not confirm an association between margin distance and recurrence risk, as the studies of Baiocchi et al. and Woelber et al. who had, in the same way, separated patients into three groups (margin < 3 mm); (margin ≥ 3 and < 8 mm); (margin ≥ 8 mm); as well as in the studies of Woelber et al. and Nooij et al., in which patients were separated into three groups in a different way (margin positive); (margin negative and < 8 mm); (margin ≥ 8 mm) [18,19,21,22]. According to Woelber et al., studies that showed an association between margin < 8 mm and local recurrence had too many confusing factors to give strong conclusions. Indeed, most of these studies compared very heterogeneous groups of patients in terms of initial disease extent, which is an important prognostic factor, and, Viswanathan et al. study excepted, did not take adjuvant treatments into consideration. In order to avoid these potential confusing factors, Woelber et al. chose to study patients only surgically treated (no adjuvant radiotherapy), with no lymph node metastases (stage I and II). They did not observe an increased risk of local recurrence in patients with margins negative and < 8 mm, compared with patients with margins negative and ≥ 8 mm [22].

Several studies analyzed other margin distance thresholds. Only, Viswanathan et al. showed a significant decreased risk of local recurrence when margin ≥ 5 mm (HR = 0.53, 95% CI 0.31–0.9, $p = 0.002$) [3]. The other studies did not confirm that observation and did not find another margin distance threshold [19,21–23]. So, in case of positive margins, the risk of local recurrence is clearly increased but in case of negative but close margins, results of studies are conflicting [8,9,21,24].

We performed a subgroup analysis in order to study more specifically patients with close margins, between 3 and 8 mm (group 2) and very close margin, < 3 mm (group 1). This analysis was only descriptive due to small number of patients. However, it showed that histological lesions observed closest to the edge of the specimen were more often invasive or in situ carcinoma lesions in group 1 than in group 2, in which VIN lesions were mainly observed at this location. Risks associated to these lesions are not the same: in the first case there is a high risk of recurrence whereas in the second one, the main risk is to develop a second primitive tumor on a persistent degenerative field. The particularity of this study is that VIN and lichen sclerosis lesions were taken into consideration, most of the other studies did not specify whether these epithelial disorders surrounding the tumor were present or not. In this study, tumor size was not different between the three groups ($p = 0.53$). Thus, differences in tumor-free margin distances could be

explained by the tumor's location. In case of a tumor located close to the urethra or the anus, it is indeed difficult to have a macroscopically 1–2 cm tumor-free margin without mutilation or dysfunction consequences. On the other hand, we did not evaluate the impact of surgical flaps in these situations. Only 25% of patients ($n = 28$) received surgical flaps and tumor-free margin were ≥ 8 mm in 4.5% of cases ($n = 5$). Information whether a surgical flap has been done or not was not always available in our study. It could be another part of the explanation of differences observed in margin distances between patients. Moreover, histological management of surgical specimens was different between centers since in some centers, specimens were sent to the pathologist with formalin fixation and in others, with no fixation. Yet, formalin causes tissue retraction. Hence, it could also explain differences in margin distances between patients. This bias is frequent in retrospective multicentered studies. Furthermore, it is well-known that margin distance measurement is very difficult, explaining changes in the use of a minimal tumor-free margin for many cancers.

Analysis of adjuvant treatments in groups 1 and 2 showed a benefit of re-excision, alone or associated with radiotherapy on recurrence rate for patients in group 1 (no recurrence after re-excision, alone or associated; 21.4% ($n = 3$) and 35% ($n = 7$) of recurrence after radiotherapy alone and after no adjuvant treatment). In group 2, this benefit was not that clear (50% ($n = 2$) of recurrence after re-excision alone or associated, 30% ($n = 3$) and 13.8% ($n = 4$) after radiotherapy alone and after no adjuvant treatment). Ioffe et al. studied re-excision specimen, they showed that invasive and micro-invasive carcinoma lesions were found in 33% of cases when initial margins were positive for invasive or micro-invasive carcinoma, in 4% of cases when initial margins were between 1 and 10 mm and in 7% of cases when initial margins were positive for VIN lesions ($p < 0.0001$) [25]. Thus, benefit of re-excision seems the greatest in case of positive margins for invasive or microinvasive lesions. We can imagine that it is the same for very close margins, as in group 1. This could explain the better results of re-excision in this group of patients, compared with patients of group 2 who underwent the same treatment.

However, in many cases, re-excision is not possible, usually for anatomic reasons, it also depends on patient medical condition. In this situation, our study suggest a benefit of radiotherapy to prevent recurrence, especially in group 1. In group 2, we did not observe any benefit of adjuvant radiotherapy alone. On the contrary, other studies suggest a benefit of adjuvant radiotherapy, notably a significant increase in global survival in case of positive margins and also in case of positive or close margins (≤ 10 mm) and a significant increase of disease-free and global survivals in patients with lymph node metastases [26–28]. Our results in group 2 could be explained by cumulative risk factors in these patients. Indeed, among these 10 patients who received adjuvant radiotherapy, 9 patients had lymph node metastases, 7 patients a tumor > 4 cm and 9 patients a stromal invasion > 5 mm.

This study has limits. First of all, heterogeneity between groups with a significant higher proportion of patients with a stromal invasion > 5 mm in group 3, which is another risk factor for local recurrence. In general, there was an important heterogeneity between patients regarding disease extent or type of treatment received. This study was indeed conducted on a 11 years period, during which therapeutic management of vulvar has evolved. Furthermore, because of the retrospective study, we only have information on the surgical revision, but not on the presence of a residual tumor. We can't extrapolate the results of this recovery (in sano margins or not) in order to refine the results. Our results need to be confirmed by other studies, ideally prospective, on more homogenous patients, in order to limit confusing factors and evaluate the individual role of margin distance for locoregional control.

Conclusion

This study did not reveal a significant impact of tumor-free margin distance on recurrence and survival in vulvar cancer. A minimal 8 mm threshold was not confirmed. Moreover, the benefit of re-excision seems stronger when tumor-free margins are positive or very close (<3 mm), cases in which invasive or in situ lesions are often present closest to the edge of the specimen.

Conflict of interest

None.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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