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Vulvar cancer recurrence — an analysis of prognostic factors in tumour-free pathological margins patients group

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ABSTRACT

Objectives: To evaluate risk factors associated with the local recurrence of invasive squamous cell vulvar cancer in patient group with tumor-free pathological margins.

Material and methods: This is a retrospective analysis of 47 patients who underwent surgical treatment at University Hospital Brno, the Czech Republic between 2007 and 2014. 24 patients were classified as IB stage and three as II stage. A further 20 patients representing stage III showed the metastatic involvement of regional lymph nodes. Seven prognostic factors were analyzed in relation to local tumour recurrence: tumour size, margin distance, depth of invasion, lymphovascular space involvement (LVSI), midline involvement, metastatic lymph nodes and FIGO stage.

Results: All prognostic factors were found to be statistically significant with respect to the risk of local recurrence. The highest risk of local recurrence was observed for the depth of invasion > 5 mm (HR, 12.42 [95% CI; 3.44–44.84]) and for the presence of LVSI (HR, 10.83 [95% CI; 3.87–30.28]). The study also established a clear difference in the risk of local recurrence between patient groups with resection margin < 8 vs. ≥ 8 mm (HR, 4.91 [95% CI; 1.73–13.93; p = 0.003].

Conclusions: Tumour-free pathological margin of ≥ 8 mm is a major prognostic factor of local recurrence which can be influenced by the surgeon. A perfect knowledge of the extent of the disease prior to surgery supports adequately radical surgical trends. The emphasis is given on adequate radicality as well as on the reduction of overtreatment without worsening prognosis by simultaneously preserving the quality of life.

Key words: squamous cell vulvar cancer, surgical treatment, tumour-free pathological margins, local recurrence

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INTRODUCTION

Vulvar squamous cell carcinoma (VSCC) is a less frequently occurring tumour among predominantly older women. It accounts for 3–5% of all gynaecological malignancies, but its incidence has been steadily increasing over the past twenty years. Median age at vulvar cancer diagnosis is 68 years and the median age at death is 79 years [1]. Surgical treatment is a preferred treatment approach not only in the early stages but also in most locally advanced cases and recurrences [2, 3]. Surgical treatment strategies for the vulva and adjacent lymph nodes has changed considerably over the past two decades. Novel surgical approaches are primarily focused on the early stages of disease with a preference for broad local excision combined with sentinel node biopsy. Locally advanced findings are, from this perspective, more challenging and treatment results less satisfactory. The surgical strategy in these cases generally includes vulvectomy with systematic bilateral inguinofemoral lymphadenectomy [3, 4]. In the case of extensive defects which cannot be solved by a simple suture, reconstruction surgery performed by

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a reconstructive surgeon may be imperative [5, 6]. An alternative to this approach is the use of the concept of neoadjuvant chemotherapy with or without concomitant radiotherapy in patients with severe internal comorbidities [7, 8].

Approximately one-third of patients experience a recurrence of the disease, predominantly in the first two years following the end of primary therapy [9, 10]. A majority of recurrences represent isolated local vulvar recurrences which may be curatively resolved by radical wide local excision [11, 12]. However, the regional recurrence of the disease in the groin is difficult to treat and is largely associated with poor prognosis [13, 14]. The management of retroperitoneal and remote disease recurrence is based on symptom control, as radiotherapy and chemotherapy exhibit limited success rates [15].

Objectives

The aim of this retrospective study is to analyze risk factors associated with local recurrence in a group of VSCC patients classified as stages IB-IIIC according to the International Federation of Gynecology and Obstetrics (FIGO), provided there are tumour-free pathological margins at first-line surgical therapy.

MATERIAL AND METHODS

This retrospective study includes 47 patients with invasive VSCC classified as FIGO stages IB–IIIC who underwent primary surgery with tumour-free pathological margins between January 2007 and December 2014 at the Department of Gynecology and Obstetrics of the University Hospital Brno (Brno, Czech Republic). Patients with microinvasive carcinoma (FIGO stage IA) with the negative resection margins have an excellent prognosis, therefore we did not include them in the study. Based on biopsy results and local clinical findings, suitable imaging methods were employed before surgery in order to determine the expected stage of the disease and to exclude distant metastases. An ultrasound examination was generally used to evaluate possible malignant inguinofemoral lymphadenopathy while computer tomography was predominantly used to exclude pelvic lymphadenopathy and tumour dissemination above the pelvis. Scintigraphy was performed to exclude bone metastases and a PET/CT scan was employed when planning a large-scale excision with reconstruction. Only patients who were expected to complete primary staging surgery, i.e. patients without fixed inguinofemoral lymphadenopathy and with no suspicion of distant metastases, were included in the evaluation.

In all patients, the surgical procedure consisted of excision surgery on the vulva in combination with a surgical verification of regional lymph node status. Vulvar surgery was defined as a radical excision or vulvectomy, depending on the size of the tumoor and the coexistence of dystrophic and premalignant changes. Regional inguinofemoral lymphadenectomy was performed as unilateral or bilateral. In lateral tumours, only ipsilateral lymphadenectomy was performed. A unilateral tumour was defined as a lesion which does not cross the midline, with the medial margin of the tumour more than 10 mm from the midline structures. The utilized lymphadenectomy technique included systematic performance or sentinel node biopsy (SNB). SNB was performed in tumours smaller than 4 cm in case of negative clinical and ultrasound findings in the inguinofemoral lymphatic region; in case sentinel node was found to be positive, bilateral systemic lymphadenectomy was performed. Adjuvant radiotherapy for the vulva region was reported by patients with a resection margin of < 8 mm, a depth of invasion > 5 mm, a presence of lymphovascular space involvement (LVSI) and with locally advanced tumours infiltrating of surrounding organs. Adjuvant radiotherapy of the lumbar region (inguinofemoral and pelvic) was indicated in case more than one regional node was involved or extracapsular spread was presented (irrespective of the number of affected nodes).

Information on age was reported by each patient while histotype and tumour grade were determined on the basis of the performed operation. Additionally collected information included tumour size, margin distance, depth of invasion, LVSI, midline involvement and metastatic inguinofemoral lymph nodes. The staging of the disease according to FIGO was determined, and risk factors for recurrence, disease-free survival (DFS), overall survival (OS) and mortality index due to disease progression were analyzed. All enrolled patients met the regular follow-up (range, 4–105 months) criterion.

Statistical analysis

Categorial variables were reported as absolute numbers and percentages and continuous variables as means ± SD or median (range) respectively. Associations between prognostic factors and recurrence were tested using the Spearman correlation coefficient and the chi-squared test. The Cox proportional hazard ratio was assessed to estimate risk factors for recurrences. Differences in the distributions of patient characteristics were analyzed using the t-test and the Mann-Whitney test. DFS and OS were analyzed using the Kaplan-Meier test. Differences associated with $p < 0.05$ were considered significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and graphics were constructed using R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The analysis included a total of 47 patients with invasive VSCC. The youngest patient was 44, the oldest was 85 years old. All tumours included in the analysis were unifocal. When

evaluating the local tumour range on the vulva, the most common was T1b, encountered in 38 patients (80.8%), followed by T2 in the remaining 9 patients (19.2%) where local infiltration spread from the vulva to the adjacent organs (the distal third of the urethra and vagina). A large tumour of at least 40 mm in the largest dimension occurred in 42.5% of all patients. The appropriate margins ≥ 8 mm, recommended by most existing studies, were achieved in 22 patients (46.8%), close margins (< 8 mm) were observed in 25 patients (53.2%), ranging from 0.15 to 7.0 mm. The depth of invasion > 5 mm occurred in 22 patients (46.8%) with a predominance of larger tumours and a mean of 51 mm (range, 12–120 mm). LVSI was present in 25.5% of patients and was always associated with the presence of malignant inguinofemoral lymphadenopathy with an average of 4.0 metastatic nodes (range: 1–10 metastatic nodes). The tumours were predominantly involved in the midline area (76.6%), while the most frequently occurring grade was moderately differentiated. A progression to regional lymph nodes was established in 20 patients (42.5%), with six patients presented with bilateral involvement. These 20 patients were classified as stage III according to FIGO (five patients each as stages IIIA and IIIB, 10 as stage IIIC). Stage IB, observed in 24 patients, was most common (Tab. 1).

Table 2 provides an overview of the performed surgical procedures. A total of 15 patients (31.9%) were subjected to primary surgery with no need for adjuvant therapy, with a predominance of radical excision, performed in the case of 9 patients (60.0%) in this subgroup. This subgroup featured an almost identical proportion of ipsilateral and bilateral lymphadenectomy. A total of 32 patients (68.1%) underwent combined vulvar and regional node surgery followed by adjuvant radiotherapy. This subgroup most frequently included patients subjected to a combination of vulvectomy with lymphadenectomy (25 patients), the lymphadenectomy was performed as unilateral in only one case. In eight patients, supplementary reconstruction surgery of the vulva with bilateral use of the skin lobes was necessary for overlap of the defect. All 32 patients underwent adjuvant radiotherapy in the area of the vulva; nodal radiotherapy was performed in 20 patients.

During the follow-up period, 21 recurrences (44.7%) were observed, with the disease recurring in 76.2% of patients during the first two years after primary therapy. Table 3 provides an overview of the anatomical localization of recurrences, depending on analyzed prognostic factors. In 13 patients, the recurrence was observed in the vulvar region; the median recurrence period was 16 months (range, 6–82 months). Of the patients with local recurrence, 53.8% were primarily enrolled at advanced stage III with the metastatic involvement of regional lymph nodes. Three cases of regional relapse in the groin were preceded by systematic inguinofemoral lymphadenectomy, and only one patient of them had a negative surgical staging of the lymph nodes during primary

Table 1. Patient and tumor characteristics

Patient and tumor characteristics	N	%
Age (years)		
Median (range)	70.0 (44.0–85.0)	
Tumor size (mm)		
Median (range)	35.0 (6.0–120.0)	
< 40 mm	27	57.4
≥ 40 mm	20	42.6
Margin distance (mm)		
Median (range)	7.0 (0.15–20.0)	
< 8 mm	25	53.2
≥ 8 mm	22	46.8
Depth of invasion (mm)		
Median (range)	5.0 (0.5–12.0)	
≤ 5 mm	25	53.2
> 5 mm	22	46.8
LVSI[a]		
Yes	12	25.5
No	35	74.5
Involvement of midline		
Involved	36	76.6
Not involved	11	23.4
Grade		
Grade 1	7	14.9
Grade 2	31	66.0
Grade 3	9	19.1
Metastatic lymph nodes		
No metastases	27	57.4
Ipsilateral	14	29.8
Bilateral	6	12.8
FIGO[b] stage		
I	24	51.1
II	3	6.3
III	20	42.6

[a]LVSI — Lymphovascular Space Invasion; [b]FIGO — International Federation of Gynecology and Obstetrics

Table 2. Treatment characteristics

Treatment	No. patients	%
Surgical treatment only	**15**	**31.9**
Radical excision with lymphadectomy		
ipsilateral	7	14.9
bilateral	2	4.3
Vulvectomy with lymphadenectomy		
ipsilateral	1	2.1
bilateral	5	10.6
Surgical treatment with radiotherapy	**32**	**68.1**
Radical excision with lymphadenectomy		
ipsilateral	0	0.0
bilateral	7	14.9
Vulvectomy with lymphadenectomy		
ipsilateral	1	2.1
bilateral	24	51.1

Table 3. Risk factors for vulvar cancer recurrence

Risk factor	Vulvar recurrence/ No. patients (%)	Groin recurrence/ No. patients (%)	Distant recurrence/ No. patients (%)
Tumor size			
< 40 mm	7 /27 (25.9)	1/27 (3.7)	1/27 (3.7)
≥ 40 mm	6/20 (30.0)	2/20 (10.0)	4/20 (20.0)
Margin distance			
< 8 mm	9/25 (36.0)	2/25 (8.0)	5/25 (20.0)
≥ 8 mm	4/22 (18.2)	1/22 (4.5)	0/22 (0.0)
Depth of invasion			
≤ 5 mm	4/25 (16.0)	0/25 (0.0)	0/25 (0.0)
> 5 mm	9/22 (40.9)	3/22 (13.6)	5/22 (22.7)
LVSI[a]			
Yes	5/12 (41.7)	2/12 (16.7)	4/12 (33.3)
No	8/35 (22.9)	1/35 (2.9)	1/35 (2.9)
Involvement of midline			
Involved	13/36 (36.1)	2/36 (5.6)	5/36 (13.9)
Not involved	0/11 (0.0)	1/11 (7.7)	0/11 (0.0)
Metastatic lymph nodes			
No metastases	6/27 (22.2)	1/27 (3.7)	0/27 (0.0)
Metastases	7/20 (35.0)	2/20 (10.0)	5/20 (25.0)
FIGO[b] stage			
I + II	6/27 (22.2)	1/27 (3.7)	0/27 (0.0)
III	7/20 (35.0)	2/20 (10.0)	5/20 (25.0)

[a]LVSI — Lymphovascular Space Invasion; [b]FIGO — International Federation of Gynecology and Obstetrics

surgery. The median rate of regional recurrence period was 12 months (range, 10–15 months). In five patients with primary metastatic regional lymph nodes, distant metastases appeared, always as the pelvic lymphadenopathy, which was combined with pulmonary involvement in two cases and with bone metastases and brain involvement in one case respectively. The median occurrence of distant recurrences was 6 months (range, 3–10 months). We recorded the deaths of 19 patients, two of whom died without recurrence of other causes; the mortality index for the analyzed group was 40.4%. Four patients with surgically treated local recurrence are still alive and 24 patients live without recurrence.

During the follow-up period (range, 4–118 months), we observed a mean DFS of 66.7 + 6.5 months (95% CI; 54.0–79.5) (Fig. 1) and a mean OS of 69.7 + 6.2 months (95% CI; 57.6–81.8) (Fig. 2).

The univariate analysis of local vulvar recurrence established a statistical significance in all prognostic factors analyzed at $p < 0.05$. By quantifying the risk of recurrence risk using the Cox regression model, we found the highest risk of local relapse in patients exhibiting invasion depth > 5 mm compared to invasion depth ≤ 5 mm, HR 12.42 (95% CI, 3.44–44.84), and in the patients with LVSI compared to those without LVSI, HR 10.83 (95% CI; 3.87–30.28) (Tab. 4).

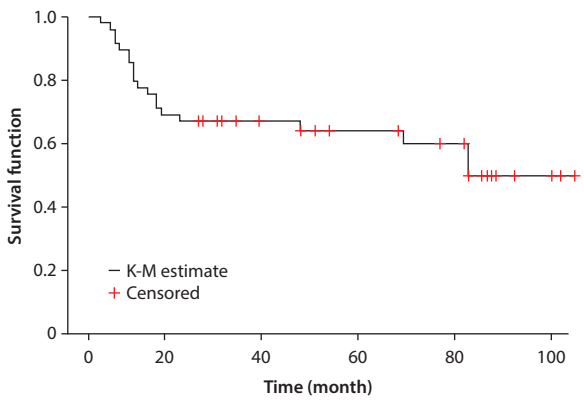

Figure 1. Kaplan-Meier estimate of survival function (DFS)

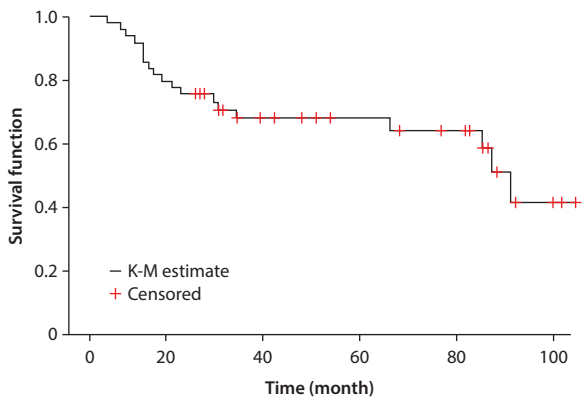

Figure 2. Kaplan-Meier estimate of survival function (OS)

Table 4. Risk factors predicting local recurrence

Risk factor	HR[c] (95% CI)	p
Tumor size (≥ 40 mm vs. < 40 mm)	2.80 (1.12–6.99)	0.027
Margin distance (< 8 mm vs. ≥ 8 mm)	4.91 (1.73–13.93)	0.003
Depth of invasion (> 5 mm vs. ≤ 5 mm)	12.42 (3.44–44.84)	< 0.001
LVSI[a] (yes vs. no)	10.83 (3.87–30.28)	< 0.001
Involvement of midline (involved vs. not involved)	7.63 (1.02–57.12)	0.048
Metastatic lymph nodes (metastases vs. no metastases)	9.64 (3.03–30.69)	< 0.001
FIGO[b] stage (III vs. I + II)	9.64 (3.03–30.69)	< 0.001

[a]LVSI — Lymphovascular Space Invasion; [b]FIGO — International Federation of Gynecology and Obstetrics; [c]HR — Cox proportional hazard ratio

In the next part of the analysis, we focused on the comparison of the risk of recurrence stratified by the time interval of recurrence. Borderline statistical significance for early recurrence in the first two years compared to late recurrence was found to be associated with depth of invasion (> 5 mm), metastatic lymph nodes and advanced FIGO stages (Tab. 5). When the associations between continuous variables (age, tumour size, margin distance, depth of invasion) were tested, statistical significance was not established between age and depth of the invasion, the borderline significant association was identified between the age and size of the tumour, other correlations were statistically significant (Tab. 6). Statistically significant associations between LVSI and metastatic lymph nodes, LVSI and FIGO stage, metastatic lymph nodes and FIGO stage respectively were observed when testing the associations between categorical variables (Tab. 7). When testing differences between distributions of continuous variables across categories, no statistically significant association between only age and midline involvement; and depth of the invasion and midline involvement respectively was not observed. The borderline significant association was determined between margin distance and LVSI (Table 8). Due to the limited number of regional and remote recurrences, no analysis of their prognostic factors was conducted.

Table 6. Associations between continuous variables

Variables	Age	Tumor size	Margin distance
Tumor size	$p^a = 0.051$	—	—
Margin distance	$p^a = 0.040$	$p^a = 0.006$	—
Depth of invasion	$p^a = 0.096$	$p^a = 0.001$	$p^a = 0.006$

[a]Spearman correlation coefficient

Table 7. Associations between categorial variables

Variables	LVSI[b]	Involvement of midline	Metastatic lymph nodes
Involvement of midline	$p^c = 0.807$	—	—
Metastatic lymph nodes	$p^c < 0.001$	$p^c = 0.129$	—
FIGOa stage	$p^c < 0.001$	$p^c = 0.129$	$p^c < 0.001$

[a]FIGO — International Federation of Gynecology and Obstetrics; [b]LVSI — Lymphovascular Space Invasion; [c]chi-squared test

Table 8. Differences in the distribution of continuous variables across categories

Variables	LVSI[c]	Involvement of midline	FIGO[d] stage
Age	$p^a = 0.012$	$p^a = 0.788$	$p^a = 0.020$
Tumor size	$p^a = 0.004$	$p^a = 0.006$	$p^a < 0.001$
Margin distance	$p^b = 0.052$	$p^b = 0.028$	$p^b = 0.001$
Depth of invasion	$p^b < 0.001$	$p^b = 0.072$	$p^a < 0.001$

[a]t-test; [b]Mann-Whitney test; [c]FIGO — International Federation of Gynecology and Obstetrics; [d]LVSI — Lymphovascular Space Invasion

Table 5. Risk factors of local recurrence — impact of the time interval to recurrence

Risk factor	Recurrence ≤ 2 years No./8 patients (%)	Recurrence > 2 years No./5 patients (%)	p[c]
Tumor size (≥ 40 mm)	4/8 (50.0)	2/5 (40.0)	0.724
Margin distance (< 8 mm)	7/8 (87.5)	2/5 (40.0)	0.070
Depth of invasion (> 5 mm)	6/8 (75.0)	1/5 (20.0)	0.047
LVSI[a]	4/8 (50.0)	1/5 (20.0)	0.268
Involvement of midline	8/8 (100.0)	5/5 (100.0)	0.991
Metastatic lymph nodes	6/8 (75.0)	1/5 (20.0)	0.047
FIGO[b] stage III	6/8 (75.0)	1/5 (20.0)	0.047

[a]LVSI — Lymphovascular Space Invasion; [b]FIGO — International Federation of Gynecology and Obstetrics; [c]maximum likelihood estimation method

DISCUSSION

Primary surgery is a preferred therapeutic approach for VSCC in case no distant metastases are present. The prognosis of primarily operated patients is strictly dependent on the metastatic involvement of regional lymph nodes, which is strongly associated with the risk of relapse and aggravated survival. This was demonstrated in our group of patients, where recurrence (regardless of its localization) occurred in 70% of patients with primary metastatic lymphadenopathy. Half of the recurrences in these patients occurred in the inguinal area or pelvic lymph nodes, which is consistent with the literature [16–18]. Most prevalently, the patients with primary extracapsular nodal involvement presented with most frequent recurrence (90%) despite adjuvant radiotherapy. In spite of this, surgical treatment followed by radiotherapy is more efficient and preferable to radiotherapy alone [3]. In case of suspected metastatic involvement of the groin nodes, a biopsy should be performed. The optimal management of these cases — inguinofemoral lymphadenectomy or groin node debulking — has not been defined yet [3, 19]. The exclusion of the presence of disease in the pelvis using PET/CT or PET/MRI is important to determine a rational treatment strategy [20, 21]. In case a patient's condition is suitable, pelvic debulking may be considered as an option despite the fact that pelvic disease is already considered a distant metastatic involvement [3].

In case of regional lymph nodes are found to be negative, a set of clinical and histopathological parameters which may affect disease recurrence must be considered. Due to the limited number of regional and remote recurrences in our study, we statistically analyze possible prognostic factors only for the risk of local recurrence. All seven analyzed prognostic factors were revealed to be statistically significant in this analysis; midline involvement achieved borderline statistical significance, likely due to more radical surgical treatment in patients with this risk factor. The highest risk of local recurrence occurred in coincidence with the presence of a deep invasion of > 5 mm and LVSI (12× or 10× higher respectively). Other intergroup analyses revealed the statistically significant associations of some continuous (tumour size, margin distance, depth of invasion) and categorical variables (LVSI, metastatic lymph nodes).

Although the total number of recurrences (local, regional, remote) reporting in our study is relatively high (44.7%), disease recurrence occurred in a quarter of the patients after more than two years from the end of the primary treatment. The proportion of local recurrences among the total number of recurrences is 62%; this correlates with recent sources which report rates in excess of 50% [10, 16, 22]. The proportion of local relapses recurring after more than two years of follow-up was almost 40% in our study. This is a substantial challenge, eliciting a discussion of the VSCC local recurrence definition, in the frame of which two factors should be considered. First, it is recurrence interval, second, the distance between localization of primary tumour and recurrence. As most recurrence cases take place during the first two years, some authors have suggested that late recurrences may, in fact, constitute de novo tumours [23, 24]. Our analysis found borderline statistical significance for an early risk of local recurrence (up to two years) in three prognostic factors (depth of invasion > 5 mm, metastatic lymph nodes, FIGO III stage). To facilitate the discussion and differentiate a real local recurrence from de novo tumour, the detailed documentation, including an image or clinical plot, appears as crucial [3, 23, 24].

FIGO I-II stages represent in our study almost 58% of all cases, which corresponds to the current distribution of the early stages of the disease in the population of Czech women [25].

Furthermore, 20 patients with stage III were included in the analysis. The inclusion of advanced-stage patients helps to validate the relationship between prognostic factors and risk of local recurrence. Thus, these results are not only limited to those with early-stage cancers but can be generalized to the more advanced tumours in that is also important to obtain adequate margins in advanced cancers for palliative surgical care to provide symptomatic relief and prevent local recurrence.

68% of our patients received adjuvant radiotherapy to the vulva, therefore the group can seem inconsistent from this perspective. However, radiotherapy for the vulva region was recommended for patients with a clear indication (a resection margin of < 8 mm, a depth of invasion > 5 mm, a presence of LVSI, locally advanced tumours infiltrating of surrounding organs). Moreover, the incidence of local, regional or distant relapses was not effectively influenced by adjuvant radiotherapy after primary surgery in our study. This can be documented by the fact that out of 13 local vulvar recurrences, only one case did not receive adjuvant treatment. In another eight relapses (three in the groin and five in pelvic lymph nodes) adjuvant radiotherapy was performed in these anatomical sites in seven patients. Further investigations and new studies dealing with the effect of adjuvant and neoadjuvant radiotherapy are the next logical steps in the assessment of this modality of treatment.

To achieve tumour-free margins is the major prognostic factor influenced by the surgeon. Our analysis reveals the statistical significance of adequate surgical margins (≥ 8 mm) in the reduction of risk of recurrence. In the case of close resection margins, no statistically significant difference in the increased risk of early local recurrence (up to two years) was observed compared to relapse after more than two

years. A recent expert opinion states that the free-resection margin should be at least 1 cm [3]. Concurrently, however, it is stressed that it is acceptable to consider less wide margins in case the tumour lies close to midline structures and preserving their function is desired [3]. The results of studies comparing the association of the width of free-resection margins and the rate of local recurrence are inconclusive and this topic remains the most controversial point in the surgical treatment of vulvar carcinoma [26–30]. Therefore, it is necessary to focus on new histopathological, genetic and epigenetic factors. Actual sources state the increased risk of recurrence based on increased tumour aggression in association with the presence of perineural invasion or epithelial-mesenchymal transition [31, 32]. Increased risk of local recurrence is also characterized by HPV tumour negativity in conjunction with differentiated VIN, lichen sclerosus and genetic alterations such as TP53 mutations [33, 34].

CONCLUSIONS

Based on the results of our study, the major prognostic factor of local VSCC recurrence influenced by the surgeon is represented by tumour-free pathological margins ≥ 8 mm. The achievement of such margins is an important prerequisite for reducing the risk of local recurrence while respecting the current trend of less radical locoregional surgery. A perfect knowledge of the extent of the disease prior to surgery as well as the definition of new molecular prognostic parameters should be to support adequately radical trends in the current surgical treatment of vulvar cancer. The emphasis is given on adequate radicality as well as on reduction of overtreatment without worsening prognosis by simultaneously preserving the quality of life.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

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