

Resection margins do not influence survival in vulvar cancer: treatment results in patients with a long-term follow-up

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Introduction. The main purpose of the study was to assess margin resection as a prognostic factor of vulvar cancer in patients with a long term follow-up.

Materials and methods. The study included 84 vulvar cancer patients who underwent radical treatment: surgery (n = 84), radiotherapy (n = 16), chemoradiotherapy (n = 5). Clinicopathological factors regarding survival and recurrence were analyzed. The median follow-up was 74 months.

Results. Resection margins were not related to progression-free survival (PFS) (p = 0.93) and overall survival (OS) (p = 0.84). On the multivariate analysis, a maximum tumor size >25 mm (p = 0.026) and inguinal lymph node involvement (p = 0.028) were factors increasing the risk of death. The risk of recurrence was related to tumor dimension >25 mm (p = 0.011), but not to inguinal node metastasis (p = 0.086).

Discussion. Inadequate surgical margin would be salvaged by adjuvant treatment.

Conclusions. A maximum tumor dimension >25 mm and metastases in the inguinal lymph nodes are independent prognostic factors for the survival of patients with vulvar cancer.

Key words: vulva, cancer, prognosis, recurrence

Introduction

Inguinal lymph node involvement is unquestionably a prognostic factor in vulvar cancer. It is believed that resection margins are also of great importance in the management of vulvar cancer. Subsequently, the main goal of surgical treatment is to achieve a wide margin (according to NCCN: 1–2 cm, ESGO – 8 mm) [1, 2]. Recently, some studies question the importance of a wide excision and show no correlation between margin width and recurrence [3, 4].

Follow-up is recommended in all patients for 4–5 years after treatment [1, 2]; conducting longer observations is difficult due to the advanced age of patients at diagnosis, limitations of healthcare, rare incidence and the dispersal of patients.

The main purpose of the study was to assess margin resections as a prognostic factor of vulvar cancer in long term follow-up. An additional aim was to identify clinicopathological and treatment related-factors (other than margin) influencing survival and affecting treatment failures in vulvar cancer patients in long term follow-up scenarios.

Material and methods

The retrospective analysis included 84 patients with vulvar cancer treated at Maria Skłodowska-Curie National Research Institute of Oncology between 2001 and 2007. Women with contraindications to surgical treatment due to advanced disease and severe comorbidities were not included. The stage of the disease was evaluated according to the 1994 FIGO clas-

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sification, which was valid at the time. For this study, staging was reclassified to the 2009 FIGO. All patients were diagnosed with vulvar squamous cell carcinoma and underwent a radical vulvectomy with inguinal lymphadenectomy. 31 patients required adjuvant treatment according to the following criteria:

- resection margin ≤ 1 mm or positive,
- metastasis to ≥ 1 inguinal lymph node.

Ten patients did not undergo adjuvant therapy due to comorbidities and poor general condition ($n = 3$), lack of consent to radiotherapy ($n = 2$), abnormal wound healing ($n = 2$), skipping appointments ($n = 1$), the patient's death ($n = 1$), unknown reasons ($n = 1$). 21 patients were treated with radiotherapy (RT, $n = 16$) and radiochemotherapy (RCT, $n = 5$).

Adjuvant external beam radiation therapy (EBRT) with linear accelerator and energy of 4–15 MeV was applied to the vulva ($n = 6$), vulva and groins ($n = 5$), groins ($n = 5$) and pelvic region ($n = 5$). A total dose of 4800–6000 cGy was administered in 24–31 fractions. In 5 patients, concomitant cisplatin intravenously was administered intravenously with a dose of 40 mg/m², once a week. The duration of RT and RCT was 31–43 and 38–48 days, respectively. Adjuvant treatment started within 6 weeks of surgery.

Follow-up: gynecological examination, transvaginal and inguinal ultrasonography were conducted every 3–4 months for 2 years, then every 6 months for the next 3 years. A chest X-ray was carried out once a year. Computed tomography or magnetic resonance were performed in patients with suspicion of relapse. After 5 years, patients continued follow-up once a year in our outpatient clinic or outpatient clinic near their place of residence. Information was obtained by telephone for those patients who carried out a gynecological follow-up outside our center. Data on death were collected from the National Cancer Registry.

Recurrence: a biopsy of the suspicious lesion was performed to obtain a histopathological confirmation; the date of the positive biopsy was considered as the moment of relapse. Locoregional recurrence was defined as relapse in the vulva and/or groins. Distant metastases were not observed in the study group. Treatment of relapse disease was presented in table I.

Age, tumor grade, staging, maximum tumor dimension, depth of stromal invasion, status of inguinal lymph nodes, and the number of metastatic lymph nodes were considered as clinicopathological factors, while margin, number of resected lymph node and lymph node ratio were treatment-related factors.

Methods of statistical analysis

Efficacy of treatment was measured by the probability of survival – overall survival (OS), progression-free survival (PFS) and cumulative incidence function (CIF) of local relapses. Survival curves were calculated using the Kaplan-Meier method. Overall survival was estimated from the date of treatment initiation to death or the last information provided when the patient was alive. Progression-free survival was measured from the date of treatment initiation to its first failure: local relapse, distant metastases or death from other causes; in the absence of treatment failure, PFS was estimated to the last clinical observation. To evaluate the influence of selected factors such as age, grading, staging, tumor size, lymph node metastases, depth of invasion, margins, total number of lymph nodes removed, and the number of metastatic lymph nodes on OS and PFS, the Cox proportional hazard model was used. The influence of these factors on the risk of recurrence was analyzed using a multivariate model for competitive risks. The modeling process used a step-by-step elimination of variables by adopting standard thresholds: off (>0.1) and on (<0.05). The analysis was carried out using the IBM SPSS Statistics 23.0 statistical package and the Bob Gray package [6].

Ethics approval

All procedures were conducted according to the Declaration of Helsinki for Medical Research involving Human Subjects. Institutional ethics committee approval was not required – the research is an ex-post analysis of clinical experience. The clinical decisions concerning the treatment were not influenced by the purpose of this paper.

Results

The clinicopathological characteristics of the study group ($n = 84$) was shown in table II. Patients' average age was 66 years

Table I. Treatment of recurrence of vulvar cancer depending on location

Treatment	Location of relapse		
	vulva (n = 23)	groin (n = 12)	vulva and groin (n = 2)
surgery	10	3	0
radiotherapy	3	3	0
chemotherapy	5	0	0
radiochemotherapy	2	1	0
brachytherapy	3	0	0
palliative	2	5	2

Table II. Clinicopathological characteristics of study group

Factor		n (%)
age (years)	<62	26 (31%)
	62–73	30 (35.7%)
	≥74	28 (33.3%)
lymphadenectomy	unilateral	10 (11.9%)
	bilateral	74 (88.1%)
median resected lymph nodes		11 (3–28)
FIGO 1994/2009	IA	1 (1.2%) / 1 (1.2%)
	IB	11 (13.1%) / 46 (54.8%)
	II	35 (41.7%) / 12 (14.3%)
	III	31 (36.9%) / 21 (25%)
	IV	6 (7.14%) / 4 (4.7%)
grading	1	29 (34.5%)
	2	37 (44%)
	3	12 (14.3%)
	unknown	6 (7.14%)
maximum tumor diameter (mm)	≤25	31 (36.9%)
	26–44	22 (26.2%)
	≥45	30 (35.7%)
	unknown	1 (1.2%)
multifocal lesion	no	79 (94%)
	yes	5 (6%)
depth of invasion (mm)	≤5	28 (33.33%)
	>5	40 (47.62%)
	unknown	16 (19.05%)
margin (mm)	positive	5 (5.95%)
	≤1	15 (17.86%)
	>1–5	30 (35.71%)
	>5	30 (35.71%)
	negative (not measured)	4 (4.76%)

(18–94). The median tumor size was 35 mm (5–90 mm). Microinvasion (depth of stromal invasion <1 mm) was found in 1 patient (1.2%). Median number of resected lymph nodes per groin was 6 (1–15). In 26 (30.95%) patients, metastases to the inguinal lymph nodes were found; 13 (17.86%) patients had involved >1 inguinal lymph node (2 metastatic LNs in 4 patients, 3 metastatic LNs in 3 patients, 5 metastatic LN in 3 patients, 8 metastatic LNs in 2 patients and 9 metastatic LNs in 1 patient).

Survival

The median overall survival (OS) and progression free survival (PFS) was 87 (95% CI: 60–114) and 60 (95% CI: 37–84) months, respectively. The overall 5- and 10-year survival rates were 62% (95% CI: 51–73%) and 39% (95% CI: 28–50%), while 5- and 10-year PFS were 51% (95% CI: 40–62%) and 32% (95% CI: 22–42%), respectively.

On the multivariate analysis, the resection margin was not related to PFS (HR = 1.033; 95% CI: 0.51–2.11; $p = 0.93$) and OS (HR = 0.84; 95% CI: 0.41–1.73; $p = 0.84$).

On the multivariate analysis, factors influencing survival were: maximum tumor size and inguinal lymph node status (fig. 1, tab. III). Other clinicopathological and treatment-related factors did not have a significant effect on survival.

Maximum tumor size was the only factor influencing PFS on multivariate analysis; nor inguinal lymph node involvement or other analyzed factors were not relevant to PFS (fig. 2, tab. III).

Failure patterns

The majority of relapses occurred within 2 years from the end of treatment and were localized on the vulva and groins. Cumulative incidence function (CIF) curves according to the site of relapse as competing risk had similar patterns for 2 years (fig. 3). At 15 years, CIF by site of relapse and non-cancer death as competing risk were: vulva 28% (95% CI: 18–38%), groin 17% (95% CI: 8.7–25%) and non-cancer death 27% (95% CI: 18–37%). Late recurrences (>5 years after the end of the treatment) affected the vulva.

Occurrence of locoregional relapse (vulva and/or groins) was significantly dependent on the maximum tumor size ($p = 0.019$). In the final model, the HR was 2.37 (95% CI: 1.15–4.89) for tumors >25 mm vs. ≤25 mm. The CIF curves are presented in figure 4. Other clinicopathological and treatment-related factors (including resection margin) did not have an influence on the risk of relapse.

Survival after recurrence

Groin recurrence influenced OS significantly ($p < 0.007$). The median survival after relapse in patients with groin recurrence vs vulva recurrence was 6.1 (95% CI: 2.7–9.5) vs. 16 (95% CI: 8.7–23.5) months, respectively.

Discussion

The principles of surgical treatment of vulvar cancer are inguinal lymph node assessment and wide margin excision. It was showed that margins ≥5 mm or ≥8 mm were significantly associated with risk of recurrence and survival [5–7]. In our study, the margin did not influence survival and recurrence. However, some patients with a close resection margin received adjuvant radiotherapy, which could affect the results. Similar results to ours were obtained in other studies [8–10]. Arvas et al. showed that a margin ≤2 mm may increase the risk of recurrence, but was not an independent predictive factor for PFS and OS [11]. Woelber et al. showed a similar rate of local recurrence in patients with a margin <8 mm vs. ≥8 mm (12.6% vs. 10.2% respectively) [12]. German recommendations accept a margin of 3 mm as sufficient [13]. Several authors claim that a positive margin is the only risk factor for recurrence; a complete resection with no lower limit (besides positive margin) should be recommended [14–16].

Long-term observation showed that a tumor size >25 mm and metastases to regional lymph nodes increased the risk

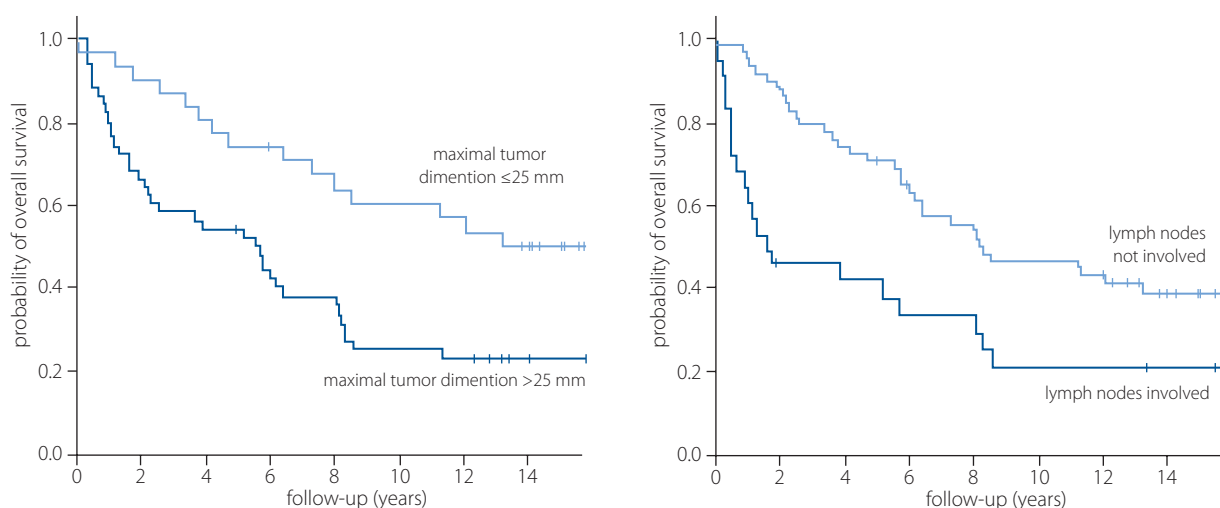


Figure 1. Overall survival by tumor dimension ($p = 0.026$) and status of inguinal lymph nodes ($p = 0.028$)

Table III. Multivariate analysis of clinicopathological factors affecting overall survival

Endpoint	Factor		HR	95% CI	p
overall survival	maximum tumor dimension	≤25 mm	1		
		>25 mm	2.038	1.091–3.808	0.026
	groin lymph nodes metastasis	no	1		
		yes	1.903	1.074–3.372	0.028
progression free survival	maximum tumor dimension	≤25 mm	1		
		>25 mm	2.208	1.203–4.055	0.011
	groin lymph node metastasis	no	1		
		yes	1.625	0.933–2.830	0.086

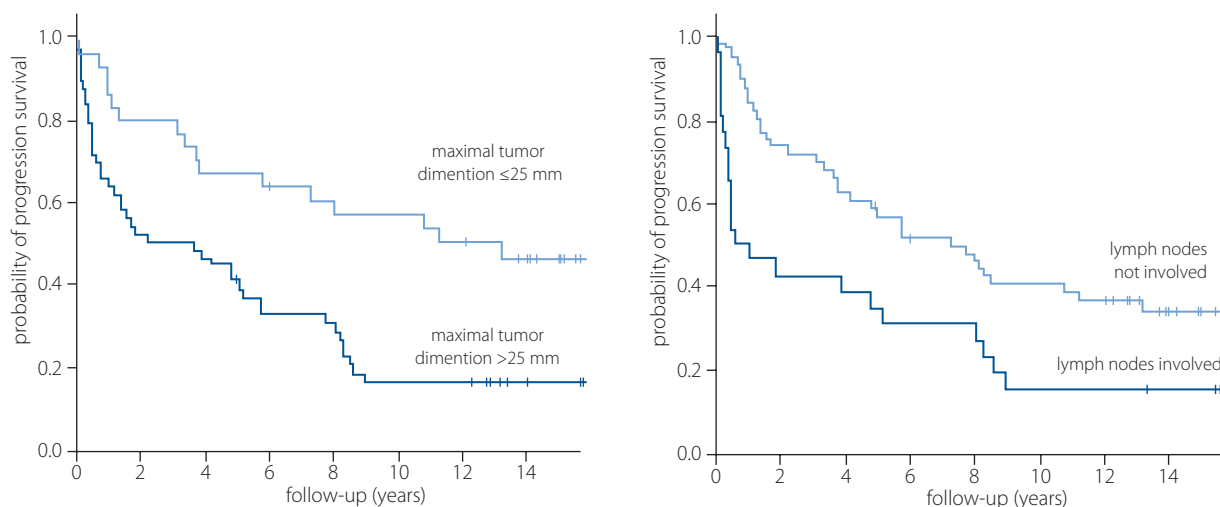


Figure 2. Progression free survival by maximum tumor size ($p = 0.011$) and status of inguinal lymph nodes ($p = 0.086$)

of death in patients with vulvar cancer. Inguinal lymph node involvement has been directly related to shorter survival, while maximum tumor size negatively influenced survival by increasing the risk of recurrence. The results of other authors also indicate that the tumor size and the involvement of regional

lymph nodes influence survival. Minar et al. showed that a tumor dimension >40 mm and metastases in inguinal lymph nodes are significantly associated with a risk of recurrence [17]. Hay et al. found that tumors >4 cm increased disease-specific mortality 4-fold, but were not related to relapse [18]. Imoto et

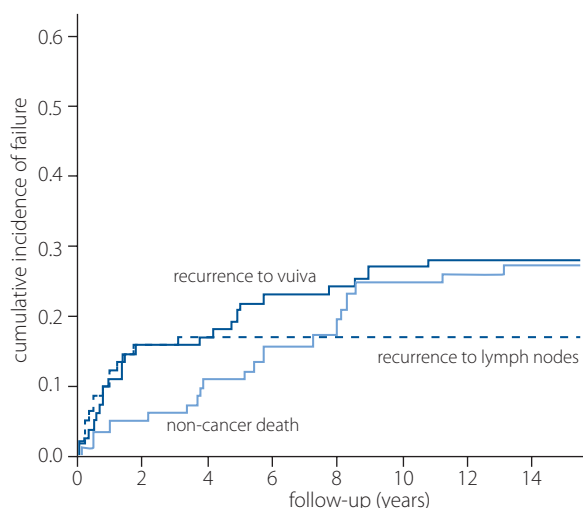


Figure 3. Cumulative incidence function (CIF) curves by site of recurrence and non-cancer death as competing risk

al., on multivariate analysis, showed that inguinal lymph node involvement influenced PFS, but not OS [5].

The extracapsular spread of lymph nodes was found to be an independent prognostic factor for recurrence (HR 13.54; 95% CI: 2.87–64.07; $p = 0.01$) and overall survival (HR 10.63; 95% CI: 1.65–68.57; $p = 0.01$) [19]. An increasing number of metastatic lymph nodes was associated with a risk of recurrence and death [20, 21]. In our study, there was no relationship between the number of metastatic lymph nodes and survival, probably due to the insufficient number of patients.

Our results, showing that tumor grade did not influence recurrence risk and survival, were consistent with other studies [8, 19, 21–24]. Although Nicoletto et al. on univariate analysis showed that grading was associated with PFS and OS (5-year survival 52% for grade 1; 24% for grade 2 vs. 0% for grade 3, $p = 0.0021$); these findings were not confirmed on multivariate analysis [25]. Mahner et al. and Polterauer et al. demonstrated that tumor grade is predictive for PFS, but not for OS [21, 26]. Multivariable analysis by Sznurkowski et al. revealed that grading was an independent prognostic factor [27].

The depth of stromal infiltration is crucial to confirm micro-invasion (≤ 1 mm; FIGO IA). In these cases, verification of inguinal lymph nodes may be omitted due to the minimal risk of metastases. The depth of infiltration in invasive disease does not influence therapeutic decisions and its impact on survival is doubtful. We did not find a relationship between the depth of invasion and the risk of relapse in the primary site, PFS and OS length. Similar results were obtained by other authors [19, 21, 23, 27, 28]. Contrary to this, Nicoletto et al. demonstrated that stromal invasion >9 mm was an important prognostic factor for PFS (HR = 3.1; 95% CI: 1.3–7.7) (25). While in the VULCAN study, stromal invasion >5 mm appeared to significantly impact overall survival [29].

The results of our study indicate the need for long-term observation of vulvar cancer patients. Relapses of the disease can occur years after the end of the treatment (fig. 4). In

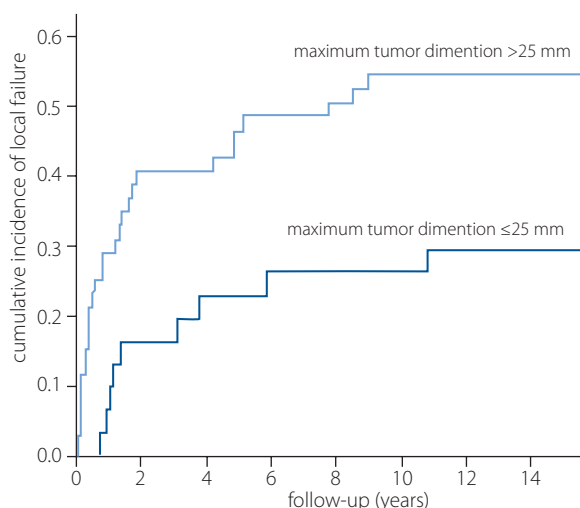


Figure 4. Cumulative incidence function (CIF) of locoregional relapse depending on the size of the tumor

our study group, all cases of late recurrence were located in the vulva. Many patients after the standard 5-year follow-up continue healthcare beside oncology unit/outpatient clinic. General practitioners or obstetricians/gynecologists as well as patients should be informed about the possibility of late relapse and its most frequent location.

The site of locoregional relapse influenced survival. Groin recurrence was associated with a much poorer prognosis than vulvar relapse. Moreover, almost all cases of inguinal relapse occurred within 2 years after the end of treatment (fig. 4). Similar observations were presented by Cormio et al., who showed that the median survival after groin recurrence was 9 months and the median time from primary surgery to groin relapse was 7 months [30].

Conclusions

The conclusions of the study are:

- a tumor size >25 mm and inguinal lymph node involvement are independent prognostic factors for survival in vulvar cancer patients,
- groin recurrence is associated with an unfavorable prognosis,
- vulvar cancer relapses may occur many years after treatment; at the time it is located on the vulva,
- an inadequate surgical margin would be salvaged by RT or RCT.

Conflict of interest: none declared

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