

# Prognostic factors in patients with carcinoma of the vulva – our own experience and literature review

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## Summary

**Aim of the study:** The objective was the analysis of prognostic factors and treatment outcomes of 104 patients with vulvar cancer, treated between 1990 and 2003 in the Center of Oncology, Maria Sklodowska-Curie Memorial Institute, Cracow, Poland. **Material and Methods:** The median age of patients was 67. Advanced disease (TNM III and IVA) was found in 54 (51.9%) patients and grade 2 and 2 in 50 (48.1%). Inguinal lymph nodes were clinically uni- or bilaterally involved in 40.4% of patients. Fifty-seven (54.8%) patients underwent radical vulvectomy with bilateral inguinal lymphadenectomy and 47 (45.2%) radical vulvectomy only. Cancer differentiation was well in 38 (36.2%) of patients, moderate in 38 (36.2%) and poor in 28 (36.6%). Adjuvant radiotherapy was applied in 30 (28.8%) cases. **Results:** Five-year overall survival rate was observed in 44.4% of patients. Depending on TNM grade, 5-year OS rates were 61.4% for grade 1, 54.9% for grade 2, 40.1% for grade 3 and 13.3% for IVA. In patients aged < 70, 5-year OS rate was 54.7% compared to 30.5% for those ≥ 70. Among patients with G1 cancer differentiation 64.4% survived five years, with G2 39.1% and with G3 24.9%, respectively. **Conclusion:** Univariate analysis revealed a statistically significant, unfavorable impact of age ≥ 70, with G3 cancer differentiation, clinically confirmed inguinal lymph node involvement and TNM classification stage on 5-year overall survival. Cox multivariate analysis demonstrated that independent prognostic factors for 5-year survival were the age of the patient, clinical status of inguinal lymph nodes and TNM classification grade.

**Key words:** Carcinoma of the vulva; Prognostic factors.

## Introduction

Carcinoma of the vulva is an uncommon disease, representing approximately 2.5-5% of female reproductive tract malignancies [1]. Vulvar cancer typically develops in women in their 7<sup>th</sup> and 8<sup>th</sup> decade of life, but recently the incidence of vulvar tumors has increased in women younger than 40 years of age [1]. Studies suggest two different etiologic types of vulvar cancer. The first, related to HPV infection and smoking, is commonly anticipated by vulvar intraepithelial neoplasia (VIN) and is seen in younger patients. The other, more common type, unrelated to HPV and seen usually in elderly women, is connected with a high incidence of dystrophic lesions adjacent to the tumor [1, 2]. The most common histological type of vulvar cancer is squamous cell carcinoma (85%), whereas adenocarcinomas, melanomas and basal cell carcinomas are much less common [1].

Surgery is the first choice for the treatment of patients with carcinoma of the vulva [2]. Radiotherapy is often applied, especially as adjuvant therapy. There are many population, pathologic and clinical factors which influence treatment methods and prognosis. The problem of prognostic indicators in patients with vulvar cancer is controversial. The range of prognostic factor values (i.e.

age, tumor growth, depth of infiltration, width of surgical margin) remains unclear. The aim of this study was to analyze the value of prognostic factors, on the basis of our own clinical material and literature review.

## Material and Methods

One hundred and four patients with invasive vulvar carcinoma were followed at the Center of Oncology, M. Sklodowska-Curie Memorial Institute, Krakow Branch in Poland between 1990 and 2003. Medium follow-up time from the date of initial treatment for all patients at the date of diagnosis was 58 months. The medium age of patients was 67. Classification of cancer stage was based on clinical TNM score [3]. Advanced disease (TNM III and IVA) was found in 54 (51.9%) patients and grade 1 and 2 in 50 (48.1%). Inguinal lymph nodes were clinically uni- or bilaterally positive in 40.4% patients and in 59.6% there was no clinical evidence of nodal metastasis. The cancer was well differentiated in 38 (36.2%) patients, moderate in 38 (36.2%) and poor in 28 (36.6%). Radical vulvectomy with bilateral inguinal lymphadenectomy from separate incisions was performed in 57 (54.8%) patients and radical vulvectomy alone in 47 (45.2%) patients. Among 57 (100%) patients treated with lymphadenectomy, inguinal metastases were found unilaterally in 28 (49.1%) and bilaterally in 17 (29.8%) patients. Uninvolved groin nodes were found in 12 (21.1%) patients. Adjuvant radiotherapy was applied in 30 (29.8%) patients due to positive surgical margins or inguinal node involvement. Survival was estimated for all of the indicators of interest using the Kaplan-Meier method. Differences between characteristics were tested with

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the two-sided chi-square test, and differences in continuous characteristics like age, were tested with a *t*-test; *p* values  $\leq 0.05$  were considered significant. Cox's proportional hazards model was used to compute risk reduction among analyzed factors [4].

## Results

The five-year overall survival rate in the study group was 44.4%. Three patients (2.9%) died due to postoperative complications and two (1.8%) due to cerebral stroke, with no evidence of cancer. Six (5.4%) patients survived five years with clinical evidence of cancer recurrence and 52 (50%) died due to treatment failure. Univariate analysis showed that BMI value, histology, clitoral involvement, tumor dimension and status of the surgical margins had no significant impact on treatment outcomes. However, age, differentiation of cancer, clinical inguinal node status and TNM stage were found to be associated with overall survival. A significantly higher 5-year overall survival rate was found in patients  $< 70$ , with well differentiated cancer, clinically negative groins and with disease in Stage I and II by TNM. Differences in 5-year overall survival are shown in Table 1. Furthermore, on multivariable analysis by forward stepwise Cox model regression, age, clinical node status and cancer stage by TNM were independent risk factors for cancer-related death (Table 2).

Table 1. — Treatment results of patients depending on population and clinical features.

Characteristics of study group	No. of pts.	5-year prognosis overall survival rate	p value
Age			
under 70	60	54.7	0.00
$\geq 70$	44	30.5	6
Body Mass Index			
under 31	86	47.5	NS
$\geq 31$	18	28.8	
Cancer histological differentiation			
well G1	38	64.4	0.05
moderate G2	38	39.1	
poor G3	28	24.9	
Clitoral involvement			
yes	18	44.7	NS
no	86	44.4	
Primary tumor size (by TNM)			
T1	23	57.9	NS
T2	61	41.0	
T3	19	35.1	
T4	1	100.0	
Inguinal node status (by TNM)			
N0	62	55.4	0.00
N1	27	33.3	3
N2	15	20.0	
Vulvar cancer stage by TNM:			
I	20	61.4	0.00
II	30	54.9	1
III	39	40.1	
IVA	15	13.3	
Surgical margins			
uninvolved	67	50.8	NS
involved	37	26.3	
Total	104		

Table 2. — Results of Cox's multivariate analysis of prognostic factors.

	Features	RR	p value
Age	under 70	1.00	–
	$\geq 70$	8.84	0.003
Clinical status of inguinal lymph nodes	N0	1.00	–
	N1 + N2	11.72	0.001
Vulvar cancer stage by TNM	I + II	1.00	–
	III + IV A	6.32	0.0013

TNM: tumor classification; RR: relative risk.

## Discussion

The population clinical and microscopic features of the study group are similar to others described in the literature [2-10]. The medium age of patients at the time of diagnosis was 67 years which is similar to other studied groups (range 60-70 years). Comparable to other authors [1], squamous cell carcinoma was found in over 90% of cases. Primary tumor location was also similar to that reported in the literature, e.g. clitoral involvement was described in 27 % by Hopkins *et al.* [8].

There are some differences between the study group and other series described in the literature. Fifty-two percent of patients had Stage III and IVA. This proportion in the literature is different and ranges from 18.3% to 51% [2, 4, 6-10]. In our study group of 104 patients the 5-year survival rate was 44.4%, which was lower than that described in the literature (50-80% rate) [6-7, 10-15]. This difference is probably due to the characteristics of our material, which consists of mostly advanced patients.

The clinical composition of the study group was unfavorable (52% of cases had Stage III and IVA) and only clinical TNM classification was applied; microscopic verification of inguinal lymph nodes was performed only in half of the cases. All these features had an important influence on survival which was lower than reported in the literature.

Treatment failure occurred in 58 (55.8%) of the patients studied. In 46.5% of the group it was only vulvar recurrence, in 37.9% recurrence was found in the vulva and groin lymph nodes and in 6.9% only in the groin lymph nodes. Distant metastases was the reason for failure in 6.9% of uncured patients. The literature review showed that loco-regional recurrence is the major reason for treatment failure in vulvar cancer patients, which was found in 60-80% of patients with treatment failure [16].

### Stage of cancer

Clinical stage is considered to be a principal prognostic factor in patients with carcinoma of the vulva (according to AJCC, FIGO, TNM) [3, 4, 6-8, 15, 17]. In Stage I vulvar carcinoma the 5-year survival rate described in the literature ranges from 90% to 98%, in Stage II - from 60% to 91%, in Stage III - from 36% to 77% and in Stage IV - from 7% to 31% [6-8, 10, 12, 14, 18, 19]. Treatment results in our group were poorer, probably because of lack of full, surgical verification of inguinal node status in all patients. In the investigated group, the 5-year survival rate

was 61.4% of cases with Stage I by TNM, 54.9% of cases with Stage II, 40.1% of cases with Stage III and 13.3% with Stage IVA. TNM stage was found to be an independent prognostic factor in Cox's multivariate analysis.

#### *Microscopic status of the inguinal lymph nodes*

The microscopic status of inguinal lymph nodes is widely considered to be the major prognostic factor for vulvar carcinoma [6, 7, 12-15, 18, 20, 21]. In most studies regional lymph node metastases were positive in 21-42% of cases [14, 18, 22, 23]. The frequency of positive inguinal nodes depends on the stage of cancer, depth of invasion, tumor size, and location and histological differentiation [3, 5, 18, 22].

In the literature, successful treatment of patients with negative inguinal nodes varies between 70 and 100% and decreases to 20%-50% if positive lymph nodes are present [6, 13, 15, 18, 24]. Many authors highlight the prognostic meaning of the number of positive lymph nodes [6, 13, 22, 23, 25], while others suggest that survival of patients with vulvar cancer is associated with the size of positive groin nodes. Origoni *et al.* evaluated patients with positive lymph node size less than 5 mm and 5-year survival rate reached 90.9%. Inguinal lymph nodes larger than 15 mm were related with a 20.6% 5-year survival rate [13]. Our data do not contain information about the microscopic status of the inguinal lymph nodes of all patients, however, in our material clinical status of the groin nodes was an independent prognostic factor (Cox's multivariate analysis). The 5-year survival rate was 55.4% in patients with clinically negative groin nodes (N0), 33.3% in patients with unilateral lymph node metastasis, and 20% in patients with bilateral lymph node metastasis.

#### *Tumor size*

Size of the primary lesion is one of the major criteria of vulvar carcinoma stage, however the impact of tumor size on prognosis remains unclear [3, 8, 12, 17, 21-23]. In the study of Rutledge *et al.* tumor size had a significant impact on survival in patients with a lesion diameter over 6 cm. Relative risk (RR) of death in this group was 2.4 times higher compared to those with a tumor size of 0-2 cm [12].

According to Rodolakis *et al.* 79.5% of patients with lesion size 2-3 cm survived five years, whereas this rate was only 52.6% in patients with lesion size over 3 cm [16]. Hopkins *et al.* suggest that size of the tumor is a prognostic factor for Stage III and IV but not in Stages I and II [8]. Other authors reported that tumor size is correlated with the hazard of local lymph node metastasis [3, 22]. In our study the statistical correlation between dimension of the primary lesion and the clinical and microscopic status of groin nodes was found but tumor size had no significant impact on survival.

#### *Surgical margin*

Most authors accept that size of the surgical margin is a prognostic factor for local recurrences and agree that an 8 mm margin is sufficient [4, 9, 10, 12, 15]. In a group of

135 patients, Heaps *et al.* discovered that none of 91 women with a negative surgical margin  $\geq 8$  mm had had a local vulvar recurrence and 21 (48%) of 44 women with a margin  $< 8$  mm, had had a local vulvar recurrence [6]. The influence of the surgical margin on overall survival is controversial [9, 10, 15]. In the study group positive surgical margins had no statistical influence on 5-year survival rate.

#### *Stage of cancer differentiation*

Some authors suggest that the stage of differentiation has a prognostic value in vulvar carcinoma patients [5, 6, 8, 14]. Moreover, the stage of differentiation influences the frequency of lymph node metastases [5]. Homesley *et al.* reported groin metastases in 26.8% of patients with G1 stage, 36.1% with G2, and 54.8% of patients with G3 stage [7].

According to Rosen and Malmstrom [10] cancer stage, tumor differentiation and age at time of diagnosis are prognostic factors in vulvar carcinoma; 5-year survival rate was 70% for well-differentiated tumors and 55% for moderately and poorly differentiated tumors. The prognostic value of tumor differentiation was reported by Malmstrom *et al.*, however in the study by Hopkins *et al.* tumor differentiation of vulvar carcinoma was a prognostic factor in a group of patients only with Stages I and II but not for patients with Stages III and IV [8, 27]. Some authors emphasize the fact that multivariate analyses do not demonstrate the prognostic value of tumor differentiation stage [3, 10, 21], and many suggest that tumor differentiation has no influence on 5-year survival [4, 6, 7, 10]. In the study group cancer differentiation had a prognostic value for 5-year survival in univariate analysis but not in Cox's multivariate analysis. Patients with well-differentiated cancer (G1) survived five years in 57.5%, with moderately differentiated (G2) in 34.9%, and with poorly differentiated (G3) in 9.1%.

#### *Age*

Most authors accept that age is an independent prognostic factor for vulvar carcinoma [5, 6, 8, 9, 10, 18]. Rosen and Malmstrom showed that there were significant differences in survival when comparing patients older than 69 years [10]. In a group of 588 patients, Homesley *et al.* discovered that local lymph node metastases was present in 25.2% of patients younger than 55 years, in 25.4% cases between the age of 55 and 64 years, in 36.4% in the group between 65 and 74 years, and in 46% of patients aged over 74 [7]. In the study group the age of patients at the time of diagnosis had a prognostic value for 5-year survival in Cox's multivariate analysis. In the group of patients under 70 years, 5-year survival was achieved in 47.1% of cases and in those aged  $\geq 70$  in 18.8% only.

#### *Primary tumor location*

Most authors accept that location of the tumor on the clitoris is an unfavorable prognostic factor. In a group of patients with lesions located on the clitoris Boyce *et al.*

and Curry *et al.* reported groin nodes metastases in about 40% of patients [23, 27]. In the group of 225 patients Magrina *et al.* discovered that urethra invasion had a significant, unfavorable impact on survival in patients with vulvar carcinoma, and it decreased the 5-year survival rate from 84.9% to 42.9%. The local recurrence rate was 57.1% and 12.4% in patients with or without invasion of the urethra, respectively [9]. In the study group cancer location on the clitoris had no prognostic value.

## Conclusions

Univariate analysis of our material showed that age, differentiation of cancer, clinical inguinal node status and TNM stage are associated with overall survival rate. Patients aged under 70, with well differentiated cancer, clinically negative groins and with disease in Stage I and II by TNM have a better survival prognosis. Multivariable analysis by Cox's model regression revealed that age, clinical node status and cancer stage by TNM were independent risk factors for cancer-related death in our patients. Those results are similar to the literature data, however, treatment outcome and 5-year overall survival were less satisfactory.

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