Clinicopathological Prognostic Factors and Patterns of Recurrence in Vulvar Cancer

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Abstract. *Background: Vulvar cancer is a rare disease and knowledge on prognostic factors is therefore limited and inconsistent. The aim of this study was to determine prognostic variables for recurrence and survival and to identify patterns of recurrence in patients with vulvar cancer. Patients and Methods: All patients (n=103) with primary vulvar cancer treated at the University Medical Center Hamburg-Eppendorf between 1996 and 2003 were retrospectively analysed regarding the prognostic relevance of different clinico-pathological variables. Recurrences were evaluated with regard to their characteristics and localisation. Results: Age, lymph node metastasis, tumor size, depth of invasion and involvement of resection margins predicted poor disease-free and overall survival in univariate analysis. In multivariate analysis, lymph node status was the most important independent prognostic factor (p=0.002). No correlation was observed between lymph node metastasis and localization of recurrent disease. Regardless of initial nodal involvement, recurrences occurred primarily in the vulvar region. Conclusion: Inguinofemoral lymph node status at initial diagnosis is of critical prognostic importance for patients with vulvar cancer. Further tumour biological characteristics need to be identified to stratify patients with nodal involvement for adjuvant radiotherapy of the vulva to prevent local recurrences.*

Despite its increasing incidence, vulvar cancer is still a rare disease, comprising about 5 percent of malignancies of the female genital tract (1). In Germany, the incidence is 3.6 cases per 100,000/year. Annually, there are an estimated 1,300 new cases and 700 deaths from this disease compared to 3,490 cases in the United States (2, 3). Vulvar cancer occurs predominantly in postmenopausal women (median age at diagnosis 69 years), although recently, an increased incidence has been observed in the age group under 50 (4, 5).

Information regarding prognostic factors for disease-free and overall survival in vulvar cancer is limited and inconclusive (6-13). Potential predictors for prognosis include stage, tumour size, depth of invasion, margin distance, lymphovascular space invasion, serum squamous cell carcinoma antigen (SCC-Ag) level before surgery, age and degree of nodal involvement. However, results are heterogeneous concerning the impact of many of these variables (14-17). The observed differences are most likely caused by small patient groups and inhomogeneous treatment strategies. Information regarding the pattern of recurrence in vulvar cancer is even more limited. The majority of recurrences are confined to the vulvar region (13, 18, 19). These may be controlled by excision and/or radiotherapy, whereas groin or distant recurrences are less frequent but often fatal. Greater age and surgical resection margins >8 mm were found to be possible risk factors for local recurrence while inguinal recurrences were correlated with advanced tumour stage and initial nodal involvement in some studies (13, 16, 20).

The aim of this study was to evaluate the prognostic impact of clinicopathological variables for recurrence and survival of patients with vulvar cancer and to identify possible patterns of recurrence, especially in patients with primary nodal involvement.

Patients and Methods

Patients. All patients with primary vulvar cancer treated with radical surgery at the University Medical Center Hamburg-Eppendorf between 1996 and 2003 were retrospectively analysed. The institutional approach to the treatment of vulvar cancer during the investigated period consisted in the resection of the primary tumour (except in women with extremely large tumours or distant metastases who were excluded from this analysis) and the inguinofemoral lymph nodes *via* triple incision. Only

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in cases of stage 1a disease (less than 1 mm invasion depth) was inguinofemoral lymph-adenectomy abandoned. Adjuvant radiotherapy of the groins and pelvis was performed if more than one inguinofemoral lymph node was positive, a metastasis was greater than 10 mm in diameter or showed extracapsular spread. Adjuvant radiotherapy of the vulva was performed if the surgical margin was less than 8 mm. Written informed consent had been obtained from all included patients to access their tissue and review their medical records when they first attended the clinic according to the Investigational Review Board and Ethics Committee guidelines. Data were retrieved from patients' records, the tumour registry and death certificates; all patients were followed up until death or June 2007. All pathological studies were performed by gynaecopathologists in the Department of Pathology of the University Medical Center Hamburg-Eppendorf. Pathological reports were retrospectively analysed for tumour size, depth of invasion, tumour classification, stage and grade, lymphovascular space involvement, presence of intraepithelial neoplasia (VIN), tumour-free surgical margins and margin distance. In case of recurrent disease, its localisation (local/groin/distant) and characteristics were analysed. For tumour staging and classification, UICC TNM classification and stage groupings were used (21).

Statistical analysis. Endpoints for this study were recurrent disease (locoregional, groin or distant), death, or last follow-up. After literature research, nine variables were chosen to be tested regarding their value as prognostic factors for recurrence and survival of patients with vulvar cancer: age, tumour classification, depth of invasion, lymphovascular space involvement, resection margin involvement, margin distance, grade, lymph node status and SCC-Ag serum level before surgery. For conclusive statistical analysis of the invasion depth and margin distance, the cases were divided into two equal groups (invasion: ≤3 mm and >3 mm, distance: <5 mm and ≥5 mm). All statistical analyses were conducted using SPSS software version 15.0 (SPSS Inc., Chicago, IL, USA). Univariate analysis was performed for each prognostic factor separately. Continuous parameters such as age and SCC-Ag value were analysed with univariate Cox regression; log-rank test was used for all categorical variables and visualised with Kaplan-Meier curves and *p*-values <0.05 were considered statistically significant. To keep an overall level of significance of 5% despite multiple testing, the level must be formally adjusted to 0.2% (corresponding *p*-value=0.002) for each test (Bonferroni method); consequences for relevance of certain variables are pointed out in the text. All variables with *p*-value <0.05 in the univariate analysis were further analysed by multivariate Cox regression.

Results

One hundred and nine patients with primary vulvar cancer underwent radical surgery at the University Medical Center Hamburg-Eppendorf between 1996 and 2003. Six cases were lost to follow up immediately after surgery and were excluded from further analysis. The median age of the remaining 103 patients was 63 years. The median follow-up was 36 months (mean 44±29, range 3-129). Detailed patient characteristics are listed in Table I, tumour classifications and other histopathological details in Table II.

Ninety-six patients (93.2%) had squamous cell carcinoma, the remaining 7 patients had a carcinoma based on Paget's disease. Primary tumours were mainly confined to the vulva (91.3% T1 or 2), 94.2% of the tumours were excised with tumour-free margins. The exact margin distance was determined in a subset of 34 patients: the mean margin distance was 8 mm and ranged from 1 to 24 mm. Seventy-four patients (71.8%) underwent inguinofemoral lymphadenectomy: lymph node metastasis was diagnosed in 21 patients (28.4%). Altogether 26.2% of the patients underwent adjuvant radiotherapy; details are listed in Table I.

Table I. *Patient characteristics*.

Patients	n=103
Age (years)	mean 63±15
(range 30-93, median 66)	
Local treatment	
Primary surgical therapy	103 (100%)
Complete vulvectomy	53 (51.4%)
Hemivulvectomy	25 (24.3%)
Wide local excision	25 (24.3%)
Inguinofemoral lymphadenectomy	
Bilateral	55 (53.4%)
Ipsilateral	19 (18.4%)
Not performed	29 (28.2%)
Number of lymph nodes examined per lymphadenectomy	mean 15 (range 1- 51)
Number of affected lymph nodes per lymphadenectomy	mean 0.6 (range 0-7)
Radiotherapy	
None	76 (73.8%)
Any localisation	27 (26.2%)
Vulva	9 (8.7%)
Groins and pelvis	10 (9.7%)
Vulva, groins and pelvis	8 (7.8%)

Of the 29 patients that did not receive lymphadenectomy (Nx), 18 had a pT1a tumour, where lymphadenectomy is not recommended. For the remaining 11 patients, groin surgery as well as adjuvant radiotherapy was omitted because of poor performance status due to age (mean age in this group 78 years) and co-morbidity. Four of these patients had a pT1b tumour and seven a pT2 tumour.

The serum-SCC-Ag concentration before surgery was available for 96 patients and ranged from 0.2 and 9.8 kU/l (mean 2.34 kU/l) with a median SCC of 0.8 kU/l. There was no statistically significant correlation between serum concentration of SCC-Ag and tumour classification or stage.

Fourteen patients (13.6%) had recurrent disease after a mean interval of 19 months (median 13, range 3-61). Three of them had had stage I disease (T1N0M0), one stage II (T2N0M0), five stage III (T1, 2, 3N1M0) and one stage IVA disease (T2N2M0). The remaining four patients did not undergo lymphadenectomy because of poor performance status at primary diagnosis (Nx, three with T2 and one with T1b primary tumour). In the majority of cases (n=8), the recurrence was located in the vulvar region. The remaining

Table II. *Histopathological characteristics.*

Tumour-classification (T)	
T1 (tumour confined to vulva and perineum; ≤2 cm in greatest dimension)	58 (56.3%)
T1a (stromal invasion ≤1.0 mm)	18 (17.4%)
T1b (stromal invasion >1.0 mm)	40 (38.8%)
T2 (tumour confined to vulva and perineum; >2 cm in greatest dimension)	36 (34.9%)
T3 (tumour of any size with adjacent spread to lower urethra, vagina or anus)	8 (7.7%)
T4 (tumour of any size invading the upper urethral mucosa, the bladder mucosa, the rectal mucosa or tumour fixed to the bone)	1 (0.9%)
Regional lymph node involvement (N)	
N0 (none)	53 (51.5%)
Nx (unknown (no lymphadenectomy)	29 (28.2%)
N1 (unilateral involvement)	17 (16.5%)
N2 (bilateral involvement)	4 (3.9%)
Distant metastasis (M)	
M0 (none)	103 (100%)
Grade of differentiation (G)	
G1 (well)	17 (16.5%)
G2 (moderate)	49 (47.6%)
G3 (poorly)	27 (26.2%)
Unknown	10 (9.7%)
Histological type	
Squamous cell carcinoma	96 (93.2%)
Adenocarcinoma	7 (5.8%)
Coexisting lesion	
None	33 (32%)
VIN	62 (60.2%)
Depth of invasion	
≤3 mm	43 (41.7%)
>3 mm	39 (37.8%)
unknown	21 (20.4%)
Lymphovascular space involvement (L)	
L0 (none)	43 (41.7%)
L1 (involvement)	25 (24.3%)
Unknown	35 (34.0%)
Resection margin	
Tumour-free resection margin	97 (94.2%)
Tumour cells in resection margin	6 (5.8%)
VIN in resection margin	16 (15.5%)
Margin distance (n=34)	mean 8.0 mm (range 1-24, median 8.0)

Table III. *Disease free survival and overall survival: Univariate analysis of clinicopathological variables (log-rank test/univariate Cox regression).*

Variable	n	Disease-free survival		Overall survival	
		p-Value	2-Year survival (%)	*p*-Value	2-Year survival (%)
Age (continous)	103	**0.034**		**0.004**	
Tumour classification	103	**<0.001**		**<0.001**	
pT1a	18		92.9		100.0
pT1b	40	0.137	83.1		94.6
pT2	36	0.013	68.8		78.4
pT3	8	0.008	46.9		46.9
pT4	1	0.001	00.0		00.0
Nodal status	103	**<0.001**		**<0.001**	
pN0	53		87.1		94.0
pN1	17	0.001	55.5		60.9
pN2	4	0.000	00.0		00.0
Nx	29	0.484	79.6		96.3
Nx, not pT1a	11	0.019			
Depth of invasion	82	**0.005**		**<0.001**	
≤3 mm	43		89.3		100.0
>3 mm	39		64.9		74.3
Lymphovascular invasion	68	0.05		0.05	
Absent	43		90.7		94.7
Present	25		61.4		67.8
Resection margin	103	**0.003**		**<0.001**	
Tumour free	97		78.7		89.1
Not tumour free	6		25.0		22.2
Margin distance	34	0.89		0.73	
≤5 mm	20		72.0		84.4
>5 mm	14		78.6		85.7
Tumour grade	93	0.17		0.10	
G1	17		81.3		94.1
G2	49		80.7		89.1
G3	27		62.0		70.7
SCC-Ag value (continuous)	96	0.49		0.14	

patients had inguinal lymph node recurrence; no skin bridge recurrence was observed. One patient with inguinal recurrence had additional distant metastasis in the liver.

Of the 21 patients with positive lymph nodes at primary diagnosis, six (28.5%) had recurrent disease, all of whom had received radiotherapy after initial surgery. In four patients, only the groin and pelvis had been irradiated, in two patients the vulva, groin and pelvis (recurrences were located inguinal in these two patients). There was no correlation between lymph node metastasis and localisation of recurrent disease, or time to recurrence and its localisation. Recurrence equally affected vulva and lymph nodes in these patients, despite completely resected primary tumours. In the Nx group, four patients had recurrent disease, located in the vulvar region (n=3) and inguinal (n=1). The median time to relapse was 17.5 months. Two of these recurrences were excised, the others were treated by radiotherapy. Nineteen patients (18.4%) died during the follow-up period.

Age, nodal status, tumour classification, depth of invasion and resection margin involvement were statistically significant predictors for disease-free survival and overall survival by univariate analysis (Table III and Figures 1, 2 and 3). With every year of age, the risk for recurrent disease increased by 3.4% (hazard ratio, HR=1.034), while the risk of dying increased by 5.6% (HR=1.056). After Bonferroni correction with an adjusted level of significance to 0.2% however, age did not persist as a significant prognostic factor in univariate analysis. Recurrence-

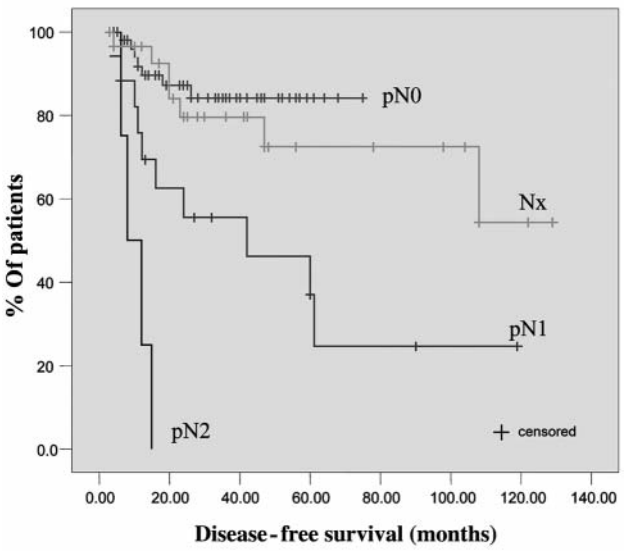

Figure 1. *Disease-free survival in relation to lymph node involvement. Kaplan-Meier survival curve for the probability of disease-free survival according to the lymph node status. Recurrence-free survival decreased with increasing nodal involvement (p<0.001). pN0: No nodal involvement; pN1: unilateral inguinofemoral lymph node metastasis; pN2: bilateral inguinofemoral lymph node metastasis; Nx: unknown node status (no lymphadenectomy).*

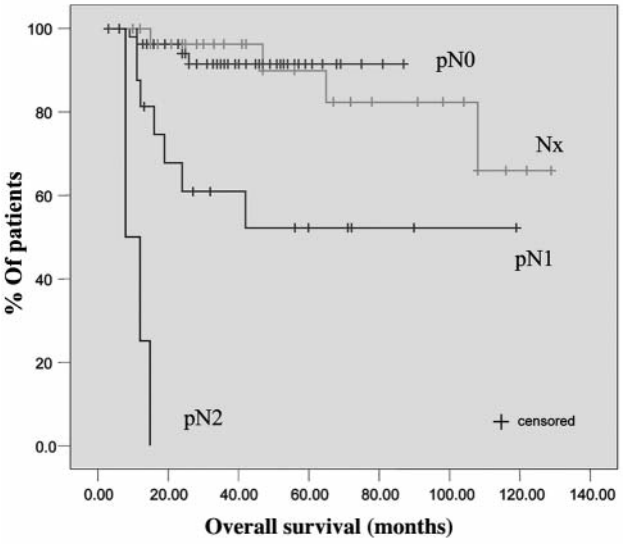

Figure 2. *Overall survival in relation to lymph node involvement. Kaplan-Meier survival curve for the probability of overall survival according to the lymph node status. Overall survival decreased with increasing nodal involvement (p<0.001). pN0: No nodal involvement; pN1: unilateral inguinofemoral lymph node metastasis; pN2: bilateral inguinofemoral lymph node metastasis; Nx: unknown node status (no lymphadenectomy).*

free and overall survival decreased with increasing tumour size, invasion depth and margin involvement (Figure 3, Table III).

Five-year recurrence-free survival in patients with unilateral lymph node metastasis was 37% , with a corresponding overall survival of 52% , while patients without groin involvement had a recurrence-free survival of 84.1% and an overall survival of 91.4% after five years.

In the Nx group, the risk for recurrent disease was higher than in the group of patients that underwent groin surgery and had no nodal involvement (pN0) (Figure 1). However, overall survival was not significantly different (Table III, Figure 2). For further analysis, the Nx group was subdivided into patients with stage Ia disease and those with a greater primary tumour but poor performance status (Figures 4 and 5). Patients with a pT1a tumour and unknown lymph node status had a significantly better prognosis for both disease-free and overall survival (p=0.004 and p=0.006).

In multivariate analysis, lymph node status and age were the only independent prognostic factors for disease-free and overall survival (Table IV). After adjusting the level of significance to 0.02% , only nodal involvement persisted as an independent prognostic factor (p=0.002).

The risk for recurrent disease was 5.1 times higher for patients with unilateral lymph node involvement and 16.9 times higher for those with bilateral lymph node involvement compared to those with negative nodes.

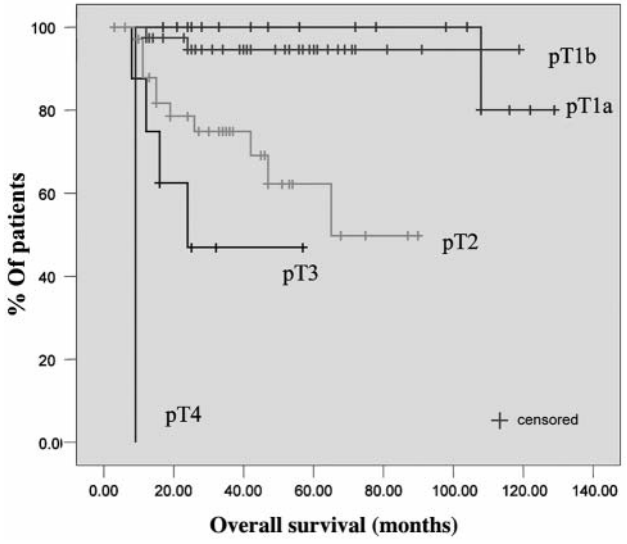

Figure 3. *Overall survival in relation to tumour classification. Kaplan-Meier survival curve for the probability of overall survival according to the tumour classification. Overall survival decreased with increasing tumour size (p<0.001). pT1: Tumour confined to vulva and perineum, ≤2 cm in greatest dimension; pT1a: with stromal invasion 1.0 mm; pT1b: with stromal invasion >1.0 mm; pT2: tumour confined to vulva and perineum, >2 cm in greatest dimension; pT3: tumour of any size with adjacent spread to lower urethra, vagina or anus; pT4: tumour of any size invading the upper urethral mucosa, the bladder mucosa, the bone.*

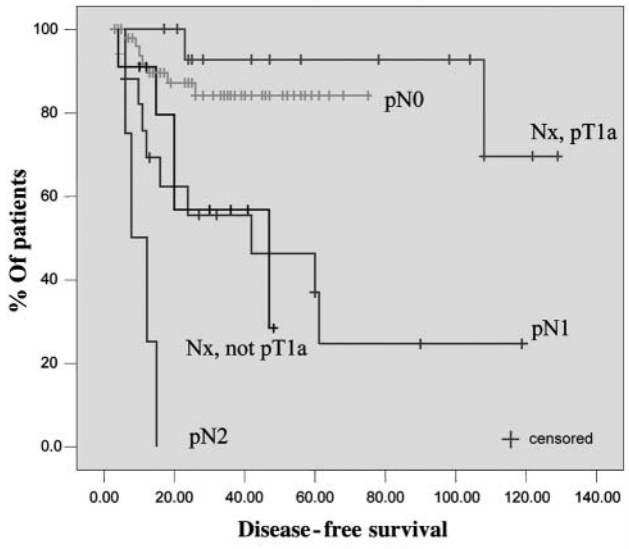

Figure 4. *Disease-free survival in relation to lymph node involvement, Nx group subdivided. Kaplan-Meier survival curve for the probability of disease-free survival according to the lymph node status under subdivision of the Nx group (no lymphadenectomy) in those who had vulvar cancer stage Ia and those with a greater primary tumour but poor performance status. pN0: No nodal involvement; pN1: unilateral inguinofemoral lymph node metastasis; pN2: bilateral inguinofemoral lymph node metastasis; Nx: unknown node status (no lymphadenectomy); Nx, pT1a: unknown node status (no lymphadenectomy) and tumour confined to vulva and perineum, ≤2 cm in greatest dimension with stromal invasion ≤1.0 mm; Nx, not pT1a: unknown node status (no lymphadenectomy) and any tumour classification except pT1a.*

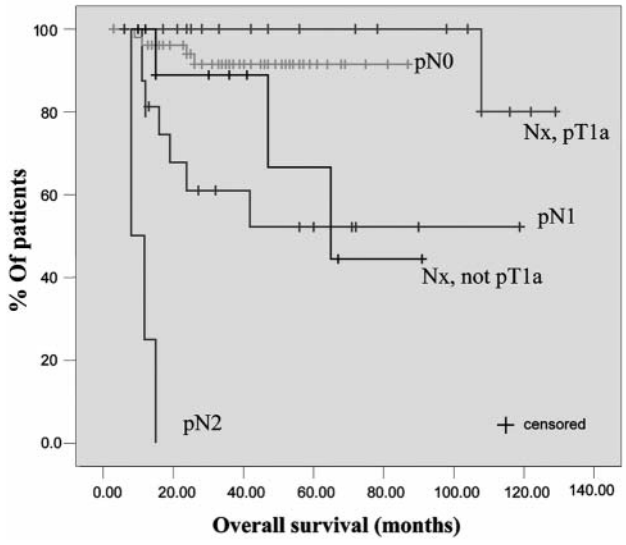

Figure 5. *Overall survival in relation to lymph node involvement, Nx group subdivided. Kaplan-Meier survival curve for the probability of overall survival according to the lymph node status under subdivision of the Nx group (no lymphadenectomy) in those who had vulvar cancer stage Ia and those with a greater primary tumour but poor performance status. pN0: No nodal involvement; pN1: unilateral inguinofemoral lymph node metastasis; pN2: bilateral inguinofemoral lymph node metastasis; Nx: unknown node status (no lymphadenectomy); Nx,pT1a: unknown node status (no lymphadenectomy) and tumour confined to vulva and perineum, ≤2 cm in greatest dimension with stromal invasion ≤1.0 mm; Nx, not pT1a: unknown node status (no lymphadenectomy) and any tumour classification except pT1a.*

Table IV. *Multivariate analysis of selected clinicopathological variables regarding disease-free survival and overall survival (Cox proportional hazard model).*

Variables	Disease-free survival				Overall survival			
	p-Value	HR	95% CI		*p*-Value	HR	95% CI	
Age	**0.017**	1.057	1.010	1.106	**0.009**	1.111	1.027	1.201
pT1	0.371				0.193			
pT2	0.194	2.029	0.697	5.907	0.070	5.460	0.868	34.340
pT3	0.955	0.938	0.100	8.754	0.236	5.322	0.335	84.496
pN0	**0.017**				**0.013**			
pN1	**0.016**	5.114	1.353	19.332	0.134	4.135	0.646	26.480
pN2	**0.004**	16.993	2.467	117.050	**0.002**	71.518	4.890	1045.983
pNx	0.436	1.740	0.432	7.014	0.685	.605	0.054	6.843
Resection margin	0.376	2.674	0.304	23.566	0.482	2.699	0.170	42.915
Depth of invasion	0.234	2.044	0.630	6.635	0.137	5.872	0.570	60.487

CI: Confidence interval.

Discussion

In this study, 103 patients with primary vulvar carcinoma underwent radical surgery and were evaluated for prognostic factors, representing a large and homogeneous cohort for investigating this rare disease. The results demonstrate that lymph node metastasis to the groin is the most important prognostic factor for disease-free and overall survival, while all other analysed factors remain secondary. Patients with unilateral lymph node metastasis had a five-fold increased risk of recurrence compared to node-negative patients; in cases of bilateral lymph node involvement, this risk was 17 times higher.

To date, few studies have been published investigating various prognostic factors in vulvar cancer, with relatively inconclusive results (10, 12, 13, 22-30). The majority of them also found lymph node involvement to be of central prognostic relevance (6, 9-11). In a retrospective analysis of 389 cases of vulvar cancer, Raspagliesi *et al*. identified nodal status as the most significant prognostic factor among all tumour-related variables and proposed that certain variables related to positive nodes (such as extracapsular spread) could be critical for further risk assessment (10). In contrast to these results, a retrospective population-based study by Rhodes *et al*. demonstrated an unfavorable survival for patients with positive inguinal lymph nodes only in univariate analysis; after multivariate analysis, it did not retain its prognostic significance (11). These inconsistent findings are most likely caused by heterogeneous treatment strategies in the investigated population, as Rhodes *et al*. also observed that the management of vulvar cancer varied widely between different centres, many of which treated only very few patients per year.

Besides lymph node involvement, all other factors analysed in this study were of secondary importance. Depth of invasion, resection margin involvement and tumour classification had prognostic relevance in univariate analysis only. The correlation between nodal involvement and invasion depth and size of the primary tumour shown in previous studies could be a possible explanation (31, 32).

Although age did not persist as an independent prognostic factor after adjusting the level of significance (Bonferroni method) in this cohort, the risk for recurrence increased by 3.4% and the risk of death by 5.6% with every year of age. This might be partially attributed to deviation from the standard treatment protocol in the subgroup of older patients as similar disease-free survival rates were observed for patients with initial nodal involvement after lymphadenectomy and radiotherapy, and those who did not receive lymphadenectomy because of poor performance status and/or old age (mean age in this group 78 years). Overall survival nevertheless was longer for the second group despite their age and performance. Presuming that only a certain proportion of that group of patients actually had nodal involvement at initial diagnosis, their risk of recurrent disease may have been increased by omitting lymph node dissection. In case of recurrent disease however, these patients were expected to tolerate secondary surgery and/or radiation. With the demographic changes in western countries, it is important to provide standardised treatment regardless of a patient's age, solely based on the individual performance status.

In this study, serum SCC-Ag concentrations were neither of predictive value nor correlated with tumour classification or stage. To the Authors' knowledge, this is the largest cohort study evaluating the prognostic relevance of serum SCC-Ag levels before surgery in SCC of the vulva. These results are only partially consistent with previous studies. Some authors reported that the serum SCC-Ag concentration had no prognostic value; others found that it was an independent prognostic variable for survival (17, 24, 33, 34). These discrepant findings are most likely due to small patient groups. However, in analogy to the results in cervical cancer patients, SCC-Ag measurements might predominantly be useful in monitoring treatment response and detecting recurrent disease early rather than in evaluating the preoperative risk (35).

Information regarding the pattern of recurrence in vulvar cancer is extremely limited. As Woolderink and other authors described, the majority of recurrences are confined to the vulvar region (6, 13, 20). This raises further questions about recurrence patterns in patients with initial lymph node metastasis: even in these patients, recurrences occurred predominantly in the vulvar region. There was no correlation between lymph node metastasis and localisation of recurrent disease, or the time to recurrence and its localisation. The group of patients with primary nodal involvement and recurrent disease was small (n=6). Nevertheless, the interesting fact of vulvar recurrence in patients with nodal involvement at initial diagnosis has been described before by Burger *et al*. (6). In their study, patients were treated with surgery and adjuvant radiation of the groin. The inguinofemoral lymph node status at initial diagnosis was found to be of critical importance for prognosis. However, as observed in this study, recurrences occurred primarily in the vulvar region and not in the groin or as skin-bridge metastases. These findings suggest that surgical excision combined with adjuvant radiotherapy of the inguinofemoral region is very effective in achieving local control in the groin but not necessarily in the vulvar region. Some of the patients with initial nodal involvement might have specific tumour biological characteristics that increase the risk for local recurrence regardless of sufficient surgical margins at primary excision. Thus, further molecular characterization of node-positive vulvar carcinomas is highly desirable. In particular, the potential role of pre-existing genital human papilloma virus infection in multiple local recurrences and groin metastases needs to be elucidated and considered for future treatment options.

A possible limitation of this study is its retrospective and monocentric nature, but the low prevalence of vulvar cancer makes prospective studies difficult to complete. However, the high number of patients with vulvar cancer treated at this institution and the uniform treatment by a specialised surgical and radio-oncological team might be strengths of this study, as inter-patient variability in treatment regimens was very low.

Further studies are needed to elucidate the molecular background of these findings. In analogy to other gynaecological malignancies, molecular and clinicopathological patterns could

help to stratify patients for adjuvant radiotherapy of the vulva and intensified vulvoscopic follow-up to prevent multiple local recurrences.

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