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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Unilateral versus bilateral lymph-nodal metastases and oncologic outcome in vulvar cancer patients

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Abstract

Purpose To evaluate the difference in oncologic outcome between vulvar cancer patients with uni- and bilateral inguino-femoral lymph nodal involvement and to identify factors affecting their oncologic outcome

Materials and methods Patients who underwent inguino-femoral lymphadenectomy for vulvar cancer were classified into three groups according to their lymph nodal status at the histology analysis (negative, positive one side, positive bilaterally). PFS and OS survival were calculated using the Kaplan–Meier method. Univariate and multivariate analyses were performed to analyze factors predicting overall survival and progression-free survival. Multivariable models were used for variables reporting a p value ≤ 0.1 at the univariate analysis. p values ≤ 0.05 were considered statistically significant.

Results One hundred and forty-six patients were considered for the analysis. Patients with bilaterally negative lymph nodes had significantly longer PFS and OS as compared to patients with unilateral and bilateral involvement. Patients with unilateral lymph nodal involvement had better PFS than patients with bilateral lymph nodal involvement. Among these patients, the difference in the OS approached but did not reach statistical significance. At the multivariate analysis, the tumor size affected PFS and lymph nodal involvement affected OS.

Conclusion Vulvar cancer patients with bilateral positive lymph nodes have worse oncologic outcome as compared to patients with unilateral lymph nodal involvement; similarly, patients with unilateral lymph nodal involvement have worse oncological outcome as compared to patients with bilateral negative lymph nodes. Furthermore, tumor size and lymph nodal status are independent factors predicting recurrence rate and overall survival, respectively.

Keywords Vulvar cancer · Lymph node metastases · Progression-free survival · Overall survival

Introduction

Vulvar cancer is a rare gynecological malignancy, with an incidence of 3/100,000 women per year. Squamous cell carcinoma (SCC) accounts for 95% of all vulvar cancers, more uncommon types include Paget disease of the vulva or melanoma. Squamous cell carcinoma can be grouped into two categories, depending on the predisposing factors: HPV-related SCC, which derives from a vulvar intraepithelial neoplasia (uVIN, usual type), and is common in younger patients, and a non HPV-associated type, which arises on the background of a chronic inflammatory dermatosis or lichen sclerosus of the vulva via dVIN (differentiated type intraepithelial neoplasia). The second type occurs in elderly patients and has a distinct oncogenic pathway (Alkatout 2015; Van de Nieuwenhof 2011).

Historically, radical excision of the tumor with radical inguino-femoral lymphadenectomy was gold standard in therapy of vulvar cancer (Van der Zee 2008). The modern approach involves sentinel lymph node (SLN) mapping in selected cases (tumor < 4 cm, clinically negative inguinal lymph nodes), which leads to a significant reduction of morbidity in these patients (Levenback 2008; te Grootenhuis

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2016; Hacker 2012). The GROINSS-V I study reports a rate of lymphedema of 1.9% in cases with sentinel lymph node removal vs 25.2% in case of radical inguino-femoral lymphadenectomy (te Grootenhuis 2016).

Whereas depth of invasion seems to be relevant for local recurrences, lymph node status is the most important prognostic factor for overall survival in vulvar cancer. Five-year survival rates can reach 90% with tumor free lymph nodes, and rapidly drop down to 50% in case of lymph node involvement (te Grootenhuis 2016). Size and number of affected lymph nodes, as well as extracapsular growth, are further notable prognostic factors (Hacker 2012; Fons 2009a, b).

In lateralized tumors < 4 cm and positive sentinel lymph node on the affected side, an ipsilateral inguinal lymphadenectomy will be performed. It remains disputed if by presence of a tumor free sentinel lymph node on the contralateral side, a lymphadenectomy should be conducted here. Van der Zee et al. report 4.3% non-sentinel metastasis on the contralateral side in their population (Van der Zee 2008). A further controversial issue is application of adjuvant radiotherapy in case of intra capsular metastasis of the sentinel lymph node alone (Fons 2009a, b).

The role of other histopathological factors such as perineural and vascular invasion or tumor grading in the prognosis of the disease also remains unclear. Furthermore, data is scarce regarding chemotherapy employment in vulvar cancer (Hacker 2012).

The aim of the current study is to evaluate the difference between uni- and bilateral inguino-femoral lymph nodal involvement on progression-free survival (PFS) and overall survival (OS) and factors affecting oncologic outcome in vulvar cancer patients.

Materials and methods

A retrospective analysis of patients with vulvar cancer who were treated surgically at the Department of Obstetrics and Gynecology, University Hospital of Bern and University of Bern was performed. Demographic, clinical and pathologic data were retrieved from an electronic database. Surgical reports and clinical charts were used to integrate missing data. The study was IRB approved (KEK 261/2015).

Patients with histologically confirmed vulvar cancer undergoing surgical treatment at our Institution were included in the study. Patients who were subjected to neoadjuvant treatment or not undergoing a surgical assessment of the inguino-femoral lymph nodes or with a diagnosis of vulvar melanoma were excluded from the study.

Surgery consisted of radical vulvectomy, hemi-vulvectomy or radical wide excision, based on tumor diameter and localization. A small group of experienced gynecological oncologists performed these surgeries thus ensuring uniformity in management.

Patients with early stage, unilateral, unifocal, vulvar cancer with tumor size < 4 cm and clinically negative lymph nodes, underwent a sentinel lymph node (SLN) mapping. This procedure was performed with a combination of tracers: Tc-99 m in combination with a blue dye or indocyanine green. Tc-99 m was injected the day prior to surgery in the nuclear medicine Department and was followed by a SPECT-CT to define number and localization of the SLNs. A full inguino-femoral lymphadenectomy was performed in case of evidence of metastatic disease to the SLNs at frozen section.

All patients were staged according to the FIGO stage 2009 (Petru 2009). Adjuvant radiotherapy and/or chemoradiotherapy were delivered in case of pathological evidence of metastatic disease to the lymph nodes. PFS was calculated from the date of initial surgery to the date of first recurrence. OS was calculated from the date of initial surgery to the date of last follow-up or death.

The patients were divided into three groups: (1) Patients with negative inguino-femoral lymph nodes; (2) Patients with unilateral inguino-femoral lymph nodal metastases; (3) Patients with bilateral inguino-femoral lymph node metastases. Demographic, clinic-pathologic characteristics and surgical data were analyzed using basic descriptive statistics. Duration of follow-up was calculated from the date of surgical treatment to the date of death or last follow-up. PFS and OS survival were estimated using the Kaplan–Meier method. Multivariable models were carried out for variables reporting a p value ≤ 0.1 in univariate analysis. p values ≤ 0.05 were considered statistically significant.

Analyses were performed using the GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego, CA) and Microsoft SPSS version 20.0 for Mac.

Results

Between 2000 and 2016, 146 patients with invasive vulvar cancer treated at our institution fit the selection criteria and were considered for the analysis. Clinical and pathologic characteristics of the patients, including median age, BMI, tumor diameter, FIGO stage and lymph nodal involvement are summarized in Table 1. Briefly, for our cohort of patients median age was 72.2 years, median BMI was 26.1 kg/m^2, median tumor diameter was 2.2 cm.

FIGO stage was distributed as follows: stage I for 89 (61%) patients; stage II for 13 (8.9%) patients, stage III for 43 (29.5%) patients and stage IV for 1 (0.6%) patient. Of the 146 patients included in the analysis, 96 (65.8%) had negative lymph nodes. In 50 (34.2%) patients, the inguino-femoral lymph nodes were affected. Inguino-femoral lymph

Table 1 Characteristics of the patients

	N = 146 (%)
Median age in years (range)	72.2 (23.6–95.3)
Median BMI in kg/m2 (range)	26.1 (15.6–46.7)
FIGO stage	
I	89 (61)
II	13 (8.9)
III	43 (29.5)
IV	1 (0.6)
Median tumor diameter in cm (range)	2.2 (0.2–15)
Tumor grade	
Grade 1	16 (11)
Grade 2	104 (71.2)
Grade 3	26 (17.8)
Patients with negative LNs	96 (65.8)
Patients with unilateral LN involvement	34 (23.2)
Patients with bilateral LN involvement	16 (11)
Adjuvant therapy	43 (29.5)

nodes were affected uni- and bilaterally in 34 (23.2%) and 16 (11%) patients, respectively.

Patients with bilaterally non-affected lymph nodes had a significantly longer PFS and OS as compared to patients with unilateral involvement ($p = 0.016$ for PFS and 0.016 for OS) and bilateral involvement ($p = 0.000025$ for PFS and 0.000016 for OS). Among patients with lymph nodal metastases, patients with unilateral involvement had significantly better PFS ($p = 0.048$) as compared to patients with bilateral involvement, however, OS did not differ significantly among the two groups ($p = 0.567$) At univariate analysis PFS was influenced by adjuvant radiotherapy (HR: 0.49; 95CI 0.26–0.92; $p = 0.02$), tumor diameter > 2 cm (HR: 2.62; 95CI 1.38–4.96, $p = 0.003$), FIGO stage III and IV (HR: 2.75; 95CI 1.52–5.06, $p = 0.001$) and lymph nodal involvement (HR: 2.67, 95CI 1.45–4.92, $p = 0.002$). At multivariate analysis only tumor diameter > 2 cm maintained statistical significance (HR: 2.08; 95CI 1.05–4.12, $p = 0.03$) (Table 2). At univariate analysis OS was influenced by FIGO stage III and IV (HR: 3.88; 95CI 1.34–11.2, $p = 0.01$) and lymph nodal involvement (HR: 5.67, 95CI 1.77–18.11, $p = 0.003$). At multivariate analysis only lymph nodal involvement maintained statistical significance (HR: 5.69; 95CI 1.01–31.9, $p = 0.04$) (Table 3).

Table 2 Univariate and Multivariate Cox regression analysis for progression-free survival (All patients, $n = 146$)

	Progression-free survival			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (≥ 65 vs < 65)	0.71 (0.38–1.34)	0.29		
BMI (≥ 35 vs < 35)	0.45 (0.06–3.34)	0.44		
Adjuvant RT (yes vs no)	0.49 (0.26–0.92)	0.02	1.29 (0.54–3.05)	0.56
Tumor diameter (> 2 cm vs ≤ 2 vs)	2.62 (1.38–4.96)	0.003	2.08 (1.05–4.12)	0.03
FIGO stage (III-IV vs I-II)	2.75 (1.52–5.06)	0.001	1.8 (0.38–8.46)	0.45
Surgery (radical vulvectomy vs radical tumorectomy)	0.84 (0.43–1.62.)	0.6		
LN status (positive vs negative)	2.67 (1.45–4.92)	0.002	1.47 (0.34–6.37)	0.6

Table 3 Univariate and Multivariate Cox regression analysis for overall survival (All patients, $n = 146$)

	Overall survival			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (≥ 65 vs < 65)	0.34 (0.09–1.22)	0.09	2.39 (0.65–8.79)	0.18
BMI (≥ 35 vs < 35)	1.63 (0.51–5.21)	0.4		
Adjuvant RT (yes vs no)	0.34 (0.12–1.009)	0.05	1.06 (0.25–4.39)	0.93
Tumor diameter (> 2 cm vs ≤ 2 vs)	2.98 (0.99–8.96)	0.05	1.6 (0.5–5.11)	0.42
FIGO stage (III-IV vs I-II)	3.88 (1.34–11.2)	0.01	0.82 (0.13–5.06)	0.83
Surgery (radical vulvectomy vs radical tumorectomy)	0.53 (0.14–1.93)	0.34		
LN status (positive vs negative)	5.67 (1.77–18.11)	0.003	5.69 (1.01–31.9)	0.04

Discussion

Our results suggest that bilateral involvement of inguinofemoral lymph nodes is associated with worse prognosis in patients with positive nodal status. In univariate analysis, the factors that significantly affected prognosis were primary tumor size, adjuvant radiotherapy, positive nodal status and FIGO stage. However, under multivariate analysis, tumor size and positive nodal status were the only independent factor affecting PFS and OS, respectively. Comparing laterality of nodal status, we found that bilateral involvement resulted in significantly worse progression-free survival compared to unilateral involvement. As for overall survival, the difference approached statistical significance ($p = 0.056$).

Lymph node status in vulvar cancer is known to be the most important prognostic factor (Homesley et al. 1993; Baiocchi et al. 2013; Fons et al. 2009b). Our study showed that the hazard ratio for overall survival was 5.6 with positive lymph nodes (95% CI 1.01–31.9. $p = 0.04$). This corresponds to most of the studies looking at prognostic factors for vulvar cancer.

In 1991, Homesley et al. in a seminal GOG trial, found that unilateral lymph node involvement has a survival of 70.7% versus 25.4% in bilateral lymph node involvement (Homesley 1991). Baiocchi et al. (2013) found that bilateral lymph node involvement was associated with worse overall survival (44.6% vs 25.9%, $p = 0.012$) and disease specific survival (49.1% vs 36.9%, $p = 0.088$). However, when they analyzed only patients with two or more positive lymph nodes who underwent bilateral lymphadenectomy, there was no significant difference in recurrence or survival between patients with bilateral and unilateral lymph nodes. Fons et al. also showed that laterality did not affect survival when only patients with 2 or more lymph node metastases were analyzed (Fons 2009a, b). Interesting, since lymph node metastases are found in only about 25% of vulvar cancer patients, most patient would be overtreated by radical groin lymphadenectomy. Therefore, after the GROINSS-V study, sentinel lymph node biopsy is the mainstay surgery for unifocal tumors < 4 cm with clinically negative groin nodes (Van Der Zee 2008). Johann et al. also suggested that sentinel lymph node biopsy in early-stage vulvar cancer is a safe alternative to inguinofemoral lymphadenectomy to reduce morbidity (Johann 2008). Other effective surgical strategies to reduce the risk of lymphedema after full lymphadenectomy, such as the use of microsurgical lympho-vascular anastomoses has been described, however, sentinel lymph node biopsy represents the best solution (Morotti 2013).

Other aspects of lymph node involvement like number of involved nodes, size of lymph node metastasis and the presence of extracapsular spread are also prognostic factors. Baiocchi et al. found that removal of < 12 lymph nodes in patients with positive lymph nodes resulted in higher recurrence and lower survival (Baiocchi 2013). Oonk et al. demonstrated that risk of non-sentinel node metastases increases with size of sentinel node metastasis (Oonk 2010). They also suggest that all patients with sentinel node metastasis should have groin treatment as the risk of non-sentinel node metastasis was 4.2%, even in patients with isolated tumor cells in sentinel node.

Tumor size > 2 cm is associated with an increased risk of nodal metastasis, which leads to worse prognosis (Homesley et al. 1993). Furthermore, when excising larger lesions, the risk of obtaining positive or close margins raises thus increasing the risk of a local recurrence. Our results showed that tumor size more than 2 cm is significantly associated with worse progression-free survival. In a group of 194 patients, Aragona et al. found that number of positive lymph nodes, extranodal growth, tumor size and depth of stromal invasion were independent prognostic factors (Homesley 1993). This study identified a group of high risk patients with tumor size ≥ 6 cm and depth of stromal invasion > 4 mm or size ≥ 8 cm independent of other factors, which survival falls sharply (Aragona 2014). Ayhan et al. found that tumor size more than 1 cm is associated with higher recurrence rate (Ayhan 2008). They also found that patients who had local wide excision had a higher recurrence rate than those who had radical surgery. Our study found no statistically significant difference in prognosis with regards to type of surgery performed. In a large multicenter study of 486 patients, tumor diameter and extracapsular nodal spread are important prognostic factors (Tabbaa 2012). A systematic review by Luchini et al. also showed that extranodal extension is associated with higher all-cause mortality, cancer-specific mortality and recurrence (Luchini 2016).

Under univariate analysis, our study showed that adjuvant radiotherapy is significantly associated with better overall and progression-free survival. However, it was not an independent factor after multivariate analysis. Woelbar et al. suggested that the potential benefits of radiotherapy are reduced by the presence of multiple nodal metastases (Woelber 2012). Fons et al. (2009a, b) also reported that the effects of radiotherapy is diminished with lymph node involvement. Bogani et al. (2017) observed that adjuvant radiotherapy did not improve rates of recurrence. In a large multicenter cohort, the AGO-CaRE study found that adjuvant radiotherapy is associated with better outcome in patients with 2 or more positive lymph nodes but not in patients with 1 positive lymph node (Mahner 2015). This study also showed that the prognosis of patients with node positive disease remains poor even after adjuvant radiotherapy. The GOG 37 study in patients with positive groin nodes showed that adjuvant radiotherapy after radical vulvectomy and bilateral groin

lymphadenectomy significantly reduced local recurrence and cancer-related deaths (Kunos 2009).

The limitation of our study is its retrospective nature which may affect the results through reporting bias, missing data and evolving management strategies. There are also pathological variables concerning lymph node metastasis like number of involved lymph nodes, extracapsular spread and size of metastasis, which were not explored in this study.

Conclusion

Our study showed that vulvar cancer patients with bilateral positive lymph nodes have worse oncologic outcome as compared to patients with unilateral lymph nodal involvement; similarly, patients with unilateral lymph nodal involvement have worse oncological outcome as compared to patients with bilateral negative lymph nodes. Furthermore, tumor size and lymph nodal status are independent factors predicting recurrence rate and overall survival, respectively.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest. Nothing to declare.

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