

RESEARCH ARTICLE

Midline Involvement as a Risk Factor for Vulvar Cancer Recurrence

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Abstract

Objective: This observational study was to identify risk factors for vulvar cancer recurrence. **Materials and Methods:** In the study 107 patients with primary vulvar cancer were analyzed. Surgical treatment consisted of radical excision of the primary tumor in combination with unilateral or bilateral superficial and deep inguinofemoral lymphadenectomy through separate incisions. Patients with deeper tumor invasion >1 mm or wider than 2 cm and/or groin lymphnode metastases were referred for adjuvant radiotherapy. Those with large primary vulvar tumors received neoadjuvant radiotherapy of 30Gy followed by surgical treatment and adjuvant radiotherapy. **Results:** Most of patients had only primary radiotherapy to the vulva and inguinal lymph nodes and only 34.5% of patients were eligible for surgical treatment. In 5 year follow-up period 25.2% (27) patients were alive without the disease, 15.0% (16) were alive with the disease and 59.8% (64) were dead. 60.7% (65) patients experienced local recurrence and 2.8% (3) patients had distant metastases. Median survival for patients without recurrent disease was 38.9±3.2 months and 36.0±2.6 months with no statistically significant difference. Patients with early stage vulvar cancer had longer mean survival rates-for stage I 53.1±3.4 months, 38.4±4.4 months for stage II and 33.4±2.6 and 15.6±5.2 months for patients with stage III and stage IV vulvar cancer, respectively. The only significant prognostic factor predicting vulvar cancer recurrence was involvement of the midline. **Conclusions:** Patients having midline involvement of vulvar cancer has lower recurrence risk, probably because of receiving more aggressive treatment. There is a tendency for lower vulvar cancer recurrence risk for patients over 70 years of age and patients who are receiving radiotherapy as an only treatment without surgery, but tendency for higher risk of recurrence in patients with multifocal vulvar cancer.

Keywords: Vulva - cancer - recurrence - midline involvement

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Introduction

It is estimated by American Cancer Society that 4,490 women will be diagnosed with and 950 women will die of cancer of the vulva in 2012 (Howlader et al., 2012). The median age at diagnosis for cancer of the vulva is 68 years of age and median age at death for cancer of the vulva is 79 years of age (Howlader et al., 2012). Treatment for early stage vulvar cancer consists of radical excision of the tumor with ipsilateral or bilateral inguinofemoral lymphadenectomy. Most of vulvar cancer recurrences occur in inguinal region and very rarely in the primary site of tumor excision (Magrina et al., 1979; Kelley et al., 1992; Sidor et al., 2006; Hampl et al., 2009). Several studies have described inguinal lymph node recurrences in up to 2.4% of cases (Hacker et al., 1983; Bell et al., 2000; Rodolakis et al., 2000; Ate van der Zee et al., 2008). Groin lymph-node metastases have been discovered as a most significant prognostic factors for vulvar cancer recurrence with a 5-year survival of 70-93% in patients with negative inguinofemoral lymph-nodes compared to 25-41% in patients with lymph-node metastases (Gadducci

et al., 2006).

Objective of this observational study was to identify risk factors for vulvar cancer recurrence.

Materials and Methods

In the study 107 patients with primary vulvar cancer were analyzed. Surgical treatment consisted of radical excision of the primary tumor in combination with unilateral or bilateral superficial and deep inguinofemoral lymphadenectomy through separate incisions. A unilateral tumor was defined as a lesion that does not cross the midline, with the medial margin of the tumor more than 1 cm from the midline structures. The primary tumor was excised with a margin of at least 1 cm of normal skin. Unilateral excision was performed for tumors less than 2 cm in the diameter and with a deeper invasion less than 1mm, unless involvement of labia minora and positive ipsilateral lymphnodes were detected. Patients with deeper tumor invasion >1 mm or wider than 2 cm and/or groin lymphnode metastases were referred for adjuvant radiotherapy. Patients with large primary vulvar

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Table 1. Patient Characteristics

Mean age, years (range)		72.5 (37-96)
Tumor locularity, % (n)	Unilocular	91.6 % (98)
	Multilocular	8.4 % (9)
Involvement of midline, % (n)	Involved	50.5 % (54)
	Not involved	49.5 % (53)
Metastatic lymphnodes, % (n)	Ipsilateral	29.0 % (31)
	Bilateral	23.3 % (25)
	Contralateral	2.8 % (3)
	No metastases	44.9 % (48)
FIGO stage, % (n)	Stage I	17.8 % (19)
	Stage II	19.6 % (21)
	Stage III	58.9 % (63)
	Stage IV	3.7 % (4)

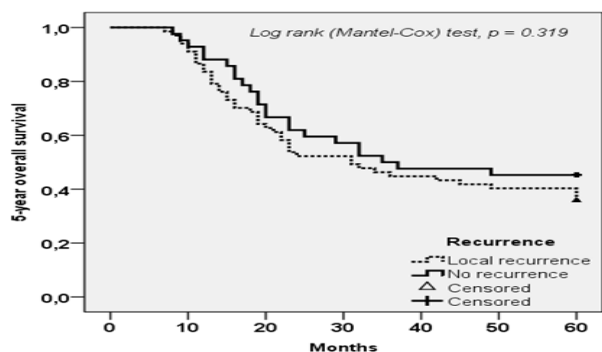


Figure 1. 5-Year Overall Survival of Patients with Vulvar Cancer Recurrence

tumors received neoadjuvant radiotherapy of 30Gy with a following surgical treatment and adjuvant radiotherapy. To evaluate risk factors for vulvar cancer recurrence age, FIGO stage, tumor morphology, unilocularity or multilocularity, involvement of midline, involvement of lymphnodes, extent of surgery, radiotherapy, recurrences, distant metastases and 5 year survival rates were assessed. All analyses were performed using SPSS software, version 20.0 (SPSS Inc, Chicago, IL). Differences in the distributions of patient characteristics were analyzed with the t test. Overall survival analysis was done using Kaplan-Meier test. Cox proportional hazard ratio was assessed to estimate risk factors for vulvar cancer recurrences. Differences associated with a $p < 0.05$ were considered significant.

Results

All patients had squamous cell carcinoma. Most of them had stage III cancer with unilocular primary lesions involving midline and having metastases in the ipsilateral, contralateral or bilateral inguinal lymphnodes (Table 1). Most of patients had only primary radiotherapy to the vulva and inguinal lymphnodes and only 34.5% of patients were eligible for surgical treatment. In 5 year follow-up period 25.2% (27) patients were alive without the disease, 15.0% (16) were alive with the disease and 59.8% (64) were dead. 60.7% (65) patients experienced local recurrences and 2.8% (3) patients had distant metastases. Median survival for patients without recurrent disease was 38.9 ± 3.2 months and 36.0 ± 2.6 months for patients with local recurrences and there was no statistically significant difference in 5-year overall survival of patients with or

Table 2. Treatment Characteristics

		% (n)
Surgical treatment only	Radical vulvectomy	33.6 % (36)
	Radical excision	0.9 % (1)
Inguinal lymphadenectomy	Bilateral	8.5 % (9)
	Unilateral	6.5 % (7)
	No lymphadenectomy	85.0 % (91)
	Radiotherapy	
Radiotherapy	Radiotherapy only	64.5 % (69)
	As adjuvant treatment	31.8 % (34)
	No radiotherapy	3.7 % (4)

Table 3. Risk Factors Predicting Vulvar Cancer Recurrence

Risk factors	HR (95% CI)	p
Age, > 70 years	0.61 (0.36-1.05)	0.07
Multilocular lesion vs. Unilocular lesion	1.91 (0.91-4.01)	0.08
Involvement of midline vs. lateral lesion	0.46 (0.28-0.76)	0.02
Lymphnode metastases vs. no metastases	0.83 (0.51-1.36)	0.46
Inguinal lymphadenectomy	0.75 (0.40-1.40)	0.36
Preoperative and postoperative radiotherapy vs. only postoperative radiotherapy	1.66 (0.98-2.81)	0.06
Late stage (FIGO III and IV) vs. early stage (FIGO I and II) cancer	0.67 (0.40-1.10)	0.12

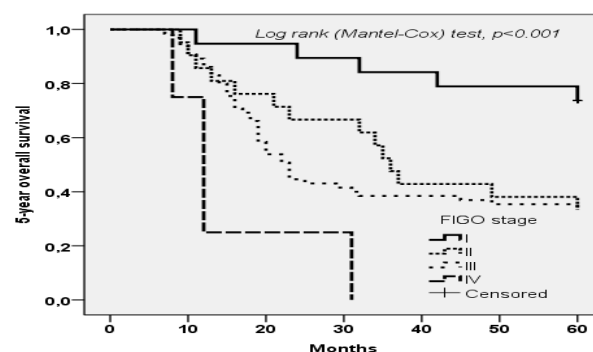


Figure 2. 5-Year Overall Survival of Patients with Vulvar Cancer by Stage

without local vulvar cancer recurrence (Figure 1).

Patients with early stage vulvar cancer had longer mean survival rates-for stage I 53.1 ± 3.4 months, 38.4 ± 4.4 months for stage II and 33.4 ± 2.6 and 15.6 ± 5.2 months for patients with stage III and stage IV vulvar cancer, respectively (Figure 2). The only significant prognostic factors predicting vulvar cancer recurrence was involvement of midline (Table 3).

Discussion

Results from the studies regarding prognostic factors for prognostic factors in vulvar cancer are controversial and can be explained by small sample size included in the retrospective studies and heterogenous treatment approaches (Iversen et al., 1980; Burger et al., 1995; Gonzalez et al., 2005). Potential risk factors for vulvar cancer recurrences include stage, tumour size, depth of invasion, tumor free margin, lymphovascular space invasion, age and nodal involvement. Although the importance of these risk factors is inconclusive and varies across the studies (Andreasson et al., 1985; Podratz et al., 1983; Heffler et al., 1999; Chan et al., 2007).

In this study, 107 patients with primary vulvar carcinoma were treated either with primary radical surgery following adjuvant radiotherapy or only radiotherapy in patients who were not appropriate for surgical treatment and were evaluated for risk factors of vulvar cancer recurrence.

In our study the only statistically significant risk factor preventing vulvar cancer recurrences was tumor involvement of midline (HR 0.46; $p=0.02$). This can be explained by more aggressive treatment of patients with midline involvement and thus better prognosis and less recurrences. Statistically there were no differences of vulvar cancer recurrences in patients with or without groin metastases ($p=0.46$), although this has been described in literature as a most significant risk factor predicting recurrent disease. In the study of Woelber et al. (2009) groin lymph node metastasis was the most important prognostic factor for disease-free and overall survival - 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.

Almost significant risk factors predicting vulvar cancer recurrence in our study was age over 70 years, tumor characteristics such as multilocular or unilocular and combined treatment of neoadjuvant radiotherapy following surgical treatment and adjuvant radiotherapy versus radiotherapy alone. There was a tendency for fewer vulvar cancer recurrences in patients over 70 years of age (HR 0.61; $p=0.07$). However, in the study of Woolderink et al. vulvar cancer recurrences more often were found in elderly patients (Woolderink et al., 2006).

Almost twice higher risk for vulvar cancer recurrence was observed in patients having multifocal disease in contrast to patient with unilocular lesion, although this factor didn't reach statistical significance (HR 1.91, $p=0.08$). This finding can be explained by tumor lesions that were left undiagnosed and thus led to tumor recurrence.

The last risk factor found to be very close to reach statistical significance was neoadjuvant radiotherapy following surgery and adjuvant radiotherapy versus radiotherapy as an only treatment option (HR 1.66; $p=0.06$). Such finding can be explained by larger tumors and more widespread dissemination in patients receiving pre- and postoperative radiotherapy. Although patients who are receiving radiotherapy as an only treatment are not appropriate for surgical treatment because of tumor spread, part of them are referred for radiotherapy because of co-morbidities and risk of wound dehiscence and not only because of wide tumor dissemination.

In our study we didn't evaluate a number of involved groin lymphnodes and neither involvement of pelvic lymphnodes, but there are some studies not showing any association between the number of metastatic lymphnodes and the risk of recurrence, while in other analyses involvement of two or more nodes, extracapsular spread and large size of the metastases were predictive of vulvar cancer recurrence (Orioni et al., 1992; Paladini et al., 1994; Van et al., 1995; Lataifeh et al., 2004).

In the literature as a risk factors predicting vulvar

cancer recurrence have been described also intracapsular lymph-node metastasis, lymphangio invasion and large primary tumours (Burger et al., 1995; Woelber et al., 2009; Oonk et al., 2010).

To get clear conclusions of vulvar cancer prognostic factors, large multicentric, prospective trial with uniform treatment approach is needed. In conclusions, patients having midline involvement of vulvar cancer has lower recurrence risk, probably because of receiving more aggressive treatment. There is a tendency for lower vulvar cancer recurrence risk for patients over 70 years of age and patients who are receiving radiotherapy as an only treatment without surgery, but tendency for higher risk of recurrence in patients with multifocal vulvar cancer.

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