

Prognostic value of lymph node status and number of removed nodes in patients with squamous cell carcinoma of the vulva treated with modified radical vulvectomy and inguinal-femoral lymphadenectomy

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Summary

Purpose of investigation: To assess the outcome of patients with squamous cell vulvar carcinoma treated with deep partial or total vulvectomy and inguinal-femoral lymphadenectomy. **Materials and Methods:** The authors assessed 87 patients who underwent primary surgery. **Results:** Tumor recurred in 34 patients, and the first relapse was local in 19, inguinal in ten, and distant in five. Five-year disease-free survival was 56.7% and was related to Stage ($p < 0.0001$), grade ($p = 0.023$), and node status ($p < 0.0001$). Groin failure occurred in 4.9% of node-negative patients compared with 29.6% of node-positive patients ($p = 0.0096$). Distant recurrences only developed in women with positive nodes. Among the 47 patients who underwent bilateral lymphadenectomy and who had negative nodes, groin recurrence occurred in 12% of those who had ≤ 15 nodes removed and 0% of those who had > 15 nodes removed. **Conclusions:** Stage and node status were the most important prognostic variables. There was a trend favoring a better groin control in patients with node-negative disease who underwent extensive lymphadenectomy.

Key words: Vulvar carcinoma; Prognosis; Recurrence; Survival; Inguinal-femoral lymphadenectomy.

Introduction

Radical vulvectomy with bilateral inguinal-femoral lymphadenectomy by an en-bloc excision has been long-considered as the standard surgical therapy for squamous cell carcinoma of the vulva [1-4]. Five-year overall survival (OS) ranged from 70% – 93% for patients with negative nodes to 25% – 41% for those with positive nodes, and morbidity was high, with frequent extensive wound breakdown, sexual dysfunction, lymphocele, and leg edema. To decrease surgical-related complications, the current approach is aimed to reduce and to tailor the extension of vulvar resection and to perform node dissection with separated inguinal incisions [4-8]. Furthermore, recent data suggest that sentinel lymph node mapping is a safe procedure in selected early-stage cases [9]. Node status is the strongest prognostic factor, and the incidence of positive groin nodes is mainly related to tumor size, depth of stromal invasion, tumor grade, and lymph vascular space involvement [1, 2, 4, 10-14]. Among the lymph node-related variables, the number of positive nodes, the presence or absence of extra-capsular spread, and the size of nodal metastasis are independent predictors in several papers [1, 12-19]. On the other hand, limited data are currently available in the literature regarding the prognostic relevance of the extension of inguinal-femoral lymphadenectomy in patients with histologically proven negative nodes [20-22]. The aim of this retrospective study was to assess the clinical outcome of patients with squa-

mous cell carcinoma of the vulva treated with deep partial or total vulvectomy and inguinal-femoral lymphadenectomy with separate incision technique and the prognostic value of the number of removed nodes in patients with node-negative disease.

Materials and Methods

This retrospective study was conducted on 87 patients with squamous cell carcinoma of the vulva who underwent primary deep partial or total vulvectomy and inguinal-femoral lymphadenectomy at the Departments of Gynecology and Obstetrics of the University of Pisa and Mauriziano Hospital of the University of Turin between August 1995 and July 2010. Patients who had surgery without lymphadenectomy because of Stage IA1 disease or poor performance status, as well as those who received primary chemo-radiation followed by individualized surgery for locally-advanced disease, were not included in the present analysis. Surgical treatment of the vulva was classified according to the glossary of terminology proposed by Micheletti *et al.* [23]. The surgical excision encompassed the lesion with a free margin of at least a one cm of clinically normal skin, and removed a portion of the vulva in all its thickness from the surface to the urogenital diaphragm. Deep partial vulvectomy indicated that the vulvar excision was limited to a portion of the vulva (anterior vulvectomy, posterior vulvectomy, hemivulvectomy), whereas deep total vulvectomy denoted the removal of the entire vulva. Deep partial vulvectomy was usually performed in patients with T1 disease when the lesion was unifocal and the remainder of the vulva was normal. Deep total vulvectomy was the standard treatment for patients with T1 tumor and with multifocal disease, widespread intraepithelial vulvar neoplasia, or lichen sclerosis, as well as for those with more advanced tumor. Unilateral or bilateral inguinal-femoral

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lymphadenectomy were always performed with surgical incisions separated from vulvar incision. Lymph node resection was usually unilateral in patients with well-lateralized T1 lesion, if ipsilateral groin was free of disease, otherwise bilateral lymphadenectomy was used. The tumor Stage of each case was determined according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO) 1988 [13]. Postoperative management was individually established on the basis of histological findings on surgical specimens, patient age and general conditions, after an exhaustive discussion directly with the patient. Patients with histologically proven positive nodes usually underwent adjuvant inguinal-pelvic radiotherapy. Irradiation field encompassed both groins, obturator, external and internal iliac areas, and sometimes the primary tumor bed, and patients received a total dose of 45 – 50 Gy in five – 6.5 weeks. Personalized adjuvant radiotherapy in the vulvar area was sometimes only used in patients with negative nodes but with close surgical margins. The median follow-up of the survivors was 61.4 months.

Statistical methods

The time from surgery to recurrence was defined as disease-free survival (DFS), and the time from surgery to death or last observation was the OS. Stage, grade, size, node status, and number and laterality of positive nodes were related to DFS and OS. The number of removed nodes in patients who underwent bilateral lymphadenectomy and who had histologically negative nodes was related to groin failure rate.

The cumulative probability of DFS and OS was estimated by the product-limit method. The log-rank test was used to compare the homogeneity of DFS and OS functions across strata defined by categories of prognostic variables.

Results

The median age of women was 72 years (range 32 to 87). The surgical treatment of the vulva consisted of deep partial vulvectomy in 23 (26.4%) patients and deep total vulvectomy in 64 (73.6%) patients. Inguinal-femoral lymphadenectomy was bilateral in 65 patients (74.7%) and unilateral in 22 (25.3%) patients. As far as plastic reconstructive procedures are concerned, local fasciocutaneous skin-flaps, and regional myocutaneous skin-flaps were used in 26 (29.9%) and four (4.6%) cases, respectively. FIGO Stage was I in 35 women (40.2%), II in 24 (27.6%), III in 20 (23.0%), and IV in eight (9.2%). Tumor grade was well-differentiated in 25 (28.7%), moderately-differentiated in 43 (49.4%), and poorly-differentiated in 19 (21.8%). Tumor size was ≤ 2 cm in 34 (39.1%), $> 2 - 3$ cm in 26 (29.9%), $> 3 - 4$ cm in 12 (13.8%), and > 4 cm in 15 (17.2%). Histologically assessed groin nodes were positive in 26 (29.9%) and negative in 61 (70.1%) patients, respectively. Among the 26 patients with metastatic nodes, ten (38.5%) had one positive node and 16 (61.5%) had two or more positive nodes. Metastatic nodes were unilateral in 18 (69.2%) and bilateral in eight (30.8%) women, respectively.

Postoperative complications were as follows: wound breakdown in 22 (25.3%) patients, moderate to severe groin lymphocele in 14 (16.1%), moderate to severe lymphoedema in 13 (14.9%), deep venous thrombosis in two (2.3%), cellulitis in one (1.1%), and urinary incontinence in one (1.1%).

Nineteen patients (21.8%) underwent adjuvant inguinal-pelvic irradiation, and two patients (2.3%) received adjuvant irradiation in the vulvar area only. Cisplatin-based concurrent chemotherapy was added to radiotherapy in three cases.

Thirty-four (39.1%) patients developed recurrent disease. The first relapse was local in 19 (55.9%) patients, inguinal in ten (29.4%) (associated with local recurrence in one case), and distant in five (14.7%) (associated with groin recurrence in one case). Median time to recurrence was 35 months (range 5 to 134) for local failure, six months (range 3 to 68) for groin failure, and seven months (range 1 to 9) for distant failure.

Table 1 shows the recurrence rate by prognostic variables. It is noteworthy that groin failure occurred in three out of 61 (4.9%) patients with negative nodes compared with seven out of 26 (26.9%) with positive nodes ($p = 0.0096$, two-tailed Fisher's exact test). Distant recurrences developed in none of the former and five (19.2%) of the latter ($p = 0.0018$), and in particular in one out of ten (10%) patients with one positive node and in four out of 16 (25.0%) patients with two or more positive nodes.

The median number of removed nodes in 47 patients who underwent bilateral inguinal-femoral lymphadenectomy and who had histologically-proven negative nodes was 15. Groin recurrence occurred in three out of the 25 (12%) patients who had ≤ 15 removed nodes compared to none of the 22 (0%) patients who had > 15 nodes removed ($p = 0.2368$).

DFS was significantly related to Stage ($p < 0.0001$), grade ($p = 0.023$), node status ($p < 0.0001$), and laterality of positive nodes ($p = 0.034$) (Table 2).

Treatment at recurrence was as follows: as far as the 19 women with local failure are concerned, 15 underwent surgery and four underwent radiotherapy. Of the former, seven are alive with no evidence of disease after a median follow-up of 39 months from recurrence, seven died of disease after a median time of 12 months, and one died of intercurrent disease with no evidence of tumor after 47 months. Three of the four patients with local recurrence treated with radiotherapy died of disease after eight, ten, and 12 months, respectively, and one was lost to follow-up after completion of radiotherapy. Regarding the ten women with groin failure, four patients underwent surgery (followed by radiotherapy in one case), one patient received radiotherapy, and five patients had no further treatment. Of the four surgically-treated women, one is alive with no evidence of disease after 19 months, two died of disease after two and seven months, and one died of intercurrent disease with no evidence of tumor after four months. The other six patients with groin failure died of disease after a median time of two months. Of the five women with distant failure, three patients received chemotherapy (cisplatin plus paclitaxel in two cases and single-agent paclitaxel in one case) and died of disease after four, five, and six months, respectively, and two patients underwent no further treatment and died after three and four months, respectively. OS was related to Stage ($p < 0.0001$) and node status ($p < 0.0001$) (Table 3).

Table 1. — Recurrence rates by prognostic variables.

Variable	Patients		Recurrences		
	n.	Local (n.)	Groin (n.)	Distant (n.)	Overall (n. %)
FIGO Stage					
I-II	59	14	3	0	17 (28.8%)
III-IV	28	5	7	5	17 (60.7%)
Tumor grade					
Well-differentiated	25	5	0	1	6 (24.0%)
Moderately/poorly-differentiated	62	14	10	4	28 (45.2%)
Tumor size					
≤ 4 cm	72	16	6	4	26 (36.1%)
> 4 cm	15	3	4	1	8 (53.3%)
Lymph node status					
Positive	26	4	7	5	16 (61.5%)
Negative	61	15	3	0	18 (29.5%)
Numbers of positive nodes					
1	10	2	2	1	5 (50.0%)
≥ 2	16	2	5	4	11 (68.8%)
Laterality of positive nodes					
Unilateral	18	3	3	3	9 (50.0%)
Bilateral	8	1	4	2	7 (87.5%)

Table 2. — DFS in patients with squamous cell carcinoma of the vulva.

Variable	Patients n.	Two-year DFS	Five-year DFS	p value
Entire series	87	75.4%	56.7%	–
FIGO Stage				
I-II	59	90.5%	71.7%	< 0.0001
III-IV	28	42.1%	20.1%	–
Tumor grade				
Well-differentiated	25	86.0%	75.5%	0.023
Moderately/poorly-differentiated	62	66.5%	48.6%	–
Tumor size				
≤ 4 cm	72	78.3%	59.8%	0.205
> 4 cm	15	63.7%	42.5%	–
Lymph node status				
Negative	61	90.9%	68.9%	< 0.0001
Positive	26	35.0%	25.5%	–
Number of positive nodes				
1	10	46.3%	28.1%	0.118
≥ 2	16	27.5%	27.5%	–
Laterality of positive nodes				
Unilateral	18	44.7%	36.5%	0.034
Bilateral	8	11.0%	0%	–

Discussion

Stage [1, 11, 13, 16, 24] and node status [1, 2, 4, 10-14] are the most important prognostic factors for squamous cell carcinoma of the vulva. The number and characteristics of nodal metastases (i.e. size and extra-capsular spread) are taken into consideration in the new 2009 FIGO staging system which provides a better reflection of prognosis than the former 1988 staging system [25]. On the other hand, the prognostic relevance of tumor grade and size are uncertain. Grade had no prognostic value in several series [12, 16, 18], whereas it correlated with the clinical outcome in the study of Podratz *et al.* [1] and in

Table 3. — OS in patients with squamous cell carcinoma of the vulva.

Variable	Patients n.	Two-year DFS	Five-year DFS	p value
Entire series	87	81.0%	70.7%	–
FIGO Stage				
I-II	59	98.1%	89.3%	< 0.0001
III-IV	28	42.1%	22.5%	–
Tumor grade				
Well-differentiated	25	88.0%	78.2%	0.648
Moderately/poorly-differentiated	62	77.9%	67.5%	–
Tumor size				
≤ 4 cm	72	84.6%	74.7%	0.201
> 4 cm	15	65.7%	54.8%	–
Lymph node status				
Negative	61	98.0%	84.8%	< 0.0001
Positive	26	38.0%	38.0%	–
Number of positive nodes				
1	10	50.0%	50.0%	0.092
≥ 2	16	28.7%	28.7%	–
Laterality of positive nodes				
Unilateral	18	47.5%	47.5%	0.110
Bilateral	8	22.2%	0%	–

that of Lavie *et al.* [24]. Tumor size has been reported to be a prognostic variable by some papers [1, 11, 16]. Conversely, Raspagliesi *et al.* [18] found that tumor diameter (< 2 cm vs 2 – 4 cm vs > 4 cm) was not related to OS, both in the whole series and in the subset of patients with nodal metastases. In the present study, tumor recurred in more than one-third of the women, and the first relapse was local in 55.9% of the cases, inguinal in 29.4%, and distant in 14.7%. DFS was related to Stage ($p < 0.0001$), grade ($p = 0.023$), node status ($p < 0.0001$), but not with tumor size. Groin failure occurred in 4.9% of patients with negative nodes compared with 26.9% of those with positive nodes ($p = 0.0096$). Distant recurrences developed only in patients with positive nodes, and in particular in 10% of those with one positive node and 25% of those with two or more positive nodes.

The prognostic relevance of the number of removed groin nodes is still debated [20-22]. A retrospective study, including 85 patients who underwent radical vulvectomy and bilateral inguinal-femoral lymphadenectomy, revealed that a total number of removed nodes < 10 was the only independent predictor of shorter time to first progression (hazard ratio [HR] = 12.88, 95% confidence interval [CI] = 1.47 – 112.89, $p = 0.021$) and shorter disease-specific survival (HR = 11.41, 95% CI = 2.21 – 58.86, $p = 0.004$) [20]. The Gynecologic Oncology Group [GOG] conducted a trial for patients with early-stage and small size squamous cell vulvar carcinoma who underwent superficial inguinal lymphadenectomy and who had clinically and pathologically negative nodes, with the aim to assess whether a low count of removed nodes correlated with first recurrence in the groin [21]. Of the 113 patients eligible, nine failed first in the groin. The median number of negative nodes removed per groin was seven, with no significant difference between the patients who had a first recurrence in the groin and those who did

not. The analysis of 164 patients with clinical Stage III disease and histologically-proven negative groin nodes identified from the Surveillance, Epidemiology and End Results (SEER) program showed that five-year disease-specific survival was 85% for those who had > ten removed nodes vs 60% ($p = 0.02$) for those who had \leq ten removed nodes [22]. In the present series, among the 47 women who underwent bilateral inguinal-femoral lymphadenectomy and who had histologically proven negative nodes, groin recurrence occurred in 12% of the patients who had ≤ 15 removed nodes compared to none of those with > 15 removed nodes.

Conclusions

Stage and node status are the most important prognostic variables for squamous cell carcinoma of the vulva. Although the difference was not statistically significant because of the low number of cases, the authors found a trend favoring a better groin control in patients with node-negative disease who underwent a more extensive lymphadenectomy. An adequate management of the groin is critical for the clinical outcome, since the prognosis of patients with inguinal failure is unfavorable [11, 21]. In the present series, only one of the ten women with groin recurrence was still alive with no evidence of disease after 19 months from salvage surgery. A thorough inguinal-femoral lymph node dissection should be the goal in the primary treatment of this malignancy, and the benefit from this surgical procedure could be due to the removal of undetected micrometastases [22]. The use of sentinel node mapping should be reserved to selected patients with early-stage disease.

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