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An analysis of reported independent prognostic factors for survival in squamous cell carcinoma of the vulva: Is tumor size significance being underrated?

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HIGHLIGHTS

- A new high-risk group was identified based on independent prognostic factors of current interest and relevance.
- In-depth knowledge of the significance of tumor size and its relationship with other variables is necessary to individualize treatments.

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ABSTRACT

Objective. To assess independent prognostic factors described in the literature. Thus, to identify different risk groups.

Methods. Review of the records with a diagnosis of primary vulvar squamous cell carcinoma (January/1992–January/2012). Inclusion criteria: depth of stromal invasion (DSI) >1 mm, pathological tumor size >2 cm, and pathological tumor-free margin ≥8 mm. Patients who underwent neoadjuvant therapy due to locoregionally advanced vulvar cancer were excluded. All the patients underwent radical, both local and regional, surgery. Adjuvant radiation therapy was administered to all patients with positive nodes. Features of lymph nodes, tumor size, age, grade, lymphovascular space invasion (LVSI), DSI, type of radical surgery, pathological margin distance and stage were evaluated by univariate and multivariate analysis.

Results. 194 patients were included. Median age: 67 years. Median follow-up: 62 months. 5-year OS and DFS: 65.5% and 58.2%. Positive lymph nodes were found in 91 (46.9%) patients. After a multivariate analysis, the number of positive lymph nodes, extra-nodal growth, pathologic tumor size and DSI proved to be independent prognostic factors. A high risk group for failure to survive (5y-OS 24%) was identified: tumor size ≥6–7.9 cm and DSI >4 mm or ≥8 cm irrespective of DSI; and extra-nodal growth or ≥2 positive lymph nodes irrespective of tumor size and DSI.

Conclusions. A new high-risk group was identified based on different cutoff values for tumor size, extra-nodal growth and number of positive lymph nodes. This could be very important in the tailored treatment of a specific group of patients with bulky primary tumors and a poorer prognosis.

Introduction

Vulvar cancer is still a rare disease despite its increasing incidence. Information regarding prognostic factors for both disease-free and overall survival (DFS, OS) is limited and inconclusive. These inconsistent findings are most likely the result of heterogeneous treatment strategies in the population under study; they vary remarkably among different centers, many of which treat a limited number of patients per year.

Undoubtedly, the most important prognostic factor in squamous cell carcinoma of the vulva is the presence of metastatic regional lymph nodes [1–10].

Not only the number of nodes involved has proved to be important but also the morphology of the node metastasis (diameter of the metastasis, intra — or extranodal tumor growth) has proved to have a significant prognostic value, so much so that it was included in the latest modification of the staging system of the *Fédération Internationale de Gynécologie et d'Obstétrique* (FIGO), made in 2009 [11–15].

Another important prognostic factor of survival and recurrence is tumor size [5,7,16–19]. However, not many reviews or diagnostic-therapeutic guidelines have yet focused on this concept. Furthermore, FIGO current staging system has grouped prior 1988 stages I and II

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into a single stage I, minimizing the effect of size on prognosis even more when the lesion is confined to the vulva or perineum. This could be especially important in the case of large tumors with negative nodes.

Based on long term observation, the authors have found that large tumors seem to have a surprisingly more torpid evolution, even in the presence of negative nodes, and when they may clearly be resectable (which leads to good surgical radicality). This concept encouraged the authors to conduct this analysis.

The objective of this study is first to assess those independent prognostic factors described in the literature delving into the significance of tumor size as such; and second, to identify different risk groups on the basis of the results obtained.

Materials and methods

This retrospective study includes a single-institution series. We thoroughly reviewed the clinical and pathology records of 387 patients with a diagnosis of primary vulvar squamous cell carcinoma seen at the Oncology Hospital of Buenos Aires *Marie Curie* between January/1992 and January/2012.

Inclusion criteria:

- Depth of stromal invasion >1 mm, measured from the epithelial–stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion [14,20].
- Pathological tumor size >2 cm, defined as the largest tumor diameter measured in the fresh surgical specimen state.
- Primary treatment given: radical surgery (wide local excision, radical vulvectomy or pelvic exenteration) plus complete bilateral inguinofemoral lymphadenectomy.
- Pathological tumor-free margin of at least 8 mm (after formalin fixation).

Exclusion criteria:

- Patients who underwent neoadjuvant therapy due to locoregionally advanced vulvar cancer, defined as vulvar disease without distant metastasis beyond curative surgical resection with standard radical vulvectomy [21].
- Patients with an indication for adjuvant therapy who have not completed such treatment according to the technique described below.
- Distant metastasis (stage IVB).
- Concomitant malignancies at the time of diagnosis.

All the patients included in this study underwent radical, both local and regional, surgery. Radical surgery was performed by means of the triple incision technique in all the cases. Whether *Radical vulvectomy* or w*ide local excision* (defined as a tailored vulvectomy according to the primary site of the neoplasia) was performed, the dissection was carried down to the fascia lata, and at least a 2 cm-macroscopic margin around the primary tumor was obtained. Also in both cases, resection of the distal urethra, vagina and/or anus (if necessary in order to achieve adequate radicality) was included within the procedure definition. As mentioned in the inclusion criteria, a subsequent confirmation of at least an 8 mm-tumor-free margin by histological examination was required. Bilateral inguino-femoral lymphadenectomy was performed according to the recommendations made by de Hullu et al. [22]. It was defined as the removal of fatty tissue within the femoral triangle. The anatomical margins of dissection were the inguinal ligament superiorly, the adductor longus muscle medially, the sartorius muscle inferolaterally and the pectineus muscle forming the floor of the femoral triangle. The procedure systematically consisted in the removal of nodal tissue between the superficial fascia and the fascia lata over the femoral triangle. The dissection was carried 2 cm above the inguinal ligament to include all the inguinal nodes. The saphenous vein was tied off and the fascia lata was split longitudinally. Femoral lymph nodes situated medial to the femoral vein within the opening of the fossa ovalis were then removed. The standard protocol for handling the lymph nodes specimens consisted in a ribbon of hematoxylin–eosin-stained sections taken at 3–4 different levels. Lymph node metastases were defined as clusters of tumor cells of any size detected on hematoxylin–eosin slides. All the patients were operated on by the same team of surgeons, that is, oncology gynecologists from the University of Buenos Aires, accredited by the Argentine Association of Oncological Gynecology.

A very small group of carefully selected patients who underwent ultraradical primary surgery instead of neoadjuvant therapy was included in the study. Infralevator pelvic exenteration with radical vulvectomy and complete bilateral inguinofemoral lymphadenectomy was performed following the surgical criteria described above.

Adjuvant treatment was administered to all patients with positive nodes, even in single-node-positive-cases. No other patients included in this study underwent adjuvant treatment. External beam radiation therapy was delivered to the inguinofemoral and lower pelvic nodes through anterior–posterior/posterior–anterior fields to a cumulative dose of 50.4 Gy over a period of 5 weeks. Since 2002, weekly cisplatin-based chemosensitization (50 mg/m^2) was added to radiotherapy.

Regarding nodal spread, the following pathological parameters have been taken into account in the analysis: number of positive lymph nodes, laterality and intra- or extranodal growth. Pathological tumor size was classified into lesions between >2–3.99 cm, 4–5.99 cm, 6–7.99 cm and ≥8 cm. Stages were defined according to the FIGO last surgical staging (2009) [14]. Age, differentiation grade, lymphovascular space invasion (LVSI), depth of stromal invasion (DSI), type of radical surgery, pathological margin distance and FIGO stage were considered for the analysis. All slides were re-reviewed specifically for this study by at least one trained gynecological pathologist in order to confirm histological variables.

Recurrence patterns were considered according to the definitions made by *Rouzier* et al.: local relapse (defined as any tumor recurrence involving the skin and the subcutaneous tissues) included *primary tumor site recurrence* (up to and including 2 cm from the vulvectomy scar), *recurrence at a distance from the primary tumor site* (more than 2 cm from the vulvectomy scar), and *skin bridge recurrence* (between the groin and vulvar incision). Nodal relapses were considered as regional not local relapses [23]. With respect to the presence of competing risks when assessing sites of recurrences, the authors have chosen to treat distant metastasis as censored observations.

OS and DFS, defined as time from diagnosis to death and progression or date of last follow-up respectively, were estimated by the Kaplan–Meier method. The relationship between each of the variables and survival was assessed by the log-rank test. Multivariate analysis was performed using the Cox proportional hazards regression model. A p-value <0.05 was considered to be statistically significant. Statistical analysis was performed using SPSS version 20.

Results

The study included 194 patients. Clinicopathological parameters considered for this study are shown in Table 1. In this patient cohort, the median age was 67 years (range: 36–87) and the median follow-up was 62 months (range: 3–160). 5-year OS and DFS were 65.5% and 58.2% respectively (S2 and S3). Median OS was 68 months (95% CI 65–70) and median DFS was 63 months (95% CI 59–66). 5 patients (4 stage IVA and 1 stage IIIC with anal canal involvement) underwent pelvic exenteration. The median number of resected lymph nodes was 11 (range: 5–16). The median pathological size was 5.2 cm (range: 2.1–12). Positive lymph nodes were found in 91 (46.9%) patients; 12 of them (13.2%) had bilateral positive lymph nodes, and extranodal growth was detected in 40 (44%) of them. All the 91 patients with positive nodes started and completed adjuvant treatment according to the technique described. Adjuvant radiotherapy was given to 52 of them, and 39 received adjuvant chemoradiation.

Table 1
Clinicopathological parameters.

	n	%
Age (years)		
<44	11	5.7
45–64	68	35
65–70	37	19
>70	78	40.2
Type of radical surgery		
LWE + BL	50	25.8
RV + BL	139	71.6
PE + RV + BL	5	2.6
Microscopic margin distance (mm)		
≥8–10	114	58.7
>10	80	41.3
Pathological tumor size (cm)		
>2–3.99	85	43.8
4–5.99	54	27.8
6–7.99	33	17
≥8	22	11.3
Depth of stromal invasion (mm)		
>1–4	110	56.7
>4	84	43.3
Grade		
G1	66	34
G2	96	49.5
G3	32	16.5
LVSI		
No	170	87.6
Yes	24	12.4
Number of positive lymph nodes		
0	103	53.1
1	36	18.5
2	28	14.4
3–5	18	9.3
>5	9	4.6
Laterality		
Unilateral positive lymph nodes	79	40.7
Bilateral positive lymph nodes	12	6.2
Negative lymph nodes	103	53.1
Nodal spread		
Intra-nodal growth	51	26.3
Extra-nodal growth	40	20.6
Negative lymph nodes	103	53.1
Stage (FIGO 2009)		
IB	73	37.8
II	25	12.8
IIIA	32	16.5
IIIB	20	10.3
IIIC	40	20.6
IVA	4	2

LWE: local wide excision, RV: radical vulvectomy.
LB: bilateral lymphadenectomy, PE: pelvic exenteration.

Table 2
Distribution of recurrences according to the different variables analyzed at 5 years follow-up.

	n	%	RR (%)
Type of radical surgery performed			
LWE + BL	13	17.3	26
RV + BL	59	78.7	42.4
PE + RV + BL	3	4	60
Microscopic margin distance (mm)			
≥8–10	47	62.7	41.2
>10	28	37.3	35
Stage (FIGO 2009)			
IB	15	20	20.5
II	8	10.7	32
IIIA	8	10.7	25
IIIB	11	14.7	55
IIIC	30	40	75
IVA	3	4	75
Pathological tumor size (cm)			
>2–3.99	23	30.6	27
4–5.99	17	22.7	31.5
6–7.99	18	24	54.5
≥8	17	22.7	77.3
Number of positive lymph nodes			
0	26	34.6	25.2
1	11	14.6	30.5
2	15	20	53.6
3–5	16	21.4	88.9
>5	7	9.4	77.8
Laterality			
Unilateral positive lymph nodes	43	57.3	54.4
Bilateral positive lymph nodes	6	8	50
Negative lymph nodes	26	34.7	25.2
Nodal spread			
Intra-nodal growth	18	24	36
Extra-nodal growth	31	41.3	77.5
Negative lymph nodes	26	34.7	25.2
Age (years)			
<44	5	6.7	45.4
45–64	27	36	39.7
65–70	12	16	32.4
>70	31	41.3	39.7
LVSI			
No	59	78.7	34.7
Yes	16	21.3	66.7
Depth of stromal invasion (mm)			
>1–4	31	41.3	28.2
>4	44	58.7	52.4
Grade			
G1	24	32	36.4
G2	42	56	43.7
G3	9	12	28.1

RR: recurrence rate.
LWE: local wide excision, RV: radical vulvectomy.
LB: bilateral lymphadenectomy, PE: pelvic exenteration.

Upon completion of 5 year-follow-up period, 75 out of 194 patients (38.6%) had recurrent disease and 90 (46.4%) were free from disease. Of the remaining 29 patients, 5 (2.6%) were lost to follow up, and 24 (12.4%) have not yet completed the 5-year follow up period, and were still free from disease when this paper was written. As for the recurrence rate, 49 patients exhibited at least one positive node and therefore underwent adjuvant therapy (27 radiotherapy, 22 chemoradiation). No significant relationship was found between the patients with recurrence and the type of surgery performed ($p = 0.21$) or the size of the pathological margin ($p = 0.85$). The locations of the recurrent disease were as follows: tumor site recurrence in 54 (72%), primary site recurrence + groin recurrence in 8 (10.7%), recurrence at a distance from the primary tumor site in 5 (6.7%), isolated groin recurrence in 4 (5.3%) and skin bridge metastasis in 2 (2.6%). Two patients (2.6%) had distant metastasis. One of them had pelvic nodes metastasis + primary tumor site recurrence. The other patient had isolated distant metastasis (lung). The distribution of recurrences according to the different variables analyzed is listed in Table 2.

In our univariate analysis, number of positive lymph nodes, extra-nodal growth, pathologic tumor size, stage, LVSI and DSI were found to be statically significant for both OS and DFS (Table 3). No differences were observed between patients with negative nodes or with only one positive node ($p = 0.084$). On the contrary, the p value was 0.003 when patients with 2 positive nodes were considered. Bilateral involvement did not reach statistical significance ($p = 0.365$). The analysis revealed that the larger the tumor the worse the prognosis ($p < 0.001$). 5-year OS for pathological tumor lesions >2–3.99 cm, 4–5.99 cm, 6–7.99 and ≥8 cm were 78.7%, 77.5%, 36% and 12.4% respectively (S4). Similar percentages were obtained for DFS (72.2%, 64.7, 33.9 and 11.4% respectively) (S5). Comparing the different sizes, a significant difference was seen when comparing 4–5.99 to 6–7.99 cm ($p = 0.009$) and 6–

Table 3
Univariate analysis of clinicopathological variables (log-rank test).

	Overall survival		Disease-free survival	
	5-year survival (%)	p-Value	5-year survival (%)	p-Value
Age (years)		0.904		0.992
25–44	30.3		30.3	
45–64	62.4	0.852	57.8	0.815
65–70	69.6	0.323	64	0.663
>70	66.4	0.451	55.8	0.731
Type of radical surgery		0.387		0.468
LWE + BL	79.6		73	
RV + BL	59.7	0.92	53.8	0.467
PE + RV + BL	50	0.487	0	0.496
Microscopic margin distance (mm)		0.476		0.658
≥8–10	62.8		56.2	
>10	68.8	0.476	60.4	0.658
Stage		**<0.001**		**<0.001**
IB	90.3		79.2	
II	83.6	0.049	65.2	0.054
IIIA	68.8	0.828	73.2	0.202
IIIB	34.2	0.22	21.6	0.01
IIIC	0	<0.001	10.3	<0.001
IVA	33.3	0.2	0	0.018
Pathological tumor size (cm)		**<0.001**		**<0.001**
>2–3.99	78.7		72.2	
4–5.99	77.5	0.053	64.7	0.059
6–7.99	36	0.009	33.9	0.007
≥8	12.4	0.012	11.4	0.013
Depth of stromal invasion (mm)		**<0.001**		**0.001**
>1–4	79.6		69.2	
>4	45.2	<0.001	42.6	0.001
LVSI		**0.022**		**0.001**
No	70.1		62.2	
Yes	24.5	0.022	20.2	0.001
Number of positive lymph nodes		**<0.001**		**<0.001**
0	85.1		72.5	
1	68	0.084	69.8	0.918
2	33.9	0.003	25.5	<0.001
3.5	0	0.058	0	0.053
>5	0	0.567	0	0.843
Laterality of positive lymph nodes		0.365		0.850
Unilateral	40.6		40.9	
Bilateral	54	0.365	48.6	0.850
Nodal spread		**<0.001**		**<0.001**
Intra-nodal	63.6		61.5	
Extra-nodal	0	<0.001	10.3	<0.001
Grade		0.654		0.543
G1	63.7		55.4	
G2	63.8	0.371	57.1	0.470
G3	74.1	0.774	66.8	0.468

Bold data indicates statistically significant result.

Table 4
Multivariate analysis of pathological variables regarding OS and DFS (Cox proportional hazard model).

		Overall survival				Disease-free survival			
		p-Value	HR	95% CI		p-Value	HR	95% CI	
Pathological tumor size (cm)	>2–3.99	***<0.001***				***<0.001***			
	4–5.99	*0.067*	1.586	0.968	2.599	*0.197*	1.334	0.861	2.065
	6–7.99	***<0.001***	**2.785**	**1.261**	**4.556**	***<0.001***	**2.493**	**1.551**	**4.008**
	≥8	***<0.001***	**7.518**	**2.331**	**14.415**	***<0.001***	**6.831**	**3.611**	**12.924**
LVSI	No	*0.69*				***0.007***			
	Yes	*0.69*	1.633	0.963	2.77	***0.007***	**2.023**	**1.209**	**3.385**
Depth of stromal invasion (mm)	>1–4	***0.015***				*0.13*			
	>4	***0.015***	**1.570**	**1.094**	**2.255**	*0.13*	1.327	0.920	1.915
Number of positive lymph nodes	0	***<0.001***				***<0.001***			
	1	*0.071*	1.887	0.948	3.758	*0.515*	0.741	0.3	1.83
	2	***<0.001***	**5.875**	**2.673**	**12.911**	***<0.001***	**3.985**	**1.852**	**8.575**
	3–5	***<0.001***	**8.896**	**3.272**	**24.183**	***<0.001***	**8.273**	**3.412**	**20.062**
	>5	***<0.001***	**11.839**	**2.715**	**51.619**	***<0.001***	**10.135**	**3.535**	**29.052**
Nodal spread	Intra-nodal growth	***<0.001***				***<0.001***			
	Extra-nodal growth	***<0.001***	**5.212**	**2.425**	**11.202**	***<0.001***	**6.401**	**2.690**	**15.23**

HR: hazard rate.
Bold and italic data indicates statistically significant result.

Table 5
Frequency and overall survival between tumor size subgroups and the other significant prognostic factors (n, %, 5y-OS).

		>2-3.99 cm (n=85)	4-5.99 cm (n=54)	6-7.99 cm (n=33)	≥8 cm (n=22)
Depth of stromal invasion (mm)	>1-4	68 (80) 79%	27 (50) 96%	11 (33) 54%	4 (18) 0%
	>4	17 (20) 65%	27 (50) 47%	22 (67) 24%	18 (82) 0%
Number of positive lymph nodes	0	57 (67) 93%	26 (48) 88%	15 (45) 54%	5 (23) 0%
	1	15 (18) 60%	12 (22) 81%	4 (12) 75%	5 (23) 0%
	2	10 (12) 30%	7 (13) 0%	5 (15) 0%	6 (27) 0%
	35	2 (2) 0%	5 (9) 0%	7 (21) 0%	4 (18) 0%
	>5	1 (1) 0%	4 (7) 0%	2 (6) 0%	2 (9) 0%
Nodal spread	Intra-nodal growth	21 (75) 65%	17 (61) 72%	7 (39) 43%	6 (35) 0%
	Extra-nodal growth	7 (25) 0%	11 (39) 0%	11 (61) 0%	11 (65) 0%

Identification of the two risk groups, light grey for "low risk group" and dark grey for "high risk group".

7.99 cm to ≥8 cm ($p = 0.012$). No significant difference was observed when comparing >2–3.99 to 4–5.99 cm ($p = 0.053$).

After a multivariate analysis, the number of positive lymph nodes, extra-nodal growth and pathologic tumor size proved to be independent prognostic factors for both DFS and OS, while DSI was only significant for OS (Table 4). Nodal status proved to be the most powerful prognostic factor. Those with 2, 3–5 and >5 positive nodes experienced 5.8, 8.8 and 11.8 times a higher risk of death compared with patients with negative nodes, respectively, while the mere presence of extracapsular growth in lymph node metastasis increased the risk of death 5.2 times. The risk for failure to survive was more than doubled for patients with a tumor size ranging between 6 and 7.99 cm and 7.5 times higher for those with a tumor size ≥8 cm, as compared to those patients with a tumor size >2–3.99 cm. Frequency and overall survival between tumor size subgroups and the other significant prognostic factors are included in Table 5. Two risk groups were delineated based on proportional hazards regression model results (Table 6).

Discussion

Many independent prognostic factors have been thoroughly described in the literature. However, potentially relevant information is heterogeneous and sometimes contradictory. However, it has been historically accepted that nodal status is the most important independent prognostic factor for survival in vulvar cancer followed by primary tumor size, extra-nodal growth and LVSI [5–13,23].

In this study, we report a decreased survival for patients with two or more positive lymph nodes compared with those with negative or single positive lymph nodes but no difference between two or more positive lymph nodes, which is in agreement with prior studies reported in the literature [3,4,7,11,12,24,25]. Also, our results support the finding that extracapsular spread is a powerful independent prognostic factor, and should be taken into account when referring to the patient's prognosis [11–13,15]. With respect to DSI, evidence is limited to date. Other authors have described DSI as a significant prognostic factor with varied cutoff points [14,25,26]. Similarly to the results reported by Chan et al. [25], our analysis reports that the presence of DSI >4 mm increases the risk of death 1.4 time. LVSI was significant only in univariate analysis, which differs from other authors [10].

Tumors >2 cm are more likely to develop node metastasis as widely reported, which clearly leads to a worse prognosis [9]. This concept of tumor size as a predictive factor of nodal status currently seems to lose some value as all patients with stage IB or more have an indication for lymphadenectomy, and therefore, a pathologic confirmation of prognostic variables. Furthermore, the current staging system dedicates an entire subgroup (stage III) to evaluate regional nodal special features. To date, the sentinel node biopsy procedure is not recommended for tumors >4 cm [27,28]. Despite changes in the staging system (clinical to pathological), FIGO has kept this 2 cm cut off point to date even though there may be a group of patients with larger tumor lesions and a poor prognosis, sometimes even regardless of either positive or negative nodes. Our data was useful to clearly identify a high risk group for failure to survive (5y-OS 24%, n = 78) which includes those patients with a tumor size between ≥6–7.9 cm and DSI >4 mm or ≥8 cm irrespective of DSI. This high-risk group includes also extra-nodal growth or patients with ≥2 positive lymph nodes, in both cases irrespective of tumor size and DSI. These findings remind us of the paper by Homesley et al., describing a high risk group (5y-OS 29%, n = 87) including those patients with a tumor size >8 cm and two unilaterally positive nodes, ≥3 positive nodes or bilaterally positive nodes [7]. Apart from similarities and differences among publications on this topic, we find it striking that the concept of tumor size as a prognostic survival factor has not yet been contemplated further. Interestingly at analyzing separately the stage II, survival declined from 87% for tumors between 2.1 and 3.99 cm to figures around 50% for those between 4 and 7.99 cm. More than 15 papers identifying tumor size as a powerful prognostic factor have been published [2,5,7,11,13,16–19,23,24,29–31]. Moreover, tumor lesions >2 cm have proved to have a good prognosis [2,7,16,18,30].

We agree with the suggestion made by Le et al. [32] about performing an as complete as possible inguino-femoral nodal dissection. In our study the mean number of resected lymph nodes was 11 (range: 4–16). It is well known that vulvar cancer patients with positive groin nodes benefit from adjuvant radiation [33]. However, the benefit of radiation in those with metastatic involvement of a single node remains unclear [34]. It has been adopted as the standard-of-care in our department, and used for some time now, that even those patients with a single positive node must be irradiated. We are currently in the process of reviewing those standards. Based on previous reports [25,35,36], we established a microscopic margin ≥8 mm as one more inclusion criteria. Also, we decided to determine whether a statistically significant difference could be observed with greater microscopic margins since a significant percentage of our patients actually had significant margins (41.3% with microscopic margins >10 mm). When a margin >10 mm as compared to 8–10 mm was considered, no statistical significance was observed in either the risk of recurrence or death ($p = 0.659$; $p = 0.488$), for this reason we assume that a microscopic margin of at least 8 mm could be considered safe in terms of surgical radicality. However, we also believe it is important to pay attention to studies recently published by Groenen et al. and Höckel et al. who introduced the concept of vulvar tumor resection based on the ontogenetic anatomy of embryogenetic compartments [37,38].

This study identified a cut off value of ≥6 cm of diameter plus DSI >4 mm or ≥8 cm of diameter irrespective of any other factor, from which value, survival drops remarkably. This could be very important in the tailored treatment of a specific group of patients with bulky primary tumors and a poorer prognosis, most frequently but not always accompanied by positive nodes, extranodal growth or an unresectable clinical presentation.

This was a single-institution trial. It should be noted that our hospital is a leading referral center in oncology not only in Argentina but also for other neighboring countries. This fact, together with socio-cultural factors linked to the reality of developing countries and closely related to conditions involving the lower genital tract of the woman (particularly cervix and vulvar cancer) leads to a high incidence of large tumors at the time of diagnosis. We assume that this study has the limitations of a retrospective design. Moreover, given the non inclusion of tumors ≤2 cm in diameter and nodal metastasis size within the variables assessed we are not able to present even more encompassing conclusions.

As reported in the literature [39], we confirmed that most of the cases of recurrence are confined to the vulvar region. Even in these patients with initial lymph node metastasis, recurrence occurred predominantly in the vulvar region and not in the groin or as skin-bridge metastases. In order to avoid recurrence and improve OS in bulky tumors, some authors have suggested that more extensive resections may be appropriate [35]. In our analysis no relationship was found

Table 6
Risk groups.

Low risk group	Tumor size >2 and <8 cm + negative or single positive lymph node
n = 116	Tumor size >2 and <6 cm (irrespective of DSI)
5y-OS 89%	Tumor size >6 and <8 cm + DSI >1 up to 4 mm
High risk group	Tumor size ≥6 cm and <8 cm + DSI >4 mm
n = 78	Tumor size ≥8 cm
5y-OS 24%	Extra-nodal growth
	≥2 positive lymph nodes

between the type of surgical procedure performed and prognosis, as long as it respects a microscopic radicality of at least 8 mm. However, at this point we have the following concerns:

- Since with current management, these surgically managed patients have poorer survival than patients with surgically unresectable disease treated with chemoradiation [40], even if most recurrences are confined to the vulvar region, in terms of prognosis and therapeutic tailoring, are other therapeutic strategies necessary for patients with bulky primary tumors? Does neoadjuvant treatment play a role in these circumstances?
- Apart from the positive nodes, which is a clear indication for adjuvant therapy recommended at present for patients with 2 or more positive nodes as described above, there is a group of patients who is unprotected if untreated with adjuvant? More precisely, we are talking about a subgroup of patients in stages IB and II included in our high risk group, which represents 18% of this group.

Further studies are needed in order to improve our understanding of this disease and its behavior, as well as to compare the results available.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ygyno.2013.12.022.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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