



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



Alejandro M. Aragona<sup>a,\*</sup>, Nicasio A. Cuneo<sup>a</sup>, Alejandro H. Soderini<sup>a</sup>, Elsa B. Alcoba<sup>b</sup>

<sup>a</sup> Department of Gynecologic Oncology, Oncology Hospital of Buenos Aires Marie Curie, Autonomous City of Buenos Aires, Argentina

<sup>b</sup> Department of Pathology, Oncology Hospital of Buenos Aires Marie Curie, Autonomous City of Buenos Aires, Argentina

### 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.

### ARTICLE INFO

#### Article history:

Received 24 September 2013

Accepted 16 December 2013

Available online 11 January 2014

#### Keywords:

Vulvar cancer

Survival

Prognostic factors

### 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  $\geq$  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  $\geq$  6–7.9 cm and DSI >4 mm or  $\geq$  8 cm irrespective of DSI; and extra-nodal growth or  $\geq$  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.

© 2013 Elsevier Inc. All rights reserved.

### 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

\* Corresponding author at: Colon 155 3A CP1878 Quilmes, Buenos Aires, Argentina.  
E-mail address: [alearagona2@gmail.com](mailto:alearagona2@gmail.com) (A.M. Aragona).

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 inguino-femoral 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 *wide 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 inguino-femoral 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 inguino-femoral 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<sup>2</sup>) 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.

Download English Version:

<https://daneshyari.com/en/article/6182814>

Download Persian Version:

<https://daneshyari.com/article/6182814>

[Daneshyari.com](https://daneshyari.com)