



How important is the pathological margin distance in vulvar cancer?

G. Baiocchi^{a,*}, H. Mantoan^a, L. de Brot^b, L. Badiglian-Filho^a,
L.Y. Kumagai^a, C.C. Faloppa^a, A.A.B.A. da Costa^c

^aDepartment of Gynecologic Oncology, AC Camargo Cancer Center, Sao Paulo, Brazil

^bDepartment of Anatomic Pathology, AC Camargo Cancer Center, Sao Paulo, Brazil

^cDepartment of Medical Oncology, AC Camargo Cancer Center, Sao Paulo, Brazil

Accepted 27 September 2015

Available online 22 October 2015

Abstract

Purpose: The ideal pathological margin in vulvar squamous cell carcinoma (VSCC) is still debated. Our aim was to analyze the value of tumor-free pathological margin distance with regard to local recurrence in VSCC.

Methods: We analyzed a series of 205 patients who were treated for VSCC from January 1980 to November 2007. Patients were categorized into 3 groups, based on pathological free margin (PFM): <3 mm (n = 18); ≥3 and <8 mm (n = 61); and ≥8 mm (n = 126).

Results: The median age was 69 years. The median PFM was 10 mm (range: 1–65). Of 168 patients who underwent lymphadenectomy, 64 (38.1%) developed LN metastasis. After a median follow-up of 36.2 months, 78 (38%) cases recurred—47 (60.2%) experienced a local recurrence (LR). LR occurred in 16.7% of patients with a PFM of <3 mm, 24.6% with a PFM ≥3 and <8 mm, and 22.2% of those with a PFM ≥8 mm (p = 0.77). PFM did not correlate with LR when analyzed continuously (p = 0.98). The 5-year disease-free survival (DFS) for LR was 79.6%. Margin distance did not negatively impact DFS (p = 0.94); the presence of perineural invasion was the only variable that negatively influenced DFS (p = 0.009).

Conclusions: Although our results suggest no correlation between LR and pathological margin distance, the tumor-free resection margin remains significant with regard to locoregional control in vulvar cancer. A more conservative surgical approach may be considered in certain situations, such as margins near the clitoris, urethra, and anus.

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Keywords: Vulvar cancer; Margin distance; Recurrence; Prognosis

Introduction

Vulvar cancer accounts for approximately 3%–5% of all gynecological malignancies.¹ It usually affects women with a median age of 65–70 years,^{1,2} and most cases are squamous cell carcinoma.^{1,2} Surgery is the cornerstone treatment for vulvar cancer, and its prognosis is linked to inguinal lymph node (LN) metastasis.^{1–4} The current management of vulvar cancer depends on the extent of disease and includes primary tumor resection with a safety margin

and inguino-femoral LN staging.^{2,4,5} If LN metastasis is observed, the standard postoperative therapy is inguinal and pelvic radiotherapy.⁵ For patients who have unifocal disease, tumors up to 4 cm, and clinically negative groins, the sentinel node procedure should be offered. In cases with positive sentinel nodes, a complete inguino-femoral lymphadenectomy should be performed.²

Due to the low incidence of vulvar cancer, there are few evaluable randomized trials, and controversies remain regarding the best treatment approach. The ideal surgical margin is still debated—the current consensus is that final pathological margin should be at least 8 mm, which might correspond to intended surgical margins of 1–2 cm.² This concept may drive to mutilation or neoadjuvant radiotherapy, especially in tumors that lie close to the clitoris,

* Corresponding author. Departamento de Ginecologia Oncológica, AC Camargo Cancer Center, Rua Antonio Prudente, 211, 01509-010, São Paulo, Brazil. Tel.: +55 11 2189 5110.

E-mail addresses: gbaiocchi@yahoo.com.br, glaucobaiocchi@accamargo.org.br (G. Baiocchi).

urethra, or anus. Thus, our aim was to determine the value of pathological free margin distance with regard to local recurrence (LR) in a retrospective series of patients with vulvar squamous cell carcinoma (VSCC) who were treated at our institution.

Methods

We analyzed a series of 205 patients who were treated for VSCC from April 1980 to October 2013 at AC Camargo Cancer Center. We excluded patients who received neoadjuvant treatment. Twelve (5.8%) patients received wide local resection, and the remaining subjects underwent radical vulvectomies. Because our primary objective was to correlate pathological free margin with LR, we included 37 (18%) patients who did not undergo inguinal lymphadenectomy for medical reasons and stage IA. Ten (4.9%) patients received vulvar adjuvant radiotherapy and the indication was per assistant's discretion.

The pathological free margin (PFM) was defined as the distance from the tumor edge to the edge of the specimen, as measured after formalin fixation; these values were retrieved from the medical records. The patients were divided into 3 groups, based on PFM: <3 mm (n = 18; 8.8%); ≥ 3 and <8 mm (n = 61; 29.8%); and ≥ 8 mm (n = 126; 61.5%). PFM categorization was based on previous study.⁶

Follow-up time spanned the date of surgery to the last date for which information was available. Disease-free survival (DFS) of LR was defined as the time from surgery to the date of LR or last follow-up. Overall survival (OS) was defined as the time from surgery to the date of death or last follow-up. Disease-specific survival (DSS) was considered the time from surgery to the date of death due to vulvar cancer or last follow-up.

A database was constructed using SPSS, version 20.0 for Mac (SPSS, Inc., Chicago, IL). The associations between margin distance categories and clinicopathological variables were assessed by chi-square, Fischer's exact and Kruskal–Wallis tests. Mann–Whitney test was used for association between local recurrence and margin distance as continuous variable. Survival curves were generated by Kaplan–Meier method and compared by log-rank test. Multivariate analysis was performed by Cox regression. For all tests, an alpha error of up to 5% ($p < 0.05$) was considered to be significant.

Results

Clinical and pathological characteristics

Clinical and pathological characteristics are listed in Table 1. The median age was 69 years (range: 28–91). The median tumor size was 4.2 cm (range: 0.3–18), and the median depth of invasion was 8.5 mm (range: 0.1–32). The median PFM distance was 10 mm (range:

1–65). Of 119 patients with lymphovascular invasion with evaluable data, 25 (21%) were positive. Of 118 patients with perineural invasion with evaluable data, 25 (21.2%) were positive. A total of 99 (63.1%), 43 (27.4%), and 15 (9.6%) cases had histologic grade 1, 2, and 3, respectively—these data were missing for 48 subjects. Sixty-four (38.1%) patients had LN metastasis, with a median of 18 LNs resected (range: 1–51) and a median of 2 metastatic LNs (range: 1–16).

Recurrence

After a median follow-up of 78 months (range: 1–318) among alive patients, 78 (38%) cases recurred: 37 (47.4%) had only LR, 24 (30.8%) occurred in the groin, 7 (9%) were distant, and 10 (12.8%) experienced both local and distant recurrence. Altogether, 47 of 78 (60.2%) patients had an LR. At the end of the follow-up, 81 (39.5%) patients were alive with no disease, 7 (3.4%) were alive with evidence of disease, 74 (36.1%) died of cancer, and 43 (21%) died from other causes.

LR occurred in 16.7% (3/18) of patients with a PFM <3 mm, 24.6% (15/61) with a PFM ≥ 3 and <8 mm; and 22.2% (28/126) with a PFM ≥ 8 mm ($p = 0.77$). Also, in patients with a PFM of <8 mm and ≥ 8 mm, there was no significant difference in LR—18 of 79 (22.8%) and 28 of 126 (22.2%) experienced a LR, respectively ($p = 0.92$). PFM did not correlate with LR when analyzed continuously ($p = 0.98$).

The median and mean time of LR was 11.1 months (range: 0.7–166) and 34.8 months (SD 46.7), respectively. Notably, 24 (52.1%) and 32 (69.6%) LRs occurred during the first 1 and 2 years of follow-up, respectively. Moreover, the median PFM in patients who recurred before and after 2 years of surgery was 8 mm (range: 1–30) and 11 mm (range: 2–40), respectively ($p = 0.19$).

After LR, 14 (30.4%) had surgery, 11 (24%) underwent surgery followed by radiotherapy and/or chemotherapy, 6 (13%) received only chemotherapy, 1 (2.2%) was administered isolated radiotherapy, and 14 (30.4%) did not undergo further treatment.

Survival

The 5-year OS and DSS rates were 51.4% (median, 76.8 months) and 64.6% (median, 165 months), respectively. The 5-year DFS rate was 79.6%.

Margin distance did not negatively impact DFS ($p = 0.77$) (Fig. 1), nor did age, presence of lichen sclerosus, lymph node dissection, type of vulvar surgery, lymphovascular invasion, histological grade, or vulvar radiotherapy (Table 2).

Perineural invasion was the only variable that negatively influenced DFS (5-year DFS of 61.7% vs. 88.8%; $p = 0.009$) (Fig. 2). Patients with lymph node metastases had worse DFS rates (65.4% vs. 84.7%) ($p = 0.076$).

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