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CLINICAL ARTICLE

Prognostic factors for recurrence and survival among patients with invasive vulvar Paget disease included in the VULCAN study



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ABSTRACT

Objective: To identify prognostic factors associated with recurrence and overall survival among patients with invasive vulvar Paget disease. **Methods:** An analysis was conducted of patients with invasive vulvar Paget disease included in VULCAN, an international multicenter retrospective study of patients diagnosed with vulvar cancer between January 1, 2001, and December 31, 2005. Data regarding diagnosis, treatment, and follow-up were obtained from the patients' medical records. Univariate and multivariate analyses were performed. **Results:** Among 1727 patients registered in the VULCAN database, 38 patients had invasive vulvar Paget disease. The mean follow-up time for these patients was 44.1 ± 35.7 months, the overall recurrence rate (local lesions and distant metastases) was 58%, and the mean overall survival time was 58.5 ± 0.5 months. Case load at the treating center inversely correlated with local recurrence ($P = 0.01$). Tumor size and FIGO stage were associated with the presence of distant metastases ($P < 0.001$ for both). Adjuvant therapy (radiotherapy or chemotherapy) was associated with a reduced risk of distant metastases and increased overall survival ($P < 0.001$ for both). **Conclusion:** Local recurrences of invasive vulvar Paget disease were associated with the case load at the treating center. Distant recurrences were associated with tumor size and FIGO stage. It is possible that adjuvant radiotherapy or chemotherapy could offer patients benefits by increasing overall survival rates.

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1. Introduction

Paget disease of the vulva is a rare intraepithelial lesion that accounts for less than 1% of all vulvar malignancies [1,2]. The disorder usually presents as a heterogeneous skin lesion, and biopsy sampling is needed confirm the histology and possible invasion [2]. Koss et al. [3] found that vulvar Paget disease was associated with epidermal invasion such as Paget disease of the breast. Moreover, Boehm and Morris [4] found that 28 of the 100 patients in their study had an underlying apocrine gland carcinoma. Similarly, Chanda [5] found that 47 (24%) of 196 patients with extramammary Paget disease had an underlying cutaneous or adnexal carcinoma, a finding confirmed by MacLean et al. [6].

Consequently, surgical evaluation of vulvar Paget disease is of great importance given that 20%–30% of cases might be associated with malignancy [7].

Wilkinson and Brown [8] proposed a classification scheme that subdivides extramammary vulvar Paget disease into two groups. Primary (cutaneous) Paget disease is defined as an intraepithelial adenocarcinoma that occurs within the epidermis or the underlying skin appendages. By contrast, secondary (non-cutaneous) Paget disease originates from an underlying non-cutaneous adenocarcinoma [2,8].

Surgical excision is considered the standard treatment for vulvar Paget disease; however, postoperative recurrence rates of 21%–61% have been reported [2,9,10]. The factors associated with local recurrence remain poorly defined.

The VULCAN (VULvar CANcer) study, an international multicenter retrospective study of patients diagnosed with vulvar cancer, aimed to determine the prognostic factors associated with the recurrence rate

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and overall survival in patients with vulvar cancer. The present analysis was focused on patients with invasive vulvar Paget disease included in the study.

2. Materials and Methods

The VULCAN study involved 100 different centers in 11 European countries and included patients diagnosed with vulvar cancer (any histotype) between January 1, 2001, and December 31, 2005. Inclusion criteria for the present analysis were a diagnosis of Paget disease of the vulva by pathology, and primary treatment performed at the participating center. Patients who received primary treatment at another center were excluded.

Approval for VULCAN was obtained from the institutional review board of La Paz University Hospital, Madrid, Spain (Reference number PI-1274). Informed consent was not required to review participants' medical charts after approval by the institutional review board.

The 2009 International Federation of Gynecology and Obstetrics (FIGO) classification system [11] was used for tumor staging. Primary treatment and treatment at recurrence were recorded.

Standardized criteria were established for the present study variables. Surgical procedures were defined as simple vulvectomy (includes vulvar skin and subcutaneous tissue), wide excision (tumor excision with > 1 cm of free margin), and skinning (includes removal of vulvar skin only). Assessment of sentinel nodes was performed using blue dye. The distance between the lesion and the surgical incision, which corresponds to the disease-free tissue, was defined as the surgical margin.

Follow-up comprised general and gynecologic examinations; cytological investigation of the vulva and cervix; and imaging (either computed tomography or magnetic resonance imaging, depending on availability at each participating center). Invasive vulvar Paget disease was defined as the presence of Paget cells that had penetrated the basement membrane and invaded the dermis. Local recurrence was defined as the appearance of a tumor at the original site after a minimum disease-free period of 6 months. Distant recurrence was defined as the appearance of a tumor in a new location after treatment.

Data were analyzed using SPSS version 15.0 (IBM, Armonk, NY, USA) and SAS version 8.0 (SAS Institute, Cary, NC, USA). Quantitative data were described using the mean with standard deviation. Qualitative variables were described using the absolute number and percentage. Between-group quantitative data were evaluated using the Student *t* test and analysis of variance. Categorical variables were compared using the χ^2 test. A multivariate analysis was performed to identify potential prognostic factors. Survival was analyzed using the Kaplan–Meier and Cox proportional hazards methods. All comparisons were two-tailed and the α error was set at 5%.

3. Results

Among 2453 patients identified, 1727 were finally registered in the VULCAN database; full data for the other 726 were not available. Baseline and surgical characteristics of the 38 patients with invasive vulvar Paget disease are presented in Table 1. The mean age at diagnosis was 65.2 ± 11.3 years and 34 (90%) patients were postmenopausal at the time of diagnosis. In addition, 4 (11%) patients were smokers and 2 (5%) presented with previous vulvar intraepithelial neoplasia.

Overall, 36 (95%) patients were symptomatic at the time of diagnosis. Symptoms included itching ($n = 18$, 47%), presence of vulvar mass ($n = 15$, 39%), and bleeding ($n = 3$, 8%).

Vulvoscopy was performed among 23 (61%) patients. As shown in Table 1, 29 (76%) patients had a single lesion and 10 (26%) tumors involved the midline. Six (15%) patients had a pathologic, palpable inguinal lymph node. The mean lesion size was 46.7 ± 40.9 mm.

Regarding surgical treatment, most patients ($n = 26$; 68%) underwent simple vulvectomy (Table 1). The mean free surgical margin was 6.4 ± 8.8 mm. Sentinel node biopsy was performed in 1 (3%) case

Table 1

Baseline and surgical characteristics of patients with invasive vulvar Paget disease ($n = 38$).^a

Characteristic	Distribution
Age, y	65.2 ± 11.3
Smoking	
Yes	4 (11)
No	15 (39)
Unknown	19 (50)
No. of lesions	
1	29 (76)
>1	9 (24)
Lesion size, mm	46.7 ± 40.9
Midline affection	10 (26)
Stromal invasion, mm	2.3 ± 3.5
FIGO stage [11]	
I	29 (76)
II	5 (14)
III	2 (5)
IV	2 (5)
Free margin, mm	6.4 ± 8.8
Surgical procedure	
Skinning	3 (8)
Local wide excision	9 (24)
Simple vulvectomy	26 (68)
Lymphadenectomy	
Yes	4 (11)
No	34 (89)
Surgical reconstruction	8 (21)
Radiotherapy	
Yes	2 (5)
No	36 (95)
Chemotherapy	
Yes	1 (3)
No	19 (50)
Unknown	18 (47)

Abbreviation: FIGO, International Federation of Gynecology and Obstetrics.

^a Values given as mean \pm standard deviation or number (percentage).

and bilateral inguinal lymphadenectomy in 4 (11%) cases, all with separated incisions. Metastatic groin lymph nodes were found among all the patients who underwent lymphadenectomy. Pelvic reconstruction was performed in 8 (21%) cases, 6 (75%) of them with rotation flap. Postoperative radiotherapy was administered to 2 (5%) patients. In addition, 1 (3%) patient received adjuvant chemotherapy.

The mean follow-up time was 44.1 ± 35.7 months and global recurrence was recorded in 22 (58%) patients (19 [50%] with local recurrence and 3 [8%] with distant metastasis). The mean time to onset of recurrence was 59.5 ± 6.2 months (Fig. 1). For local recurrence, the mean time to onset of recurrence was 64.2 ± 7.2 months versus 44.9 ± 1.7 months for distant recurrence. The mean overall survival time was 58.5 ± 0.5 months; 2 (5%) patients died during follow-up as a result of other diseases.

A multivariate analysis was conducted to identify factors associated with the rate of recurrence. The only identified association for the local recurrence rate was an inverse correlation with the number of cases diagnosed annually in each center ($P = 0.01$). No statistically significant association was detected between the positive margin after surgical excision and the recurrence rate. Factors associated with distant recurrence were FIGO stage and tumor size ($P < 0.001$ for both). Finally, adjuvant therapy (radiotherapy or chemotherapy) was associated with a reduced risk of metastases (distant recurrence) and increased overall survival ($P < 0.001$ for both).

4. Discussion

The present analysis found that the case load of the treating center was associated with local recurrence of invasive vulvar Paget disease after surgery. In addition, FIGO stage, tumor size, and adjuvant therapy

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