PREDICTIVE FACTORS FOR RECURRENCE IN CLINICALLY LOCALIZED SQUAMOUS CELL CARCINOMA OF THE PENIS. ANALYSIS OF OUR CASE SERIES


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Summary.- OBJECTIVE: To evaluate the predictive factors for relapse in clinically localized squamous cell carcinoma of the penis undergoing surgical treatment.

METHODS: Forty-nine patients were diagnosed with cancer of the penis in our Service between 1999 and 2009. In the present study we excluded 18 subjects: 9 due to the presence of palpable adenopathies, 6 due to histological characteristics other than squamous cell carcinoma, two lost to follow-up, and one due to death at the time of diagnosis.

Diagnosis was based on physical examination and biopsy findings. The primary lesion was treated by circumcision, partial surgery or total penectomy. Disease relapse was defined by lymph node or metastatic involvement after three months from surgery.

Univariate and multivariate analysis were carried out using the chi-squared test and logistic regression to identify the factors involved in tumor relapse.

RESULTS: Thirty-one patients were included in the study. Mean follow-up was 36 months (median 29). The histopathological study yielded the following profile: 55% pT1 cases, 32% pT2 cases and 13% pT3 tumors. Regarding histological grade, the distribution was G1: 29%, G2: 32%, G3: 39%. Recurrence and mortality rates were 38.7% and 35.5%, respectively.

In the univariate analysis, location of the lesion (p=0.004), type of surgery (p=0.008), tumor stage (p=0.003) and cellular grade (p<0.001) were significantly correlated to disease relapse.

In the multivariate analysis, only cellular grade proved statistically significant (p=0.01).

CONCLUSION: In our series, only histological grade could be regarded as an independent predictor of tumor relapse.

Keywords: Cancer of the penis. Multivariate analysis. Relapse.

Resumen.- OBJETIVO: Evaluar los factores predictores de recidiva del carcinoma epidermoide de pene clínicamente localizado tratado con cirugía.

MÉTODOS: 49 pacientes fueron diagnosticados de cáncer de pene en nuestro servicio entre 1999 y 2009.

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INTRODUCTION

Cancer of the penis is an infrequent neoplasm that mainly affects males in the sixth decade of life (1). If accounts for 10% of all malignant tumors in Africa, Asia and South America, with an incidence of 4.2 cases per 100,000 inhabitants. In Europe and the United States, cancer of the penis accounts for 0.4-0.6% of all tumors, with an incidence of 0.1-1 case per 100,000 inhabitants (2). These geographical variations are related to sociocultural and religious differences.

The most important underlying etiological factors are chronic irritative processes, phimosis, ultraviolet radiation exposure and human papilloma virus (HPV) infection (3).

The most common histological type is squamous cell carcinoma (95%), and the classical variant is the most commonly observed (50%) (4).

The lesions tend to be asymptomatic, and the most common location is on the glans (48%). At the time of diagnosis, approximately 58% of all patients have palpable inguinal adenopathies, and of these, one-half correspond to metastatic spread, while the other half correspond to inflammatory disease (5).

Cancer of the penis has strong lymphatic affinity, and spreads through the lymphatic system by means of an embolization rather than a cell permeation mechanism. As a result, distant spread associated to vascular dissemination is exceptional in the early stages of the disease (6).

Traditionally, the primary lesion has been treated by total or partial amputation of the penis, leaving a 2-cm tumor-free resection margin (7). However, the psychological impact and consequences for the sexual activity of the patients has stimulated the development of penis-preserving management strategies such as local tumor excision, gland resection, radiotherapy or topical chemotherapy (8).

A retrospective multicenter study conducted by Leijte et al (9) showed most relapses to occur in the first two years (74.3%), with 92.2% of all relapses occurring in the first 5 years after treatment. Likewise, 100% of all metastatic presentations occur in the first 5 years.

The overall survival rate of cancer of the penis after 5 years is 52%. This figure increases to 66% in those cases without lymphatic involvement, and drops to 27% among the patients with lymph node invasion (6).

OBJECTIVES

To evaluate the factors predicting relapse in clinically localized squamous cell carcinoma of the penis subjected to surgical treatment.

MATERIAL AND METHOD

Forty-nine patients were diagnosed with cancer of the penis in our Service between 1999 and 2009 (both years included).

The diagnosis of the primary lesion was based on the physical examination and biopsy findings. Lymph node involvement was assessed by physical...
examination and ultrasound, with thoracoabdominal-pelvic computed tomography in the cases where distant metastatic disease was suspected.

Eighteen patients were excluded from the study due to the following reasons: 9 patients with palpable adenopathies, 6 with histological characteristics other than squamous cell carcinoma (4 melanomas and 2 urethral urothelial tumors), two lost to follow-up, and one due to death prior to treatment. All included patients were treated and followed-up on in our center due to squamous cell carcinoma of the penis.

Tumor histological grading was based on the classification of Broders (10), and the pathological stage was established according to the TNM classification of the UICC of 1992 (11).

Treatment of the primary lesion consisted of circumcision in those cases where the disease was limited to the prepuce, conservative surgery (gland resection and local excision), partial penectomy and total penectomy with perineal urethrostomy. We leave a safety margin of healthy tissue of at least 5 mm without intraoperative biopsy of surgical margins (11,12). The patients subjected to conservative surgery have been analyzed jointly with the patients subjected to partial penectomy. We do not make prophylactic lymphadenectomy or sentinel node biopsy.

Follow-up was based on physical examination and inguinal ultrasound. The patients subjected to partial resection were followed-up on every 3 months for the first two years, and then every 6 months until completion of the first 5-year period. In the cases of total amputation, follow-up was carried out on a semestrial basis for the first two years, and then annually until completion of the first 5-year period. In all cases, follow-up was carried out once a year after the fifth year.

Disease relapse was defined by lymph node or metastatic involvement from three months after the local treatment. In cases of lymph node relapse, radical lymphadenectomy of the affected side was performed with extirpation of superficial and deep lymph nodes defined by Dasseler (14). Metastatic disease in turn was treated with systemic chemotherapy based on platinum drug schemes.

A standard descriptive analysis was made of the quantitative and qualitative variables. The Kaplan-Meier method was used for the analysis of survival. A univariate and multivariate analysis was carried out using the chi-squared test and logistic regression, respectively, to identify the tumor relapse prognostic factors. Statistical significance was accepted for $p \leq 0.05$. The SPSS version 15.0 statistical package was used throughout.

### RESULTS

A total of 31 patients diagnosed with clinically localized squamous cell carcinoma of the penis were included in the study.

The mean age at the time of diagnosis was 71 years (range 48-89) with a median of 69. The time elapsed from appearance of the lesion to diagnosis was 13.8 months on average (range 2-60 months).

The lesions were most often located on the glans (45.16%); most of them were exophytic (38.71%), and at the time of diagnosis 54.83% of the patients were asymptomatic. The rest of the descriptive data of the patient series are shown in Table I.

The treatment for the primary lesion was partial surgery in 77.42% of the cases, total penectomy in 12.9%, and circumcision in 9.67% (Table II). Four patients (12.9%) showed disease infiltration of the

<table>
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<tr>
<td>Location:</td>
<td></td>
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<tr>
<td>- Glans</td>
<td>14 (45%)</td>
</tr>
<tr>
<td>- Balanopreputial sulcus</td>
<td>8 (26%)</td>
</tr>
<tr>
<td>- Prepuce</td>
<td>4 (13%)</td>
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<tr>
<td>- Body of the penis</td>
<td>5 (16%)</td>
</tr>
<tr>
<td>Type of lesion:</td>
<td></td>
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<tr>
<td>- Exophytic</td>
<td>12 (39%)</td>
</tr>
<tr>
<td>- Ulcerated</td>
<td>9 (29%)</td>
</tr>
<tr>
<td>- Covered due to phimosis</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>- Indurated</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Clinical presentation:</td>
<td></td>
</tr>
<tr>
<td>- No symptoms</td>
<td>17 (55%)</td>
</tr>
<tr>
<td>- Pain</td>
<td>10 (32%)</td>
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<tr>
<td>- Bleeding</td>
<td>4 (13%)</td>
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resection margins. In these cases posterior extended margin resection surgery was carried out in the form of partial penectomy in two cases and radical penectomy in the other two.

The most frequent pathological stage was pT1 (54.83%), and 38.71% of the patients presented an undifferentiated tumor (G3). The rest of the pathological data are shown in Table III.

The mean duration of follow-up was 36 months (6-99 months), with a median of 29 months.

The overall relapse rate was 38.7% (12 cases). Lymph node disease relapse was recorded in 7 cases. Two of these patients received no additional treatment, due to their poor general condition and associated comorbidities, and died in less than one year. The remaining 5 cases were subjected to radical inguinal lymphadenectomy. One patient showed no posterior relapse, and is still alive, while the remaining four patients developed distant metastases requiring chemotherapy. All of these subjects died in less than two years.

Five patients showed distant metastases with lymph node involvement in the context of disseminated disease. Three patients received chemotherapy and died in less than one year, while the remaining two subjects received no additional treatment and died in less than four months.

At the end of follow-up, 20 patients (54.5%) were still alive, while the rest had died as a result of tumor disease progression. All the patients with regional or metastatic relapse died, with the exception of a single patient with lymph node invasion subjected to radical lymphadenectomy.

In the univariate analysis, the location of the lesion (p=0.004), the type of surgery (p=0.008), the tumor (T) stage (p=0.003) and cellular grade (p<0.001) were significantly correlated to disease relapse. Tumor invasion of the resection margin tended towards statistical significance (p=0.07).

The results corresponding to the multivariate analysis showed only undifferentiated histological grade (G3) was identified as an independent predictor of tumor relapse (p=0.01) (Figure 1).

**DISCUSSION**

The literature describes a range of predictive factors of tumor relapse in cancer of the penis, though it is difficult to establish their independent validity, since the studies are characterized by different therapeutic approaches, different patient populations and heterogeneous histopathological analyses.

In relation to Spanish literature, our serie can be considered representative, with results similar to those found by other groups. The series of García Rodríguez et al (15), Di Capua et al (16) and Bañón Pérez et al (17) have a greater number of patients

<table>
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<th>TABLE III. PATHOLOGICAL VARIABLES.</th>
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<tr>
<td>VARIABLE</td>
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<tr>
<td>Pathological stage (pT):</td>
</tr>
<tr>
<td>- pT1</td>
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<tr>
<td>- pT2</td>
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<td>- pT3</td>
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<td>- G1</td>
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<td>- G2</td>
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<td>- G3</td>
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than ours although longer periods of time and including patients with no clinically localized cancer. Our group performed a univariate and multivariate analysis in search of prognostic variables while the rest of the series, except for Sánchez Merino et al (18) and Di Capua et al (16) performing a univariate analysis, only made a descriptive study (15,17,19).

Tumor biopsy is not useful for defining histopathological prognostic factors beyond the determination of malignancy. The histological subtype and tumor grade can be adequately evaluated in 70% of the cases, while other factors such as infiltration depth or lymphovascular invasion can only be correctly defined in 9% and 11% of the biopsies, respectively. Therefore, the surgical piece is recommended for evaluating prognostic factors (20) and has not been included in our analysis.

At present, the indication of prophylactic lymphadenectomy is based on the risk groups established by Solsona (21) and the European Association of Urology (EAU) (8), with three categories (low, intermediate and high risk), according to histological grade and the extent of the primary tumor (T). In this context, follow-up is indicated in low-risk cases, while lymphadenectomy is to be considered in high- and intermediate-risk cases with concomitant unfavorable factors.

Sentinel node biopsy had been abandoned by filing a false positive rate of 25% (22). Currently the technique of dynamic sentinel node biopsy using Tc-99 yields promising results related to the blockade of lymphatic drainage from the tumor, reducing the rate of false negatives whereas in the group Leijten et al 4.8% with a complication rate of 5.7% (23). The use of this technique is not widespread enough to present difficulties in its implementation by the multidisciplinary nature of it and the difficulty of learning (24).

Ficarra et al. (25) designed a nomogram for predicting the probability of lymph node involvement at 5 years, based on the 8 clinicopathological variables most commonly used: growth pattern, tumor infiltration level, histological grade, lymphovascular invasion, clinical lymph node involvement, and infiltration of the corpus cavernosum, corpus spongiosum and urethra. The concordance between the ROC curve of the nomogram is 0.876, with good discriminatory capacity – though adequate external validation is required in order to generalize its use.

Primary tumor lymphovascular infiltration is regarded as one of the main predictors of lymph node involvement. In the series published by Ornellas et al. (26), Slaton et al. (27), Lopes et al. (28) and Ficarra et al. (25), lymphovascular invasion was found to be an independent prognostic factor of lymph node metastatic disease in the multivariate analysis. Perineural infiltration has only been found to constitute an independent predictor of lymph node invasion in the study of Cubilla et al. (29). In our series we could not analyze the relation between lymphovascular infiltration and relapse because it is a fact that has been discussed from time to time by the pathology department of our hospital, being absent in a significant number of cases, particularly in the early years of the series.

The prognostic relevance of tumor infiltration depth is subject to controversy. An infiltration depth of less than 3-4 mm is associated with a minimal incidence of lymph node metastases, while depths of over 10 mm are associated with adenopathy rates in the order of 80% (29). Correlation is usually reported between low-grade tumors with superficial invasion and high-grade tumors with in-depth infiltration. In the mentioned studies published by Ornellas, Slaton and Lopes, tumor invasion depth was only significantly associated to lymph node disease relapse in the univariate analysis.
The presence of palpable adenopathies at diagnosis traditionally has been regarded as one of the main criteria of lymph node invasion. However, at present, controversy exists regarding the relationship between adenopathies identified at physical examination and the disease recurrence and survival rates [25].

A vertical growth pattern has been associated with a poor prognosis, due to the tendency towards in-depth invasion compared with the superficial and verrucose growth patterns – though no evidence to this effect has been drawn from the multivariate analysis [29]. It is necessary to distinguish this from the tumor infiltration pattern, which represents the invasive capacity of the neoplasm – the reticular pattern being more commonly associated to metastatic adenopathies (65%) than the “pushing” pattern (35%). According to Alkatout et al. [30], this parameter is an independent predictor of lymph node disease relapse.

The absence of koilocytes (epithelial cells with a clear perinuclear halo) in the histological study has been associated with higher cellular grade, an increased incidence of lymph node disease relapse, and poorer 5-year survival rates in the multivariate analysis of the study by Ornellas et al. [26]. According to these authors, tumor lymphovascular embolization and the absence of koilocytes constitute the two independent predictive factors of metastatic lymph node disease.

Cellular differentiation has been the factor most widely studied by numerous groups as a predictor of lymph node involvement. Solsona et al. [21] found the risk of lymph node invasion in patients with high-grade tumors to be 75%, versus 15% in the case of low-grade tumors. According to Alkatout et al. [30], histological grade together with the tumor growth pattern are the two independent predictors of lymph node involvement, with a sensitivity and specificity of 71.4% and 77.7%, respectively. The analysis published by Ornellas et al. [26] in 202 patients revealed an increased lymph node involvement rate and mortality in patients with higher cellular grades. Ficarra et al. [25] Slaton et al. [27] and Fraley et al. [31] likewise found histological grade to be significantly correlated to the development of adenopathies.

In the multivariate analysis of our series, only histological grade was significantly correlated to the risk of posterior disease relapse. Of the 12 patients with relapse, 11 corresponded to G3 – representing 91.6% of the 12 tumors included in this category. The remaining case of relapse corresponded to grade G2, representing 10% of the 10 patients included in this category. No relapses were documented in the 9 patients corresponding to grade G1.

In most of the large studies analyzed, only the histological grade and lymphatic infiltration showed statistical significance in the multivariate analysis. A number of studies, such as those published by Ornellas [26] or Alkatout [30], have defined the absence of koilocytes and a reticular invasion pattern as independent predictors of disease relapse. Other factors such as invasion depth, lesion location, local stage and resection margin infiltration have only shown statistical significance in the univariate analysis in the different series found in the literature, in coincidence with our own findings.

The use of molecular markers as predictors of tumor relapse is still the subject of research – no sufficient efficacy having been established for application to routine clinical practice in cancer of the penis. The genetic and molecular markers implicated in carcinogenesis may possibly play a role as markers of tumor relapse, lymph node involvement and chemotherapy response. The most widely used are HPV, p53, p16, Ki-67, MMP-9 and penile squamous cell carcinoma specific antigen. The development of molecular factors may be useful as a complement to the clinicopathological markers in the management of this disease [32].

Our study has limitations because it is a retrospective study, which determines whether there are changes in protocols of performance throughout the serie, plus we have not analyzed the lymphovascular infiltration as predictor of relapse.

CONCLUSIONS

In the multivariate analysis of our series, only undifferentiated histological grade (G3) could be regarded as an independent predictor of tumor relapse.

REFERENCES AND RECOMMENDED READINGS
(*of special interest, **of outstanding interest)

3. Dillner J, von Krogh G, Horenblas S, Meijer CJLM. Etiology of squamous cell carcinoma of


