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Prognostic Factors for Inguinal Lymph Node Involvement and Tumor Recurrence in Squamous Cell Carcinoma of the Penis

Factores pronósticos de compromiso ganglionar inguinal y recaída tumoral en carcinoma escamocelular de pene

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Abstract

Introduction   Penile carcinoma is an aggressive disease with catastrophic consequences that frequently lead to death. Therefore, further knowledge on the prognostic factors that can help identify patients in need of more aggressive treatments becomes essential.

Objective   To identify the prognostic factors for lymph node (LN) involvement and tumor recurrence in patients diagnosed with squamous cell carcinoma of the penis (SCCP).

Methods   A retrospective cohort study was conducted. Patients diagnosed and treated for SCCP at Instituto Nacional de Cancerología between 2008 and 2015 were included in the sample. Cases in which no information on recurrence was available for the follow-up were excluded, as well as patients with no initial pathology and those getting penile reconstructions after cancer.

Relevant data was retrieved from the medical records of each patient, and a descriptive analysis was performed. Subsequently, this data was used to apply a logistic regression model to determine the potential clinical and histopathological prognostic factors.

Results   A total of 104 patients were included in the present study. The average age of the sample was 59 years, while the follow-up averaged 24 months per patient. Inguinal lymphadenectomy was performed on 61 patients (59%) during the follow-up. The logistic regression model showed that lymphovascular invasion (odds ratio [OR]: 6.7; 95% confidence interval [95%CI]: 1.2–35) and poor tumor differentiation (OR: 17; 95%CI: 3.2–92) were associated with tumor recurrence. Likewise, the lymphadenectomy procedures showed that lymphovascular invasion was associated with LN involvement (OR: 3.3; 95%CI: 1.1–10).

Conclusion   Lymphovascular invasion was the strongest prognostic factor observed in our sample, aiding in the prediction of inguinal LN involvement and tumor recurrence in SCCP patients.
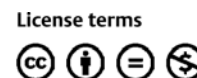
Keywords
► lymphovascular invasion
► penile carcinoma
► tumor recurrence
► degree of tumor differentiation

Resumen

Introduccion   El cáncer de pene es una enfermedad agresiva con consecuencias catastróficas que frecuentemente llevan a la muerte. Por lo tanto, es esencial un mayor conocimiento sobre los factores pronósticos que pueden ayudar a identificar a los pacientes que necesitan tratamientos más agresivos.

Objetivo   Identificar los factores pronósticos patológicos de compromiso ganglionar inguinal y recaída tumoral en pacientes con carcinoma escamocelular de pene.

Métodos   Se realizó un estudio de cohorte retrospectivo. Se incluyeron en la muestra pacientes diagnosticados y tratados por carcinoma escamocelular de pene (SCCP) en el Instituto Nacional de Cancerología entre 2008 y 2015. Los casos en los que no había información sobre la recurrencia en el seguimiento fueron excluidos, así como los pacientes sin patología inicial y aquellos que reciben reconstrucciones del pene después del cáncer. Se recuperaron los datos relevantes de los registros médicos de cada paciente, y una descripción fue realizada. Posteriormente, estos datos se utilizaron para aplicar un modelo de regresión logística para determinar los posibles factores pronósticos clínicos e histopatológicos.

Resultados   Un total de 104 pacientes fueron incluidos en el estudio. La edad promedio de la muestra fue de 59 años, mientras que el seguimiento promedió fue de 24 meses por paciente. La linfadenectomía inguinal se realizó en 61 pacientes (59%) durante el seguimiento. El modelo de regresión logística mostró que la invasión linfovascular (odds ratio [OR]: 6,7; intervalo de confianza del 95% [IC 95%]: 1,2–35) y la pobre diferenciación tumoral (OR: 17; IC 95%: 3,2–92) se asociaron con recurrencia tumoral. Así mismo, los procedimientos de linfadenectomía mostraron que la invasión linfovascular se asoció con afectación de LN. (OR: 3,3; IC 95%: 1,1-10).

Conclusión   La invasión linfovascular es el factor pronóstico independiente más importante que se asocia de manera independiente con compromiso ganglionar inguinal positivo y recaída tumoral.

Palabras-clave
► invasión linfovascular
► cáncer de pene
► recurrencia tumoral
► grado de diferenciación tumoral

Patient Summary   Lymphovascular invasion should be the main factor to determine the management and follow-up of SCCP patients.

Introduction

Squamous cell carcinoma of the penis (SCCP) constitutes a pathology with high morbidity and rapid progression. Its consequences are primarily marked in local, regional and systemic grades of involvement.[1–3]

The epidemiology of the disease presents marked geographical differences apparently related to socioeconomic and cultural factors.[4] Jewish, circumcised-at-birth males in Israel constitute the population with the lowest incidence of this disease. Developed countries also report a low incidence, with rates of 0.2 for every 100,000 males.[5] However, the incidence of penile cancer in developing countries is on the rise,[6] particularly in regions with high levels of poverty and among rural populations (such as in South America, Africa and Asia). In such regions, the disease is considered a public health issue representing up to 20% of reported malignant neoplasms.[7–9]

In Colombia, the available information on the epidemiology of SCCP is limited. The study by Ramírez and Bermúdez Puppo[10] reported an incidence of 1.11 cases for every 100,000 males. A significant percentage of the cases reported in the study (62.7%) were from rural areas. In addition, 71.5% of the cases were diagnosed in advanced stages of the disease ($\geq$ T2), reflecting the delay on the part of the patients to seek medical treatment from 6 months up to a year from the moment when the symptoms arise.[5,11]

Proper staging is crucial in the treatment and prognosis of patients with SCCP. Two factors must be considered in the staging: the level of local extension of the disease and the state of the lymph nodes (LNs), and the former is considered by the European Association of Urology (EAU) and the United States National Comprehensive Cancer Network (NCCN) as the main survival prognostic factor for this disease.[12,13]

The physical examination still is the main tool in the staging of SCCP. Even though this tool is useful in the detection of superficial inguinal adenopathies, it presents limitations, with a false negative rate of approximately 11% and 62% of the cases.[14–16] Therefore, inguinal lymphadenectomy is by far the most accurate method to detect LN metastasis and to conduct a proper staging of the disease. In addition, high-risk cases on which early lymphadenectomy has been performed show benefits regarding survival rates.[17,18] However, one of the main limitations for the widespread performance of this

procedure is the risk involved and the high morbidity (25–50%), which is worsened by longer operation and hospitalization periods.[19–21]

Given the limitations presented by the physical examination technique, current studies are evaluating other options for the diagnosis, such as ultrasonography, computed tomography (CT) scans, nuclear magnetic resonance (NMR) and positron emission tomography (PET) scans.[22–24] Fine needle aspiration biopsy, sentinel LN mapping and some prediction nomograms are the currently available techniques.[25–27]

Some authors in related published studies seek to correlate the histological factors with the possible progression of the disease. Such histological factors include lymphovascular invasion, pathologic staging and histological differentiation.[14] However, there are no such studies available performed in Colombia.

Considering the lack of information related to SCCP in Colombia, more studies are needed to deepen the understanding of the disease and its local impact. Thus, the purpose of the present study is to identify the clinical and pathological prognostic factors for inguinal LN involvement and tumor recurrence in cases of SCCP.

Methods

A retrospective cohort study was conducted. Patients diagnosed and treated for SCCP at Colombia's Instituto Nacional de Cancerología between 2008 and 2015 were included in the sample. A total of 139 cases were collected, but 35 were excluded under the following criteria: cases in which no information on recurrence was available for the follow-up, patients with no initial pathology, and patients getting penile reconstructions after the cancer treatment. In the remaining 104 cases, the clinical and histopathological aspects of inguinal LN involvement and tumor recurrence were evaluated.

The follow-up protocol contemplates the realization of inguinal radical lymphadenectomy in the presence of clinical nodal disease. In patients without clinical nodal disease, sentinel LN biopsy is performed; if the biopsy is positive, the patients are submitted to inguinal lymphadenectomy. If the result is negative, they continue with the clinical surveillance without surgical intervention.

The data was inserted into an Excel (Microsoft Corp., Redmond, WA, US) spreadsheet for a subsequent descriptive analysis, stating frequencies, central tendency and dispersion measurements using both discrete and continuous variables.

For the analytical study, the clinical and histopathological aspects evaluated were: pathological staging, lymphovascular invasion, degree of tumor differentiation, as well as nodal state. A subsequent bivariate analysis was conducted to enable the construction of a multivariate logistic regression model using statistically significant variables to determine the prognostic factors associated with the need to perform inguinal lymphadenectomy, or for the tumor recurrence subsequent to lymphadenectomy.

The presence of distant metastasis disease or pelvic LN after inguinal lymphadenectomy is considered tumor recurrence.

The statistical software used in the present study was the Stata (StataCorp LLC, College Station, TX, US), version 12.0.

Statistical significance was assumed for predictions with values of $p < 0.05$.

Results

The average follow-up was of 24.41 months per patient. Tumor recurrence was observed in 22 (21%) of the cases. The average patient age was 59 years. Most patients sought medical help given the presence of lesions in the physical examination. Most patients presented this lesion in the glans (►Table 1).

Bogota was the region of the country where most cases originated, followed by the Cundiboyacense and the Llanos regions (►Table 1). Clinically, most lesions were deemed to be in stage T2. A total of 71 (68%) of the cases were treated through surgery (penectomy).

Among the gathered medical records, only 65 (62.5%) indicated whether the patient presented phimosis or not. Out of these 65 cases, 43 (66.1%) indicated phimosis while the remaining 22 (33.8%) indicated that there was no phimosis. When reported pathologies were evaluated for the cases studied, it was determined that most patients were in pathological stage (p) T2, with stage pT1 being second in importance (specifically pT1a) (►Fig. 1).

Table 1 Demographic and clinical characteristics of the patients

| Variable	Frequency (%)
Age, years (average)	59 (27–84)
Geographical origin	
Bogotá	57 (54.8%)
Llanos Orientales	17 (16.3%)
Tolima - Huila	11 (10.5%)
Eje Cafetero	7 (6.7%)
Valle del Cauca y Nariño	5 (4.8%)
Santander y Norte de Santander	4 (3.8%)
Caribe/San Andrés	3 (2.8%)
Involved region of the penis	
Glans	41 (42%)
Balano-preputial sulcus	21 (16.5%)
Prepuce	15 (14.3%)
Penile body	9 (5.7%)
Glans + prepuce + balano-preputial sulcus	10 (10.7%)
Glans + prepuce + balano-preputial sulcus + penile body	8 (7.1%)
Clinical T stage	
Tis	2 (1.9%)
Ta	27 (25.9%)
T1	8 (7.6%)
T2	58 (55.7%)
T3	7 (6.7%)
T4	2 (1.9%)
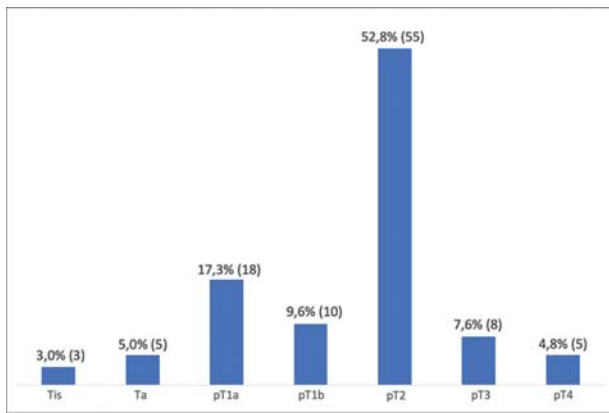
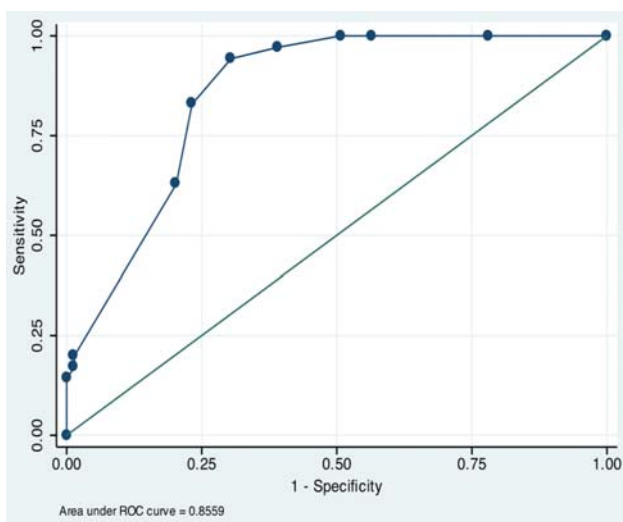**Fig. 1** Distribution of cases by pathologic staging.

Fig. 2 Statistical Analysis - Inguinal Involvement. Area under the curve ROC 0.85.
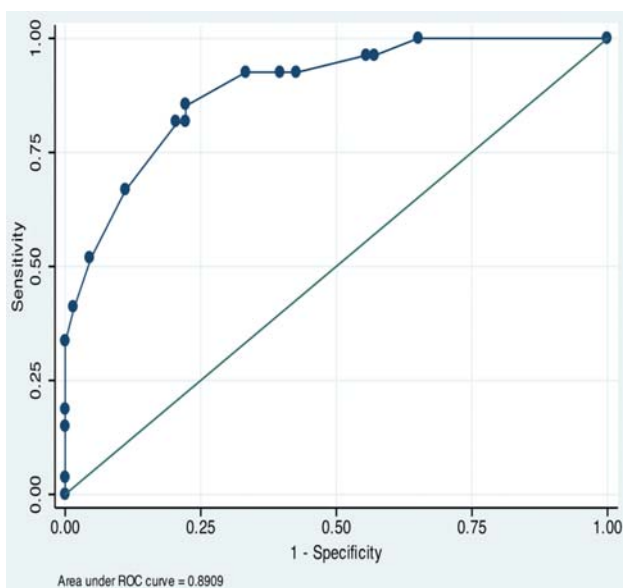

Fig. 3 Statistical Analysis - Tumor Recurrence. Area under the curve ROC 0.89.

During the follow-up, 61 (59%) out of 104 patients were submitted to inguinal lymphadenectomies, with 34 (56.3%) of the cases testing positive for LN involvement. Out of the lymphadenectomies performed, 55 (90%) were unilateral and 6 (10%) were bilateral.

The medical literature was consulted to determine which pathologic and clinical variables should be evaluated regarding their correlation with tumor recurrence and inguinal LN involvement during the follow-up.

A single-variable analysis was conducted to determine the correlation between each one of the variables and the outcomes sought to be predicted (►Tables 2 and 3). Later, the statistically significant variables were used to run a logistic regression model (the independence between the variables was previously confirmed).

The single-variable analysis showed that factors such as pathologic stage, lymphovascular invasion and degree of histologic differentiation of the tumor were associated with inguinal LN involvement and tumor recurrence. The nodal state was also a factor associated with such outcomes. However, the logistic regression model demonstrated that lymphovascular invasion (odds ratio [OR]: 6.7) and the degree of tumor differentiation (OR: 17) were the only factors associated with tumor recurrence. Moreover, lymphovascular invasion was shown to be associated with inguinal LN involvement after the performance of the inguinal lymphadenectomy (OR: 3.3).

It is worth mentioning that from the analyzed subpopulation, 19 (18%) of the cases had pelvic lymphadenectomy performed during the follow-up. Out of the population that presented tumor recurrence, close to 20 (90%) underwent chemotherapy, with cisplatin plus 5-fluorouracile being the most used treatment scheme. Only 16 (73%) patients underwent radiotherapy as part of their treatment during the follow-up.

Discussion

Penile cancer is a disease that has a higher incidence in Colombia compared with that of developed countries. In the present study, most cases originated in the Bogota and Cundiboyacense regions, with an important number of cases originating in other distant regions as well.

It is known that this pathology has a rapid progression rate, and that currently there are not enough imaging tools available to accurately determine the level of compromise caused by the disease. Such rapid progression enables the disease to reach the lymphatic system by penetrating the Buck fascia, as well as by invading the corpus cavernosum just after involving the tunica albuginea.[28] In the nodal level, it initially invades superficial LNs in the groin, followed by the deep inguinal LNs and, subsequently, the pelvis LNs. Such a progression is characteristic of a disease that has reached the metastatic stage.[5,10]

Therefore, inguinal lymphadenectomy continues to be the best technique to detect LN involvement, enabling the proper staging of the disease, which has a positive impact in the survival rate of patients in a 5-year period.[22,23,29] Such

Table 2 Single- and multiple-variable analysis of positive inguinal involvement in lymphadenectomy

Variable	Single-variable analysis			Multiple-variable analysis		
	OR	95%CI	*p*-value	OR	95%CI	*p*-value
≥ pT2	1.7	0.6–4.6	0.06	1.1	0.3–3.6	0.8
Lymphovascular invasion	**7**	**2.4–23**	**0.001**	**3.3**	**1.1–10**	**0.04**
Inguinal lymphadenectomy	52	7.6–258	0.001	31	3.9–248	0.001
Positive lymph nodes in LP	17	1.9–70	0.005	6	0.6–55	0.113
Histological degree/differentiation	3	0.8–10	0.03	2	3.4–80	0.9

Abbreviations: 95%CI, 95% confidence interval; LP, pelvic lymphadenectomy; OR, odds ratio.

Table 3 Single- and multiple-variable analysis for tumor recurrence

Variable	Single-variable analysis			Multiple-variable analysis		
	OR	95%CI	*p*-value	OR	95%CI	*p*-value
≥ pT2	3.6	1.1–13.4	0.0053	1.2	0.1–5	0.9
Lymphovascular invasion	**12.7**	**3.3–69**	**0.001**	**6.7**	**1.2–35**	**0.02**
Lymph nodes observed in the test	4.5	1.5–14	0.002	1.6	0.2–8.9	0.58
Pelvic lymphadenectomy	3.5	1–11.5	0.01	5.4	1.1–25	0.052
Histological degree/differentiation	**8.4**	**2.2–34**	**0.001**	**17**	**3.2–92**	**0.001**
cN3	4.6	1.5–13.7	0.0012	4	0.9–20	0.059

Abbreviations: 95%CI, 95% confidence interval; cN3, plapable fixed inguinal nodal mass or pelvic lymphadenopathy unilateral or bilateral; OR, odds ratio.

results can be achieved especially when the disease is in a nodal stage lower than pN2, without any extra capsular involvement of the nodule and unilateral affectations without any compromise of the pelvic LNs, cases in which a survival rate of 80% was observed.[17,18]

The study of this topic is of particular relevance when considering that 20% of the patients clinically staged as negative for cancerous cells present hidden metastases, while 77% of the patients with high-risk SCCP have negative lymphadenectomies that are negative for LN involvement. Such facts indicate that there is a high rate of patients being over-treated, while the need for a proper and effective staging of the risk of metastasis in this disease is certainly highlighted.[17,24,30]

With the purposes of predicting the risk of LN metastasis, identifying the patients that would benefit from an inguinal lymphadenectomy, as well as identifying those under risk of tumor recurrence, various clinical and histological factors have been determined: tumor staging, growth pattern, level of invasion, thickness of the lesion, degree of the tumor and nucleus, number of mitoses, vascular and lymphatic involvement, among other factors.[14,31]

The physical examination is still the main clinical tool to stage the disease, and it is primarily based on the description of the perceived affectation of adjacent structures such as the urethra, the corpus cavernosum, the scrotum, the prostate and the pubis, as well as the palpation of superficial LNs. In a Canadian study, Beech et al[3] found that nodal staging was the factor with the most significance in cancer-specific survival rates.

In 2001, Slaton et al[14] evaluated a group of 48 patients diagnosed and treated surgically for invasive SCCP. The authors also evaluated several histopathological factors regarding their effectiveness in predicting metastases in inguinal LNs. The study determined through a multivariate analysis that factors such as stages ≥ pT2 ($p = 0.012$), vascular invasion ($p = 0.005$), and poorly-differentiated tumor ($p = 0.043$) in more than 50% of the sample were closely associated with LN involvement.[14]

Another study, conducted by Ficarra et al[34] with a sample of 175 patients who underwent partial or total penectomies, also tried to determine the prognostic factors for LN involvement. The factors found to be effective in the prediction were: thickness of the tumor > 5 mm, superficial growth pattern of the tumor, high stage of the disease, lymphovascular invasion, corpus cavernosum invasion, urethral invasion and LNs testing positive under physical examination.[32–34]

In the context of the existing literature, the purpose of the present study was to evaluate the likely prognostic factors for inguinal involvement and tumor recurrence in an attempt to obtain a representative sample of the Colombian population. Clinical and histological factors were considered in the study, such as nodal evaluation during the physical examination, pathological stage, lymphovascular invasion, and degree of histological tumor differentiation. The internal correlation was evaluated using variables such as the performance of inguinal and pelvic lymphadenectomies (with the LNs testing positive), as well as tumor recurrence.

The present study showed (similar to what was concluded by Beech et al[3]) that nodal state and the presence of LNs in the physical examination is associated with inguinal LN involvement and tumor recurrence, with a high statistical significance in the single variable analysis. In line with the findings by Slaton et al[14] and Ficarra et al,[34] histopathological factors such as pT2, lymphovascular invasion and degree of histological differentiation of the tumor were shown to be connected to inguinal LN involvement and tumor recurrence, with a high degree of statistical significance in the single-variable analysis.

In the construction of the logistic regression model, we found that lymphovascular invasion was the one factor that was independently associated with inguinal LN involvement, as well as tumor recurrence, with ORs of 3.3 and 6.7 for each of the mentioned prognostic factors respectively. This result is in line with the findings of other studies, such as the one by Ficarra et al,[34] in which lymphovascular invasion is the main predictor for LN involvement (OR: 5.3), with the difference that the present study also found tumor recurrence to be connected.

Other factors that have been widely studied in the related literature were also considered in the present study. For instance, the degree of histological differentiation for the tumor was tested, and we found that there was a statistical correlation between this prognostic factor and LN involvement. However, no correlation was found between the mentioned prognostic factor and tumor recurrence. The present study also provided strong foundations, as it showed how inguinal lymphadenectomy results were associated with tumor recurrence.

It is important to mention that the models used for the present study have an area under the curve (AUC) above 80%, indicating their high level of sensitivity and specificity.

Conclusions

Lymphovascular invasion was the main prognostic factor for tumor recurrence and inguinal LN involvement in the sample of the present study. However, more studies on this topic are needed with increased follow-up, and to further investigate the effectiveness of other prognostic factors that help predict more effectively the development of the disease among cancer patients in Colombia.

This study took into account for its implementation the regulations of Article 11 of Resolution No. 008430 of 1993 (Issued by the Colombian Ministry of Health). Similarly, it considered international regulations (in particular, the Declaration of Helsinki and the ethical guidelines for biomedical research prepared by the Council of International Organizations of Medical Sciences, CIOMS) and the parameters established at the national level by Resolution 8430 of 1993 and Resolution 2378 of 2008 (issued by the Colombian Ministry of Social Protection).

Conflict of Interests
The authors have no conflict of interests to declare.

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