Original Article

Diagnostic precision of sentinel lymph node biopsy in penile cancer

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ABSTRACT

Introduction: Sentinel lymph node biopsy (SLNB) was designed as a minimally invasive method for evaluation of nodal involvement in patients with penile cancer and nonpalpable lymph nodes. Nevertheless, SLNB is not used in a regular basis due to the lack of studies that adequately characterize the performance of this procedure. The purpose of this study was to evaluate the diagnostic performance of SLNB in patients with infiltrative penile carcinoma without palpable inguinal lymph nodes in a Colombian population.

Materials and Methods: This is a retrospective observational study of 89 patients diagnosed with infiltrative penile squamous cell carcinoma with nonpalpable inguinal lymph nodes. These patients underwent partial or complete penectomy, along with SLNB, between 2008 and 2017. Those individuals with a positive SLNB underwent inguinal lymphadenectomy, while those with a negative SLNB were followed on a quarterly basis with a physical examination and imaging to assess relapse. Statistical analysis was done using the STATA 14 software. A contingency table was made to calculate sensitivity, specificity, positive predictive value, negative predictive value, and exactitude, each one with its own confidence interval (CI) of 95%.

Results: There was an average follow-up of 31.4 months, and all 89 patients were evaluated; most primary tumors were T2 (55%), followed by T1 (37%), all of which were subclassified as T1b and T3 (8%). Tumours were most frequently located in the glans (43%). All patients were classified as cN0 and underwent SLNB. Sixty-one patients (69%) tested negative in the SLNB, four of whom (6%) presented with lymph node relapse. On the other hand, 28 patients (31%) tested positive in the SLNB and consequently underwent inguinal lymphadenectomy, seven of whom had negative lymph nodeinvolvement (25% false positives). According to the results, the sensitivity was 84% (95% CI, 65.3–93.6) and the specificity was 89% (95% CI, 79.4–94.7), with a false-negative rate of 6.5%.

Conclusions: The SLNB using radiotracer can be a useful method for lymph node staging in patients with penile cancer and nonpalpable lymph nodes when performed in experienced centers.

INTRODUCTION

Penile cancer is a relatively rare pathology in developed countries, with an incidence between 0.9 and 1.5/100,000 population in Europe and the United States.[1] However, this incidence may be higher in some countries such as Brazil, reaching up to 8.3/100,000 people.[2] In particular, Colombia has an annual incidence rate of 1.1–2/100,000 inhabitants according to a study conducted by Universidad del Valle in 2004.[3]

One of the great challenges of this type of cancer is the management of patients with nonpalpable inguinal lymph node disease (cN0), since micrometastasis can exist in up to 25% of those affected, significantly impacting the short- and long-term prognosis.[4] Neither physical examination nor

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imaging has proven to be helpful in those with nonpalpable inguinal disease, with sensitivity rates ranging between 40 and 60% and false-negative rates around 10%–20%.[4,5]

To optimize the staging, those with clinically normal groins (cN0) have been subdivided into risk groups based on stage grouping, histopathological grading, and presence/absence of lymphovascular invasion of the primary tumor.[6] The European Association of Urology recommends invasive lymph node staging for high-risk pT1 stage and for T2-T4 stages, which can be done by modified inguinal lymphadenectomy or dynamic sentinel lymph node biopsy (SLNB).[7,8]

Modified inguinal lymphadenectomy, as a method of staging and treatment, has been shown to have cure rates >90% when performed early and <40% in cases of regional relapse. However, it has been associated with complication rates of up to 87% and a mortality rate of 3%.[6,9]

Dynamic biopsy of the sentinel node with radioactive tracers has been in use since 1977 when Cabañas first proposed it for the evaluation of inguinal lymph nodes in patients with penile cancer based on lymphangiography, identifying the first node of lymph drainage and also assuming that there is an orderly and sequential progression of the lymph node metastases,[10] starting at the level of superficial inguinal lymph nodes, followed by the deep inguinal lymph nodes and then to the ipsilateral pelvic lymph nodes;[11,12] all of this with the intention of reducing the most invasive procedures with higher morbidity rates.[13,14] However, the use of dynamic SLNB is not routine, in part due to contradictory results about its reliability and lack of experience in this procedure.

The purpose of this study was to evaluate the diagnostic performance of SLNB in patients with invasive penile squamous cell carcinoma (SCC) without palpable inguinal disease in a Colombian population.

MATERIALS AND METHODS

A retrospective observational study was conducted between 2008 and 2017. Data about the patients were taken from the database of a referral center for oncological pathology. These patients were identified as having penile SCC along with the absence of palpable inguinal disease during the clinical evaluation; they also had a history of partial/complete penectomy that confirmed the diagnosis of infiltrating penile SCC. The exclusion criteria were the absence of an institutional histopathology evaluation and loss to follow-up.

To perform the sentinel node biopsy, radioactive labeling was done 6–8 h prior to surgery by injecting 99mTc (2–400 μCi) at the base of the penis under local anesthesia; 1 h later, the inguinal lymphoscintigraphy was performed in several projections. Subsequently, the sentinel nodes were identified intraoperatively by measuring the radioactivity with a portable gamma probe, after which the surgical specimen was removed and sent to the pathologist (the protocol established at this referral center does not incorporate the use of intraoperative methylene blue). In the case of neoplastic involvement identified on histopathology of the resected lymph node, the patient was taken for a second surgery to perform ipsilateral inguinal lymphadenectomy. Those patients with extracapsular involvement and/or ≥2 positive inguinal nodes were taken to bilateral pelvic lymphadenectomy. If there was no tumoral compromise in the pathology of the sentinel lymph node, clinical and imaging follow-up was performed.

After this initial management, both groups of patients: those with a positive sentinel lymph node and those with a negative sentinel node were followed quarterly with postoperative physical evaluations and diagnostic imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) seeking to assess the presence of relapses. In those with a negative sentinel lymph node, the clinical/imaging appearance of nodal involvement was defined as a false negative. Likewise, those who had a positive sentinel lymph node and the absence of nodal involvement after lymphadenectomy were designated as false positives.

The statistical analysis was performed using STATA software, version 14, College Station, Texas, USA. The categorical variables were presented as absolute frequencies with their respective percentages (%). Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated, each with its respective 95% confidence interval.

RESULTS

The original pool of candidates comprised of 149 patients. Forty patients were initially excluded for not having an institutional histopathology evaluation, and 20 more were excluded from the final analysis because they were lost to follow-up, leaving a total of 89 patients [Figure 1].

The average age of the 89 patients was 60.5 years (31–90), with an average follow-up time of 31.4 months (6–122 months) [Table 1]. Most primary tumors were T2 (55%), followed by T1 (37%), all of which were subclassified as T1b and T3 (8%). They were most frequently located in the glans (43%), nd most were G2 (moderately differentiated).

61 (69%) had a negative sentinel node, of which 4 (6%) had lymph node relapse. These relapses occurred on average at 10.5 months (8–13 months) with the characteristic that two (2.2%) of these patients (with primary tumors pT2 and G2) required pelvic lymphadenectomy.

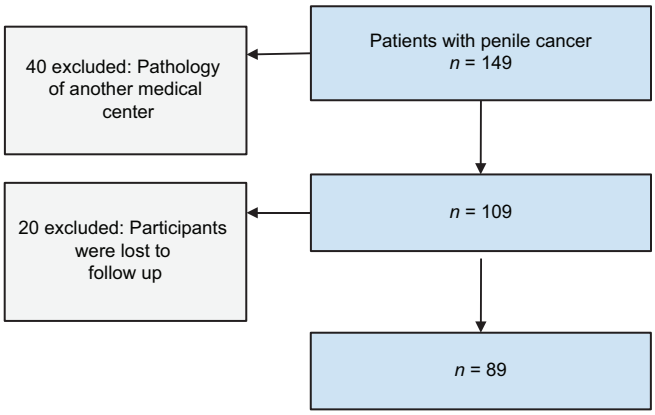

Figure 1: Forty patients were initially excluded for not having an institutional histopathology, and 20 more were excluded from the final analysis because they were lost to follow up, leaving a total of 89 patients

Table 2 shows the relationship between SLNB and the histopathological finding of malignancy in the pathology study. Dynamic SLNB had a sensitivity of 84%, specificity of 89%, false-negative rate of 6.6%, with a similarity ratio (LR+) of 7.80 (3.80–16.03) and a likelihood ratio (LR–) of 0.18 (0.07–0.44) [Table 3].

Sensitivity and specifity were calculated only for high risk T1 patients, who required superficial inguinal lymphadenectomy according to current NCCN guidelines. the sensitivity was 33% and the specificity 100% for such subgroup of patients; along with a PPV of 100%, an NPV of 93% and a diagnostic accuracy of 93.9%.

DISCUSSION

The treatment for penile cancer in patients without evidence of lymphatic involvement is dictated by a risk–benefit analysis. Current guidelines dictate performing either SLNB or inguinal lymphadenectomy in intermediate-/high-risk patients (T1b, any T2 or greater).[15] At the moment, there is not enough evidence that allows for the standardization of the SLNB to demonstrate its adequate utility.

Standard inguinal lymphadenectomy provides important information about the prognosis of the patient and it helps to remove early micrometastasis, nevertheless, the procedure has a high morbidity rate. Besides, other noninvasive methods such as the detection of metastasis with CT, MRI, high-resolution ultrasonography, and positron emission tomography/CT result in higher false-negative rates.[16]

SLNB can be offered to patients diagnosed with penile cancer with intermediate and high risk of lymph node metastasis and Stage cN0 of the disease.[17] This technique was accepted as an option for patients with undetected lymph node metastasis and is recommended for patients with nonpalpable lymph nodes, according to Horenblas *et al.*[18] However, there are a lot of issues that have kept

Table 1: Characterization of the study population

Variable	*n* (%)
Number of patients	89
Median age (years)	60.5 (31-90)
Location of primary tumor (%)	
Gln	39 (43.8)
Cor	15 (16.8)
Prep	13 (14.5)
Body	5 (5.8)
Gln + Prep + Cor	10 (10.8)
Gln + Prep + Cor + Body	7 (7.3)
pT stage at surgery (%)	
T1 (T1b)	33 (37)
T2	49 (55)
T3	7 (8)
Tumor grading (%)	
G1	36 (40.4)
G2	44 (49.4)
G3	9 (10.2)

Gln=Glans, Cor=Corona of glans, Prep=Prepuce, Body=Body of penis, pT=Primary tumors

Table 2: Relationship between sentinel lymph node biopsy and the histopathological finding of malignancy in the pathology study

SLNB \ HPN	HPN-positive	HPN-negative	Total
SLNB-positive	21 (TP)	7 (FP)	28
SLNB-negative	4 (FN)	57 (TN)	61
Total	25	64	89

SLNB=Dynamic sentinel lymph node biopsy, HPN=Histopathological node, TP=True positive, FN=False negative, FP=False positive, TN=True positive

Table 3: Diagnostic accuracy

Variable	Percentage	95% CI
Sensitivity	84	65.3-93.6
Specificity	89.2	79.4-94.7
PPV	75	56.6-87.3
NPV	93.5	84.6-97.5
Accuracy	87.8	79.4-93

PPV=Positive predictive value, NPV=Negative predictive value, CI=Confidence interval

away this procedure from routine use, the main obstacle is the high false-negative rate reported in the initial studies: Horenblas *et al.*, Gonzana-Silva *et al.*, and Pettaway *et al.*, all of which indicate a rate of 12%–25%.[19] This is possibly due to the difficulty in the identification of lymph nodes based on the anatomic location, the absence of physiological identification, and the inadequate histopathological analysis.[2]

The obstruction of lymph node drainage by tumor infiltration is another issue to consider in the interpretation of SLNB because it can alter the accuracy of the procedure. The greater the metastatic compromise, the greater the risk of disturbance in lymph node drainage, that is the reason why the routine use of SLNB is not recommended in patients with palpable inguinal disease.[20] Taking that into account, the patients included in this study did not have palpable

inguinal disease, this guarantees the use of an adequate technique with every patient and increases the diagnostic value of the procedure.

Standardization of the technique using methylene blue and an intraoperative gamma probe has led to a lower rate of false negatives have been reported in the last few years. In our study, a rate of 6.6% of false negatives was obtained. This is one of the strengths of our study due to the greater patient volumes and the expertise in SLNB that our center of reference has, in addition to the technological and human resources at our disposition. Due to the low prevalence of this disease in our population, few hospitals have enough cases to become familiar with the technique, thus SLNB should be limited to few centers.

The sensitivity and specificity rates that we found are similar to those obtained in previous studies with smaller populations. Regarding the performance of SLNB as a test, the sensitivity and specificity rates that we found are similar to those obtained in previous studies with smaller populations. For instance, in a 2016 systematic review and meta-analysis by Zou *et al.*, 29 studies demonstrated a pooled sensitivity and NPV of 88% and 99%, respectively[17]

The limitations of our study are the retrospective nature of the study, the variability in the follow-up period among the patients, and insufficient data that could explain why there was no visualization of lymph node involvement with the gamma probe in patients that later showed a relapse or lymph node metastasis.

Therefore, we consider that the SLNB is a useful diagnostic tool in patients with infiltrative penile SCC with nonpalpable lymph nodes and a cN0 stage, as some international guidelines recommend, such as that of the NCCN.[15] The specificity of this diagnostic method is acceptable, according with the data found; also, the low false-negative rate favors the routine use of the SLNB as a prognostic procedure. Nonetheless, because of the limitations that were mentioned before, we consider that more studies are required, including randomized and prospective studies, in order to better guide the clinical conduct to be followed in patients with a higher risk of lymph node metastasis and nonpalpable lymph nodes.

CONCLUSIONS

Dynamic SLNB with the use of radiotracers can be a useful method for the staging of lymph node disease in patients with penile cancer and groins with nonpalpable lymph nodes. However, further studies are required for confirmation of the data found in this study. Our study shows good reliability with a low rate of false negatives, along with an adequate sensitivity and specificity.

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Conflicts of interest
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