

DYNAMIC SENTINEL NODE BIOPSY IN CLINICALLY NODE-NEGATIVE PENILE CANCER VERSUS RADICAL INGUINAL LYMPHADENECTOMY: A COMPARATIVE STUDY

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ABSTRACT

Objectives. To evaluate the reliability and morbidity of dynamic sentinel node biopsy compared with radical inguinal lymphadenectomy (RIL) in the treatment of selected patients with squamous cell penile carcinoma.

Methods. We retrospectively considered patients with clinically node-negative Stage pT2-pT3 penile cancer. From 1994 to 2000, 48 patients (group 1, mean age 63 years) underwent penectomy and, after 4 weeks, prophylactic bilateral RIL. From 2001 to 2004, 22 patients (group 2, mean age 67 years) underwent penectomy and dynamic sentinel node biopsy. After 4 weeks, bilateral RIL was performed.

Results. In group 1, nodal disease was found in 39.6% of the patients. Early complications occurred in 21 patients (47.5%), with the most common being seroma formation. Late complications occurred in 18 patients (37.5%), with the most common being leg edema. In group 2, preoperative lymphoscintigraphy revealed no sentinel nodes in 1 patient, unilateral sentinel nodes in 7, and bilateral nodes in 14. A total of 35 sentinel nodes were seen in 42 inguinal regions (mean 0.83), including 27 (77.2%) identified with the probe and blue dye and 8 (22.8%) located with the probe only. Metastases were noted in 8 (36.4%) of 22 patients, bilaterally in 4 of them. Early minor complications occurred in 3 patients (13.6%). The technique had an 89% negative predictive value and 90% sensitivity.

Conclusions. The results of this study have shown that dynamic sentinel node biopsy is a minimally invasive technique that is easy to perform, with similar results to those of RIL, but lower morbidity. This procedure offers the possibility of less-extensive surgery for clinically node-negative penile carcinoma. UROLOGY 66: 1282–1286, 2005. © 2005 Elsevier Inc.

The timing of radical inguinal lymphadenectomy (RIL) in patients with penile carcinoma without clinical signs of nodal disease is still controversial. Early RIL provides therapeutic benefits for these patients, but it can result in significant complications. Moreover, in 30% to 82% of patients, only tumor-negative nodes are found at pathologic examination.¹

The concept of the sentinel lymph node was originally introduced by Cabañas.² Using lymphangiography, Cabañas labeled the node close to the super-

ficial epigastric vein as the sentinel node. Removal was recommended on the basis of static anatomic landmarks. After reports demonstrated the unreliability of his approach because of the unacceptably high false-negative rates,³ Morton *et al.*⁴ took the sentinel node concept a step further in patients with melanoma. They identified the sentinel node through individual visualization of lymphatic channels originating in the primary tumor using a blue dye. This technique was complemented a few years later with a radioactive tracer combined with preoperative lymphoscintigraphy and intraoperative use of the gamma ray detection probe. Horenblas *et al.*⁵ introduced this procedure in penile carcinoma and termed it dynamic sentinel node biopsy (DSNB), in contrast to the static method described by Cabañas.²

At our institution, patients with clinically node-negative Stage T2-T3 tumors had been treated with RIL until 2000. In this study, the reliability of DSNB was investigated by evaluating the results

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TABLE I. Oncologic results after radical inguinal lymphadenectomy (mean follow-up 98 months)

Result	Positive Nodes (n = 19)	Negative Nodes (n = 29)	P Value
T stage (%)			
T2	10 (52.5)	25 (86)	<0.001
T3	9 (47.5)	4 (14)	<0.001
Grade (%)			
1	0 (0)	18 (62)	<0.001
2	5 (26)	9 (31)	<0.05
3	14 (74)	2 (7)	<0.001
Overall recurrence rate (%)	79	7	0.003
5-yr Survival rate (%)	11	82	0.009

and complications of DSNB with those obtained using RIL.

MATERIAL AND METHODS

PATIENTS

We retrospectively considered 70 patients with primary Stage T2-T3 clinically node-negative penile carcinoma. From 1994 to 2000, 48 patients (group 1, mean age 63 years) underwent penectomy and, after 4 weeks, prophylactic bilateral RIL. From 2001 to 2004, 22 patients (group 2, mean age 67 years) underwent penectomy and DSNB and, after 4 weeks, bilateral RIL.

The patient and primary tumor characteristics were similar in the two groups. Stage T2 tumors represented 73% of cases in both groups. In group 1, 37.5%, 29%, and 33.5% had grade 1, 2, and 3, respectively, and in group 2, 41%, 27%, and 32% had grade 1, 2, and 3, respectively.

The results of the DSNB procedure were considered falsely negative when lymphatic dissemination was demonstrated only at RIL after negative DSNB findings or nonvisualization on lymphoscintigraphy. The false-negative rate was calculated as the number of false-negative results divided by the total of the positive results plus the false-negative results.

RADICAL INGUINAL LYMPHADENECTOMY

In the case of prior DSNB, the incision was chosen in such a way that the biopsy scar was included in the resection specimen. The boundaries of the dissection were as follows: proximally, the inguinal ligament; distally, the entrance of Hunter's canal; medially, the adductor longus muscle; and laterally, the Sartorius muscle. The floor of the dissection consisted of the fascia lata, femoral vessels, and pectineus muscle. Superficial and deep inguinal nodes were removed with the saphenous vein.

DYNAMIC SENTINEL NODE BIOPSY

Lymphoscintigraphy was performed the day before DSNB. We injected 0.2 mL technetium-99m nanocolloid (Nanocoll, Amersham Cygne), with a radioactive dose of 60 MBq, around the primary tumor. Immediately after the injection, dynamic images were taken with a radioactive gamma camera to visualize the lymphatic drainage. After 2 hours, static scintigrams were taken. A hot spot in the inguinal region was considered to be a sentinel node if an afferent lymphatic channel was visualized or the hot spot was the first one seen in a sequential

pattern. The position of the sentinel node was marked on the skin. Shortly before surgery, a dose of 2.0 mL patent blue dye (Blue patent 2.5%, Monico Spa) was intradermally injected around the primary tumor. Approximately 15 minutes later, the sentinel node was identified and harvested after dissection of the blue lymphatic vessels and detection of radioactivity with a gamma ray detection probe (Navigator gamma guidance system, Tyco). DSNB was followed by partial or total penile amputation during the same session.

PATHOLOGIC EXAMINATION

Sentinel nodes were bisected, fixed in formalin, embedded in paraffin, and cut at six or more levels. The paraffin sections were stained with hematoxylin-eosin.

FOLLOW-UP

Patients were seen at 2-month intervals during the first 2 postoperative years, at 3-month intervals in postoperative year 3, and every 6 months thereafter. Complications were assessed retrospectively, with a median follow-up of 98 months (range 52 to 115) for group 1 and 27 months (range 6 to 46) for group 2. Early complications were defined as those occurring within 4 weeks of surgery. Complications thereafter were defined as late complications.

STATISTICAL ANALYSIS

The Wilcoxon rank sum test, the chi-square test, and Fisher's exact test were used to compare the patient and tumor characteristics between the two groups. Survival analyses were performed using the Kaplan-Meier method and univariate differences in survival by the log-rank test.

RESULTS

RIL GROUP

In group 1, nodal disease was found in 19 patients (39.6%; Table I). A total of 39 complications were observed in 48 procedures (Table II). Early complications occurred in 21 patients (47.5%). The most common was seroma formation (6 cases). Major late complications occurred in 18 patients (37.5%). The most common late complication was leg edema (10 cases) severe enough to interfere with ambulation.

DSNB GROUP

Preoperative lymphoscintigraphy revealed no sentinel nodes in 1 patient, unilateral sentinel nodes in 7, and bilateral sentinel nodes in 14. Overall, we marked 49 hot spots on the skin. The day after, during surgery, a total of 35 sentinel nodes (mean 0.83) were seen in 42 inguinal regions, including 27 (77%) identified with the probe and blue dye and 8 (23%) located with the probe only, with no dye detectable in the lymphatics. Intraoperative localization and removal of the initially visualized sentinel node were successful in all cases. Metastases were noted in 8 (36.4%) of 22 patients, bilaterally in 4 of them. According to the stratification proposed by Solsona *et al.*,⁶ all 8 patients with positive DSNB findings were at high risk and none at intermediate risk ($P < 0.01$); how-

TABLE II. Complication rates by group*

Complication	Group 1 (n = 48)	Group 2 (n = 22)	P Value
Early			
Skin necrosis	4	0	
Seroma formation	6	2	
Lymphorrea	7	0	
Wound infection	4	1	
Deep venous thrombosis	0	0	
Total (%)	21 (47.5)	3 (13.6)	<0.001
Late			
Skin necrosis requiring skin graft	2	—	
Lymphocele	2	—	
Deep venous thrombosis	4	—	
Leg edema	10	—	
Total (%)	18 (37.5)	—	—

* See text for details of groups.

ever, of the patients with negative DSNB findings, 6 were at high risk and 7 at intermediate risk ($P > 0.05$).

At regional lymph node dissection, 252 nodes were removed. In the 8 patients with sentinel node metastasis, this was the only tumor-positive lymph node in 2 patients. In the other 6 patients (12 basins), 20 metastatic lymph nodes were found at inguinal node dissection (mean 1.6 per basin). In the 1 patient without visualization of a sentinel node on lymphoscintigraphy, pathologic examination revealed two metastatic nodes in the left groin at RIL. This patient had false-negative findings. In 2 of the 7 patients with unilateral visualization of the groin, metastases were found at subsequent RIL. They were localized on the same side as the sentinel node. In all cases with negative DSNB findings, 230 negative nodes were found at RIL in 27 groins. The false-negative rate was 11%. Therefore, the technique had an 89% negative predictive value and 90% sensitivity. Complications after DSNB included 1 case of wound infection and 2 cases of seroma (Table II).

COMMENT

The incidence of occult metastases in patients with clinically impalpable nodes is about 20%.⁷ In these cases, Kroon *et al.*⁸ recently demonstrated that early resection improves survival compared with delayed resection. The argument against a surveillance policy is the assumed negative impact of delayed lymphadenectomy on survival. However, the greater cure rate obtained with prophylactic RIL comes at the cost of considerable morbidity.⁹ Therefore, surgical oncology research in penile cancer has focused on minimizing the complications of surgical staging.

Bouchot *et al.*¹⁰ presented the results of modified

lymphadenectomy as a staging procedure. The rate of complications diminished by almost eight times compared with the standard procedure. However, tumor was not found in almost 95% of the patients.¹⁰

Solsona *et al.*⁶ proposed three risk groups—low (Stage T1/grade 1), intermediate (Stage T1/grade 2-3, or Stage T2-T3/grade 1), and high (T2-T3/grade 2-3)—for occult lymph node metastases in patients with penile cancer and clinically negative lymph nodes. In our series, when stratifying patients according to the DSNB findings into risk groups, 100% of those with sentinel node-positive biopsy were at high risk. However, a strategy based only on risk stratification can still result in substantial false-positive and false-negative rates.

DSNB is a promising method to detect occult metastases in patients with clinically node-negative penile carcinoma at the cost of a little morbidity. It includes a radioactive tracer and a vital dye to identify the lymph nodes on a direct drainage pathway from the primary tumor.¹¹ By using both mapping procedures (a visual test [blue dye] and a quantitative test [gamma probe]), the surgeon is reassured. The two tests are complementary, even if they do not ensure finding all the nodes to be removed.

We report our preliminary experience with sentinel node identification using the gamma probe in patients with penile cancer. We believe that a very nice way to test the reliability of the procedure would be to perform both DSNB and RIL.

An unusual finding in our results was that only 35 sentinel nodes were seen in 42 inguinal regions (mean 0.83). We noted a discrepancy between the number of the nodes we marked on the skin at the end of lymphoscintigraphy (n = 49) and the num-

ber of nodes we found intraoperatively using the gamma detection probe (n = 35). Only a part of the nodes we marked on the skin represented hot spots at surgery, and they were the ones nearest to the primary lesion.

We are aware that the procedure we used can result in a number of positive nodes at lymphoscintigraphy that are no longer detectable at surgery. It means that we lost a number of sentinel nodes owing to the limited half-life of the tracer. It would be interesting to perform the sentinel node biopsy earlier on the same day as the lymphoscintigraphy.

In the 1 patient without a sentinel node, we could not perform additional analysis at surgery, because the written consent form for the penile amputation did not include prophylactic lymphadenectomy at the same procedure.

In our experience, the DSNB technique had an 89% negative predictive value, similar to that of Horenblas *et al.*⁵ who had a 93% negative predictive value. In another study by Valdés Olmos *et al.*,¹² 2 of 52 patients with a negative sentinel lymph node at the initial evaluation developed nodal metastasis in the mapped lymphatic basin during the follow-up period.

More recently, ultrasound-guided fine-needle aspiration cytology has been assessed as a diagnostic tool to improve the staging of patients with clinically node-negative penile cancer. Because it has shown a 39% sensitivity and complete specificity, this technique cannot replace DSNB, but is a useful tool for preoperative screening of clinically node-negative groins in patients scheduled to undergo DSNB.¹³

In only 2 of our 8 patients with a positive sentinel node was the disease confined to a micrometastasis in this node. In the other 6 patients with multiple lymph node involvement, it was possible to identify, using DSNB, which was the first node to receive a metastasis, because, at the subsequent RIL, we verified that the nodal metastases were placed more distally from the primary tumor than the sentinel node.

Horenblas *et al.*⁵ reported on a series of 55 patients with Stage T2 or greater node-negative disease. A total of 108 sentinel nodes were removed, and 11 patients underwent regional nodal dissection secondary to a sentinel node positive for metastatic disease. Valdés Olmos *et al.*¹² reported on a series of 74 patients with the same characteristics; 22% of patients had positive sentinel nodes and underwent standard regional dissection.

Although all sentinel lymph nodes are generally found using the gamma ray detection probe, the vital dye should facilitate intraoperative identification. When no evidence is found of a sentinel node during lymphoscintigraphy, we believe that standard inguinal node dissection is the treatment of

choice. In the only patient without visualization of a sentinel node, pathologic examination revealed two metastatic nodes in the left groin at RIL. A possible explanation could have been inadequate injection of the tracer because of sclerosis around the tumor due to previous circumcision.

In the case of discrepancies between the two detection methods, it was our policy to perform standard RIL as the treatment of choice. We are aware that our point of view does not reflect the consensus in the published data on sentinel lymph nodes.

In our series, in 8 patients with visualization of the sentinel node during lymphoscintigraphy, no coloration occurred after blue dye injection. We hypothesized that in 2 cases the reason was a technical error, produced by uncorrected injection of blue dye through Buck's fascia into the corpora cavernosa. These 2 cases happened at the beginning of our experience. In the other 6, an explanation for the nodes being hot, but not blue, remained unclear.

Another issue to be discussed is the possibility that the radioactive tracer is diverted to another node (falsely visualized as the sentinel node). This question has recently been raised by Kroon *et al.*,¹⁴ who explained how afferent lymphatic flow can be diverted to what they defined as a neo-sentinel node. Thus, they stated that to avoid false-negative findings, the combined use of a radioactive tracer and blue dye is mandatory.¹⁴

After RIL, the more severe complication affecting ambulation was lymphedema, reported in 16% to 50% of cases by others.¹⁵⁻¹⁷ The incidence of seroma was also important. Venous thromboembolism was observed late (mean 4.1 months) in 4 patients, despite the use of elastic stockings.

No major complications were observed after DSNB. The early minor complication rate was significantly lower than the rate after RIL. The safety of the procedure was recently confirmed by Kroon *et al.*,¹⁸ with complications in 7% of cases, all minor and easily managed.

A time bias should be considered in the evaluation of our results. The DSNB group was treated more recently and the possibility of better intraoperative and postoperative care should be taken into account. Even if the surgical technique for both RIL and DSNB remained the same throughout the duration of the study, a growing experience has matured. Additionally, the introduction of better codified antibiotic prophylaxis regimens, widespread use of low-molecular-weight heparin, and consolidated use of extremity compression represents improvement in the treatment of patients undergoing surgery for penile carcinoma.

Overall, several benefits of DSNB became clear in

this comparative study. First, this minimally invasive procedure allows for decreased morbidity. A second advantage is improved staging because the pathologist can focus on one or a few nodes, those most likely to contain metastases. Another important observation is that in 25% of our cases with positive DSNB findings, no additional positive nodes were found at subsequent RIL. Our false-negative rate was 11%, lower than the 18% reported by Kroon *et al.*¹⁴ In these cases, one option could be to explore the nonvisualized groin to find a blue lymphatic or palpate a node that has been missed. Ongoing studies on DSNB may result in similar adaptations of the TNM classifications for penile carcinoma.¹⁹

CONCLUSIONS

DSNB has been shown to be a minimally invasive technique that is easy to perform and that provides similar results to those of RIL, but with lower morbidity. However, despite the growing acceptance of this technology into clinical practice, additional studies are warranted to define the role of DSNB in the staging of penile cancer.¹⁹

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