Clinical Urology

Brazilian Journal of Urology Vol. 28 (2): 123-129, March - April, 2002
Official Journal of the Brazilian Society of Urology

INTRAOPERATIVE USE OF GAMMA PROBE FOR IDENTIFICATION OF SENTINEL NODE IN PENILE CANCER

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ABSTRACT

Purpose: Lymphatic mapping and intraoperative lymphoscintigraphy has become part of the management of melanoma and breast cancer with regard to both staging and treatment. We report our technique to detect the sentinel lymph node in patients with malignant penile lesions using a probe to detect pre- and intraoperative gamma radiation.

Materials and Methods: A prospective study was initiated in July, 2000 for sentinel node identification using the gamma probe in 12 patients with T1, T2 and selected cases of T3, N0 or N1 penile cancer. Sodium fitate Technetium-99m-labeled was injected at the site of primary penile carcinoma 1/2 hour before surgery. The sentinel lymph nodes were located using the gamma probe and excised through a 2 cm inguinal incision. A full groin dissection was performed only in cases in which paraffin histopathologic examination of the node demonstrated metastasis.

Results: Eleven sentinel nodes were identified by the gamma probe and excised. In 9 patients, the sentinel nodes were negative at the paraffin histopathologic examination. In 2 patients the sentinel node revealed metastasis focus. In both cases a full groin dissection was carried out which revealed no other nodal metastases. The patients with negative sentinel node are under surveillance at a 3-month interval. Only one patient developed inguinal metastases 3 months after the procedure. To date, ten patients, including the 2 patients with metastatic sentinel node, are free of the disease.

Conclusion: The identification of the sentinel node by gamma probe may be useful to define the presence or absence of inguinal node metastasis in patients with T1, T2 and selected T3 penile cancer. This approach may spare many patients from inguinal lymphadenectomy, which is associated with long-term morbidity.

Key words: penis; penile neoplasms; lymph nodes; radionuclide imaging
Braz J Urol, 28: 123-129, 2002

INTRODUCTION

Tumor staging determines the therapeutical plan. Using the functional characteristics of tumor cells, nuclear medicine can help determine many kinds of malignant neoplasias. Thus, intraoperative gamma probes have been very useful in the evaluation of tumors hidden in lymph nodes. For this purpose, a common work between the nuclear physician and the surgeon is necessary. The nuclear physician is responsible for the preparation and the management of the radioactive material, and control of the equipment of measuring and mapping. The surgeon is responsible for handling the probe during the surgery and the management of the case after the results are obtained.

There are 2 categories of markers: specific compounds, when monoclonal anti-tumor antibodies marked with many kinds of radioisotopes are used; and non-specific compounds, whose main use is in the identification of the sentinel lymph node (1).

The sentinel lymph node concept is based on systematical and sequential lymphatic drainage beginning in the primary tumor site to a specific lymph node in the chain anatomically related to the tumor. It was Cabanas who postulated this concept in 1977, on that occasion to penile cancer (2). Morton et al. have recently manifested again the interest in Cabanas' concept, using it as a factor to predict the nodal status in the melanoma, but using patent blue stain (3). Finally, the use of low energy radio ucleotides, characterized by good tissue absorption, provided satisfactory conditions to the use of intraoperative gamma probe (1).

Penile epidermoid neoplasia disseminates mainly through lymphatics, similar to what occurs in other sites, like vulva, vagina, uterine cervix, larynx, skin, etc. The prognosis worsens in all cases if there is a compromised lymph node, with mortality varying from 43 to 46% in 5 years (4,5). Lymph nodes are enlarged at the moment of the diagnosis in about 50% of the cases. However, only half of them are effectively metastatic, what means ¼ of the initial amount. On the other hand, about 20% of the non-suspect will reveal lymphatic compromise (6).

For this reason, most of the centers specialized in urological cancer treatment do not perform inguinal node excision in the beginning, except for tumors T4, selected cases of T3 and highly suspected inguinal lymph nodes. The other cases, with a lower level of suspicion, are re-evaluated 3 to 5 weeks after the treatment of the primary neoplasia. The biggest challenge consists of the cases clinically N0, specially T1 and T2, in which only 12 to 30% demonstrated lymph node metastases.

In this area, we frequently come across some cases which return to the clinic with lymph node compromise that cannot be operated on. Some cases are justified by the fact that we don't have efficient methods to identify the incipient lymph node disease.

Despite the efforts to offer adjuvant postsurgical therapeutic techniques, there hasn't been observed expressive changes to control the disease in the cases mentioned above, specially when there is bilateral or deep lymph nodes compromise. Hence, many efforts were made in the sense of detecting or even excising early possible focus of lymphatic disease.

As the physical exam of the lymph nodes is not a reliable indicator of metastasis (7), other methods such as bipodalic lymphography (not used nowadays), and ultrasonography, which is not so accurate, specially in microscopic disease, have been used. In spite of the initial interest in Cabanas' proposal, some obstacles related to the lymphangiography feasibility and the reliability of the method, prevented its practical use (8,9).

The cytology of the material obtained through fine needle biopsy, is also not reliable, as negative results do not exclude malignity. Besides, as it's very difficult to choose a node to be aspirated, specially in cases of minor compromise, limits the method application.

Based on the successful results observed in the method of searching the sentinel lymph node using the gamma probe in melanoma and breast cancer, our objective was to define the extension of the disease as well as treating the primary tumor.

MATERIALS AND METHODS

From July 2000 to September 2001, we treated twenty-eight patients with penile cancer at the Cancer Hospital in the Instituto do Câncer do Ceará. Twelve of them participated in a prospective study to detect the sentinel lymph node in penile epidermoid carcinoma T1, T2 and selected cases of T3, N0 e N1. Lymphadenectomies were performed at the same time in cases of metastatic lymph node associated with small primary lesions and absence of infection. The follow-up of the negative cases, i.e., the ones without lymph node metastasis, was surveillance every 3 months for three years.

At the Cancer Hospital of Ceará, we use sodium fitate Technetium-99m-labeled (99 m Tc), in colloidal presentation with the total dose being 0.8mCi (29.6mBq). Four 0.2 ml injections of 99 m Tc were administered in the cardinal points (equivalent to the 3 ,6, 9, and 12-hour positions), around the penile lesion (peritumoral technique) (Figure-1). The penis is protected with a cylindrical cast made of lead to decrease the activity coming from

the points of radiopharmaceutical injection. The detection probe (American C-TRAK Care wise) is covered with a vest similar to the ones used to protect the camera and the cable in videolaparoscopic surgeries.

Detection is made through semiconduction. The scanning with the probe is performed about 30 minutes post-injection (Figure-2). After identifying the lymph node, the point of the highest number of radiopharmaceutical countings is made on the skin. The excision of the lymph node is then performed (Figure-3). The lymph node is sent to pathology after assuring that it is the one which concentrates the highest quantity of radiocolloid (Figure-4).

RESULTS

The characteristics of the 12 studied patients do not differ from the ones mentioned in the literature. Mean age was 59.2 years old. Most of the patients came from the country area (75%) and were illiterate or semi-illiterate (75%). The tumors were located in the glans (41.6%) and in the prepuce (25%). In relation to tumor staging, 41.6% of the tumors were T1 and 58.3% were T2. Two-thirds of the patients underwent a partial penectomy, 16.6% a postectomy, and hardly any of them were submitted to an excision with wide margins (8.3%). In half of the cases, the lymph node of highest intake was located on the

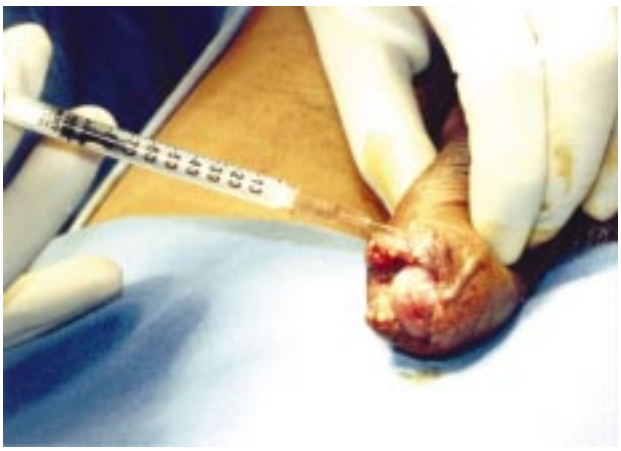

Figure 1 *- Injection of radiopharmaceutical using peritumoral technique.*

Figure 2 *- Scanning with gamma probe 30 minutes after radiopharmaceutical injection. The tumor in the penis is protected by a cylindric cast made of lead to avoid radioactive activity emanating from the places of injection.*

Figure 3 *- Excision of the lymph node which produced the highest radiopharmaceutical counting.*

Figure 4 *- Confirmation of the lymph node which concentrated the highest amount of radiopharmaceutical.*

left inguinal area, while in 25% of the cases it was located on the right, and 16% bilaterally. In one case (8.3%) there wasn't enough radiation to identify the sentinel lymph node.

Complications related to the procedure were not observed. Two patients (16.6%) had pathological reports revealing lymph node metastasis. Both of them underwent a bilateral inguinal lymphadenectomy. The pathological examination of lymphadenectomy specimens revealed that the sentinel lymph node was the only implicated node in both cases.

From the 9 patients (83.3%) whose pathological study showed lymphadenitis or reactive lymph node hiperplasia, only one developed lymph node disease.

A comparison between the findings of the inguinal physical examination and histopathology was carried out. From the 6 patients clinically considered N1, only 2 presented histopathologic disease.
Table summarizes our study.

DISCUSSION

Radiocolloids are commonly used agents to locate the sentinel lymph node. The node intake and retention depend on: the site of the injection, the size of the particles and their difusion in the lymph nodes. The migration velocity of the particles is inversely proportional to their size (10).

There are many known techniques to radiocolloid injection; however, there is no consensus concerning volume and site of injection. Doses ranging from 0.8 to 1.0 ml have been reported as well as peri or intratumoral injection sites. As we believe that the migration of the colloid inside the tumor is not so predictable as in normal tissues, and because of the risk of potential dissemination of the tumor, we decided to use the peritumoral technique. We inject 0.20 ml at 3, 6, 9, and 12-hour position, totalizing 0.8 ml. When the fitate reaches the lymph, it adds calcium to its particles, increasing their dimensions from 100 to 200 nm, which is considered ideal to the evaluation of the sentinel lymph node.

Issues on penile cancer in oncology persist until these days. When should we perform a lymphadenectomy? Should it be inguinal or ileoinguinal? Due to a combination of factors, these questions are, in a certain way, antagonistic: on one side there is high incidence of lymph node compromise; on the other, there is low sensibility and specificity of the detection methods, added to a high morbidity rate in lymphadenectomies. Consequently, the uro-oncolo-

Table 1 *- Overall findings and results.*

Patient	Probe	Histopathologic	Treatment	Follow up
I	(+)	(-)	PP	Disease free
II	(+)	(-)	PP	Disease free
III	(-)	-	Tu excision	Disease free
IV	(+)	(-)	PP	Disease free
V	(+)	(-)	PP / BIL / IRxt	Under Irxt
VI	(+)	(+)	PP / BIL / IRxt	Disease free
VII	(+)	(-)	PP	Disease free
VIII	(+)	(+)	PP / BIL / IRxt	Disease free
IX	(+)	(-)	PP	Disease free
X	(+)	(-)	PP / Em / IRxt*	Under IRxt*
XI	(+)	(-)	PP	Disease free
XII	(+)	(-)	PP	Disease free

*Probe = gamma probe examination; PP =Partial penectomy; BIL = Bilateral inguinal linfadenectomy; IRxt = Inguinal radiotherapy; Em = Emasculation (patient with scrotal tumor recorrence); IRxt * = Tumor recorrence radiotherapy.*

gist faces the dilemma of having to choose between an unnecessary treatment in about half of the cases, or surveillance, even knowing that a delay in treatment may decrease the patient's chances of survival in up to 50% (11).

The validation of the sentinel lymph node concept lead to a re-discovery of lymphoscintigraphy in oncology. Then, isolated or not, lymphatic mapping and intraoperative gamma probe have been widely used to detect the sentinel lymph node in melanoma and breast cancer. Recently, they have been used experimentally in other tumors, such as vulva and penis (12). Contrary to what is observed in cases of melanoma, there is no consensus on the real role of this novel application of lymphoscintigraphy in other tumors. In relation to melanoma, which is considered a gold standard nowadays, the identification of the sentinel lymph node occurs in more than 97% of the cases, even after considering the variety of lymph drainage in parts like neck and the trunk. Reproducibility of the method, whose rate varies from 85 to 88%, is very satisfactory (10). Similar rates are obtained in cases of axillary lymph nodes in breast cancer (13).

So far, the most representative study on malignant penile neoplasia was performed by Horenblas et al. (14). In their prospective study, 55 patients in stages T2 and T3, N0 and N1 were analyzed, using previous lymphatic mapping and probe for perioperatory detection in association with patent blue. In only 3.6 % of the cases the sentinel lymph node was not identified; in 20% of the patients, these lymph nodes were metastatic and after a 22-month follow up, only one patient with negative node developed metastasis (2.3% of the cases). It is important to mention that the probe alone was able to detect 91% of the lymph nodes, identified by lymphoscintigraphy (14). These results motivated us to start the study using only the probe in pre- and transoperatory detection.

In the present study, we were not able to identify the sentinel lymph node in only one case (8.3%). It was a T1 tumor that was excised with wide margins. In 2 patients (16.6%), the probe identified lymph nodes which were metastatic on pathology. They underwent partial penectomy with surgical margins, bilateral lymphadenectomy and radiotherapy. These three patients (3, 4, 8) are currently free of the disease (Table).

One patient (5) who presented gamma radiation intake and negative pathological evidence of metastasis, further developed bilateral inguinal metastasis. Actually, it was a case with identified inguinal mass detected in the physical examination, so it should not have been included in the study. The probe identified an inflammatory lymph node, since large lymph node masses do not intake the radiopharmaceutical due to the destruction and disorganization of the lymphatic circulation. This patient underwent a bilateral lymphadenectomy and inguinal radiotherapy and, at the moment, is free of the disease (Table).

Another probe positive and pathology negative patient (10) had tumor recurrence in the scrotum (this patient underwent penectomy in another institution), and emasculation was necessary. At the moment, the patient is undergoing radiotherapy, since the surgical margin was not appropriate.

In a recently published study on penile cancer (15), 9 sentinel lymph nodes were identified in 5 patients by intraoperative gamma probe, and then removed. In 3 of them the sentinel lymph nodes were negative. In 2 patients the sentinel lymph node was macroscopically normal, but showed a single focus of metastasis in the microscopic examination of the frozen section. In these cases, a complete dissection was carried out and no other lymph node metastasis was found. All patients are free of the disease (mean follow-up of 18 months, ranging from 16 to 23) (15).

At the present time, many uro-oncology groups are enthusiastic with this technique. We have observed some clinical studies for different types of tumors, such as prostate (16) and penis (17,18). Even Cabanas has an optimistic view of this novel perspective to an old issue (19).

We believe that nuclear medicine will become an important tool to detect the sentinel lymph node. Its application will go further than simply tumor staging. Previous detection of the tumoral implant increases the chances of cure and decreases morbidity rates, as radical lymphatic dissections are avoided. However, some technical questions have to be solved, as well as there is a need for standardization and validation of the referred method.

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Received: November 7, 2001
Accepted after revision: February 18, 2002

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EDITORIAL COMMENT

It is rewarding to know that a number of studies focusing on penile epidermoid carcinoma dissemination has been carried out. As in most cases lymphatic metastasis are responsible for mortality, it would be of utter importance to find a less aggressive method to detect them in the very beginning. Clinical staging is poor, as even with the absence of adenopathies, micro-metastasis are found in up to 39% of the cases. Patients with positive unilateral lymph nodes are positive to malignancy in up to 70% of the cases, and patients with palpable bilateral lymph nodes are positive to malignancy in up to 42% of the cases (1). Unfortunately, the concept of the sentinel lymph node, stated by Cabanas, could not be proved in subsequent studies (2,3). Our own experience showed that it fails to detect the disease in 31.25% of the cases, as 5 out of 11 patients who had a negative biopsy presented tumor recurrence. Besides, we can find positive lymph nodes out of the site stated by Cabanas associated with the sentinel lymph node negative to malignancy. It seems that it occurred with one of the patients in the present study.

This subject is complex and has been recently approached with the aid of lymphoscintigraphy. In the present study, as in another mentioned (4), there were failures in the detection in 1 and in 3 patients, respectively. We will not be able to cure the patient unless the metastatic disease is diagnosed in the very beginning; therefore, this type of study has to be carefully carried out. It cannot be used in the clinical practice without a precise protocol and without the patients' awareness of the risks involved.

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