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Tanis, P.J.

Link to publication

Citation for published version (APA):
Tanis, P. J. (2002). Methodology and implications of lymphatic mapping and sentinel lymphadenectomy

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CHAPTER ELEVEN

Penile Lymphoscintigraphy for Sentinel Node Identification

Departments of Nuclear Medicine, Surgery and Urology, The Netherlands Cancer Institute / Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands

The management of patients with clinically node negative penile carcinoma is still surrounded by controversy. Standard regional lymph node dissection (LND) results in about 40-60% overtreatment with a considerable rate of postoperative complications. In order to decrease the number of unnecessary LND and to improve the detection of occult metastases better staging procedures are mandatory. This is particularly valid for patients with stage T2 or greater, because the risk of metastasis for patients with carcinoma in situ, and T1 tumours is negligible.

In 1977, Cabañas investigated the basic concept that the lymphatic of the penis drains to one or a group of nodes, the sentinel lymph node, that appeared to be the primary site of metastases from penile carcinoma. In 1992, Morton and co-workers introduced the concept of lymphatic mapping with sentinel lymph node biopsy for melanoma. In more recent years the sentinel node procedure has been extensively validated for breast cancer and other malignancies.

The work of Cabañas, who performed lymphatic mapping by means of lymph-angiography via dorsal lymphatics of the penis, the wide experience with lymphoscintigraphy for sentinel node biopsy as well as our initial results with this procedure in carcinoma of the penis, led us to evaluate penile lymphoscintigraphy for sentinel node identification.

**Materials and methods**

The evaluation involved 74 consecutive patients (mean age 62 years, range 28 to 87 years) with squamous cell carcinoma of the penis who were referred to the Department of Nuclear Medicine for lymphoscintigraphy between January 1994 and January 2000. Only patients with clinically lymph node-negative stage T2 or greater were included.

Thirty minutes after local anaesthesia by xylocaine 10% spray, a mean dose of 65 MBq (range 40 to 131 MBq) technetium-99m ($^{99m}$Tc) nanocolloid (Amersham Cygne, Eindhoven, The Netherlands) in a volume of 0.3 to 0.4 ml was intradermally administered around the tumour, raising a wheal (figure 1). Injection was divided into three or four depots of 0.1 ml. The tracer was injected proximally from the tumour. For large tumours not restricted to the glans, the tracer was administered in the prepuce.

![Figure 1. A: Intradermal tracer administration around the primary lesion in a patient with a T2 squamous cell carcinoma of the penis. B: Dynamic image performed a few minutes after $^{99m}$Tc-nanocolloid injection (T) showing drainage to both groins with visualisation of lymph channels (open arrows) and lymph nodes (solid arrows).](image-url)
Shortly after tracer injection, anterior dynamic 20-second images of the affected region were acquired over a period of 20 minutes using a dual-head camera (ADAC, Milpitas, CA, USA) with low-energy high-resolution collimators. Subsequently, 5-minute anterior and lateral static images were obtained at 30 minutes and 2 hours with simultaneous transmission scanning using a $^{57}$Co flood source. The location of the sentinel node was defined using $^{57}$Co markers and indicated on the skin with ink. Criteria to distinguish the sentinel node from secondary lymph nodes were the visualisation of an afferent lymphatic vessel leading from the injection site to the lymph node or, if no afferent vessels were seen, the first lymph node appearing in a basin.

Shortly before surgery, which was performed the day after scintigraphy, 1 ml of patent blue (Blue Patenté V, Laboratoire Guerbet, Aulnay-sous-Bois, France) was intradermally injected around the tumour in the same way as injection of the radiopharmaceutical. Subsequently, measurements were made over the skin marks with a gamma-ray detection probe (Neoprobe® 1500/2000, Johnson & Johnson Medical, Hamburg, Germany) to confirm the location of the sentinel node as seen on scintigraphy. Following a small skin incision, the sentinel node was identified after careful dissection of the afferent blue vessel and after confirmation with the probe that the blue node was radioactive. After removal of the sentinel node, the wound was controlled for remaining radioactivity with the gamma probe. Closure of the wound was followed by treatment of the primary tumour. Pathological examination of sentinel lymph nodes included routine paraffin sections at multiple levels with hematoxylin and eosin staining in all patients as well as immunohistochemistry with CAM 5.2 (Becton Dickinson, San José, CA, USA) and pankeratin in the last 64 patients. Standard regional LND with or without iliac node dissection was reserved for patients with a sentinel node positive for metastasis. Follow-up was performed at 2-month intervals during the first 2 postoperative years, at 3-month intervals in postoperative year 3 and every 6 months thereafter.

![Figure 2. A: Dynamic sequence showing drainage from the tumour site (T) to the right groin. B: Delayed static image after 2 hours confirming unilateral drainage with visualisation of one sentinel node in the right groin.](image)

**Results**

Sentinel nodes were visualised in 72 of 74 patients (97%). Visualisation before 30 minutes occurred in 66 patients (93%), in 64 of them (88%) already during the dynamic
study. Lymph channels were visualised in 60 patients (83%). Unilateral lymphatic drainage (figure 2) was observed in 14 patients (19%), with drainage exclusively to the left groin in nine (13%) and to the right groin in five patients (6%). Lymphatic drainage to both groins was seen in 58 patients (81%). This bilateral drainage was synchronous (figure 3) in 22 of these patients (38%) and asynchronous (figure 4) in 36 (62%). In 18 patients the initial route was the left groin and in the other 18, the right groin.

![Figure 3](image1)

**Figure 3.** A: Dynamic scintigraphy showing bilateral synchronous drainage from the injection site to both groins with visualisation of lymph channels and sentinel nodes. B: Anterior static image showing further drainage to second-echelon nodes. C, D: Lateral static images, which can differentiate inguinal from iliac lymph nodes.

![Figure 4](image2)

**Figure 4.** A: Dynamic image showing drainage from the injection site (T) to the left groin with visualisation of one dorsal penile lymph vessel, two afferent inguinal lymph vessels and two sentinel nodes. B: Static image performed 2 hours after $^{99m}$Tc-nanocolloid injection showing delayed sentinel node uptake in the right groin (arrow).

A total of 173 sentinel nodes were visualised (85 in right groin, 88 in left groin). Pitfalls were caused by inguinal skin contamination during injection in four patients and by intracavernous administration in one patient. In the latter patient, at his own request, re-injection performed one day later and led to sentinel node identification in both groins.

The sentinel node was identified in all basins indicated by lymphoscintigraphy. A total
of 161 sentinel nodes were identified and removed. Sentinel node metastases were found in 16 patients (22%). These patients underwent standard regional lymph node dissection subsequently. During follow-up (median 28 months, range 3 to 74 months), two patients with a negative sentinel node developed lymph node metastases in the mapped basin at 4 and 14 months. This led to a total sensitivity of 89% (16 of 18). The negative predictive value of the method was 96% (54 of 56). Re-examination of histology of the two false-negative sentinel nodes showed a micrometastasis in one case in which immunohistochemistry had not been performed initially.

**Discussion**

Since it visualised sentinel nodes in 97% of the patients and lymph channels in 83%, penile lymphoscintigraphy appears to be a valid method for lymphatic mapping and sentinel node identification in carcinoma of the penis. Use of local anaesthesia before tracer administration ensures that the method is well tolerated and relatively easy to perform. The acquisition protocol, similar to that used for sentinel node identification in melanoma, yields good-quality dynamic and static images with adequate discrimination of lymphatic channels and first-tier and secondary lymph nodes.

In concordance with the work of Cabañas, inguinal drainage was seen in all patients in whom the sentinel node was visualised. Like Cabañas, we did not find so-called prepubic lymph nodes or lymphatic vessels draining directly to the iliac nodes. After peritumoural injection, the dorsal lymph channels of the penis were first observed, with subsequent drainage to the groin (figure 1). In contrast with the findings of Cabañas, who reported that a single dorsal penile lymphatic vessel injection opacified lymph nodes of both sides in only 12% of the cases, in our study bilateral inguinal drainage was the most frequent pattern of visualisation (81%). The difference may be explained by the fact that injection of the tracer in various sites around the tumour causes many lymphatic capillaries to be activated for drainage, leading to transport by various major lymphatic channels of the penis.

In almost two thirds of the patients, bilateral drainage was asynchronous, with visualisation of the contralateral side in delayed images. This leads us to recommend late images in patients with initially unilateral drainage.

In patients with unilateral drainage only the visualised side was explored. Only one of these patients developed lymph node metastases in the unexplored contralateral groin, at 27 months after operation.

Discrepancies between the number of nodes seen at lymphoscintigraphy and the number found at surgery may be explained in some cases by limited resolution of the gamma camera: one hot spot may correspond to two sentinel nodes, and elongated sentinel nodes may be visualised as two hot spots. However, addition of the blue dye can provide better distinction between first- and second-echelon nodes.

The lack of a gold standard is a limitation in determining the clinical value of the technique. To identify a recurrence at the earliest possible time, we therefore rely heavily on early and frequent follow-up visits during the first three years after sentinel node biopsy. One of the two false-negative biopsies was caused by a false-
negative pathology report. Therefore, immunohistochemistry was added to routine pathology analysis after the detection of a metastatic deposit, falsely reported to be tumour-negative at the time of the dynamic sentinel node procedure. The second false-negative result could have been due to purely technical factors, such as inadequate intradermal injection of the radioactive tracer, or anatomical features causing blockage of the lymphatic flow.

Despite these two false-negative cases, the sensitivity of the test was satisfactory (89%), with a high negative predictive value (96%) and detection of metastases in 22% of the patients. In almost 80% of patients in this series, an extensive lymph node dissection was avoided. This emphasises one of the most important potential clinical benefits of the procedure: the reduction of long-term complications of the treatment of penile carcinoma.

**Conclusion**

In trying to reduce the number of unnecessary lymph node dissections in penile cancer, we prospectively assessed the value of lymphoscintigraphy for study of the individual drainage pattern of the tumour. The technique is minimally invasive and seems of promise for the early identification of clinically occult metastasis requiring regional lymph node dissection. Lymphoscintigraphy may visualise uni- or bilateral groin drainage of the tumour, enabling sentinel node localisation for subsequent intraoperative identification by the gamma probe and blue dye. Regular follow-up at short intervals is mandatory in order to identify and treat recurrences at the earliest possible time.

**References**
