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REPRODUCIBILITY OF LYMPHOSCINTIGRAPHY FOR LYMPHATIC MAPPING IN PATIENTS WITH PENILE CARCINOMA

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ABSTRACT

Purpose: We evaluated the reproducibility of lymphoscintigraphy in the assessment of the location and number of sentinel nodes in patients with penile carcinoma.

Materials and Methods: A total of 20 patients were prospectively included in analysis. Lymphoscintigraphy was performed after intradermal injection of ^{99m}technetium nanocolloid around the tumor or excision scar. We performed 10-minute anterior dynamic imaging, and static anterior and lateral images were obtained at 30 minutes and 2 hours. The following day scintigraphy was repeated after a second injection of the radiolabeled colloid given in an identical fashion, preceded by acquisition of a starting image. An observer evaluated the paired images and count rates were calculated from the images.

Results: At least 1 sentinel node was visualized in all patients on the first lymphoscintigram. A total of 56 sentinel nodes were seen in 38 basins. Drainage to both groins was seen in 18 patients. In 1 of these patients drainage to the prepubic area was also observed. There were 2 patients with drainage to 1 groin. The second lymphoscintigram revealed the same drainage pattern in all patients— the same number of nodal basins and number of sentinel nodes were visualized at identical locations. All hotspots that were visualized during the first lymphoscintigram showed an unequivocal increase in radioactivity after repeat injection. Thus, the reproducibility of penile lymphoscintigraphy was 100% (95% CI 85%–100%). The Pearson correlation coefficient of the paired count rates was 0.69 ($p < 0.0001$).

Conclusions: Results of lymphoscintigraphy in patients with penile carcinoma are highly reproducible for assessment of the number and location of sentinel nodes.

KEY WORDS: penile neoplasms, radionuclide imaging, lymphatic system, sentinel lymph node biopsy, reproducibility of results

Approximately 20% of patients with clinically lymph node negative penile carcinoma harbor occult inguinal lymph node metastases.[1] Various approaches to detecting occult nodal spread have been used and there is still much debate regarding what is considered the best management. The most invasive approach is elective inguinal lymph node dissection and the least invasive is watching and waiting. The major disadvantage of elective dissection is redundancy when the regional lymph node basin is not involved, which is the case in 80% of the patients.[2,3] Another factor to be considered is the accompanying substantial morbidity. The disadvantage of a watch and wait approach is possibly a worse prognosis when tumor involved lymph nodes are treated after they become palpable during followup.[4–6]

In theory, the sentinel lymph node concept is an attractive approach in the management of penile cancer. At our institute this technique has been used since 1994 and 140 procedures have been performed since then. Sentinel node biopsy in penile carcinoma proved to be of important diagnostic, prognostic and therapeutic value at the cost of only minor morbidity.[7,8] However, an important caveat of the sentinel node procedure for penile carcinoma is the false-negative biopsy.[9] A varying lymphatic drainage pattern could be one of the causes of these false-negative sentinel node procedures. To examine this situation we evaluated the reproducibility of lymphoscintigraphy for lymphatic mapping in patients with penile carcinoma by assessing the location and number of sentinel nodes as depicted on 2 subsequent lymphoscintigrams.

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Study received ethical committee approval.
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MATERIALS AND METHODS

Between January 2004 and December 2004, 20 patients with clinically node negative T2–3N0–1 penile carcinoma were prospectively enrolled in the study. In 17 patients the primary lesion was still present and in 3 patients the lesion was excised several weeks before lymphoscintigraphy. Mean patient age was 65 years (range 40 to 84). Informed consent was obtained from all patients and the protocol was approved by the ethical committee of our institution.

Imaging. The 2 lymphoscintigrams were performed on the day and the following morning before surgery. For logistical reasons 2 patients underwent both examinations and the operation on the same day. Twenty minutes after the patients received local anesthesia by lidocaine 10% spray, an average net dose of 59 MBq (range 49 to 76) ^{99m}technetium nanocolloid (Amsterdam Cygne, Eindhoven, the Netherlands) in a mean volume of 0.3 ml (range 0.2 to 0.3) was intradermally administered around the tumor with a 25 gauge needle. The injection was divided into 3 depots of approximately 0.1 ml. The tracer was administered proximally from the tumor or excision scar. For large tumors extending beyond the glans, the tracer was injected in the prepuce. Shortly after injection a 10-minute anterior dy-

namic study was performed with a dual-head gamma camera and subsequently, static anterior and lateral images were obtained at 30 minutes and 2 hours using simultaneous ^{57}Co flood source transmission scanning for orientation. The location of the sentinel node was determined using a ^{57}Co marker and indicated on the skin with indelible ink. Just before the second lymphoscintigraphic study a 5-minute static image was obtained as a point of reference for the injection sites. Subsequently, the procedure previously described was repeated in an identical fashion by the same investigator (RAVO). The mean interval between injection of the radiolabeled colloid for the first and second lymphoscintigrams was 21 hours (range 4 to 26). The mean radioactivity of the second injection, calculated on the basis of net administered doses, was 62 MBq (range 42 to 74).

Sentinel node biopsy. Shortly before surgery 1.0 ml patent blue dye (Blue Patenté V, Laboratoire Guerbet, Aulnay-sous-Bois, France) was intradermally injected around the tumor or excision scar. The sentinel node was identified and harvested after dissection of blue lymphatic vessels and detection of radioactivity with a gamma ray detection probe (Neoprobe®, Johnson & Johnson Medical, Hamburg, Germany).

Data interpretation and analysis. Lymphoscintigraphic images were evaluated with regard to similarity of depiction of draining lymph node basins and location and number of sentinel nodes. Criteria to distinguish the sentinel node from nonsentinel nodes were visualization of an afferent lymphatic vessel leading from the injection site to the lymph node or, in case of multiple nodes with no afferent vessels seen on the lymphoscintigram, the first lymph node appearing in the basin. Radioactive count rates for the visualized sentinel nodes were measured on 5-minute anterior images by using the region of interest software linked to the gamma camera. Count rates were measured at 3 points, namely during the last image of the first lymphoscintigraphy, during the image obtained just before the second lymphoscintigraphy and during the last image of the second lymphoscintigraphy. Count rates were calculated as the maximal number of counts per pixel. The count rate for hotspots visualized during the second lymphoscintigraphy was corrected for differences in the time between injection and acquisition of the last image, differences in net administered radioactivity dose, and residual radioactivity. The 95% confidence interval (CI) of the calculated reproducibility was determined using binomial distribution. The paired count rates for each hotspot were plotted to determine the variability of lymphatic flow and tracer uptake. The correlation coefficient between the 2 sets of scintigraphic results was calculated. A statistically significant difference was indicated by $p < 0.05$. In addition, the Bland-Altman method was used to determine the amount of agreement between the count rates at the 2 scintigraphic examinations. A logarithmic data transformation was performed because the differences were proportional to the mean count rate.

RESULTS

At least 1 sentinel node was visualized in all patients on the first lymphoscintigram. A total of 56 sentinel nodes (SNs) were observed in 38 basins, with a mean number of 2.8 nodes (range 2 to 5) per patient and a mean of 1.5 nodes (range 1 to 4) per visualized basin. Drainage to both groins was observed in 18 patients. Of these patients 1 also showed drainage to the prepubic area (fig. 1). There were 2 patients who had drainage to 1 groin only (1 to the left groin and 1 to the right groin).

The second lymphoscintigram revealed the same drainage pattern in all patients. The same number and side of nodal basins, and the same number of SNs were visualized at identical locations including the prepubic area (see table, fig. 1). Thus, the reproducibility of penile lymphoscintigraphy was 100% (95% CI 85%–100%).

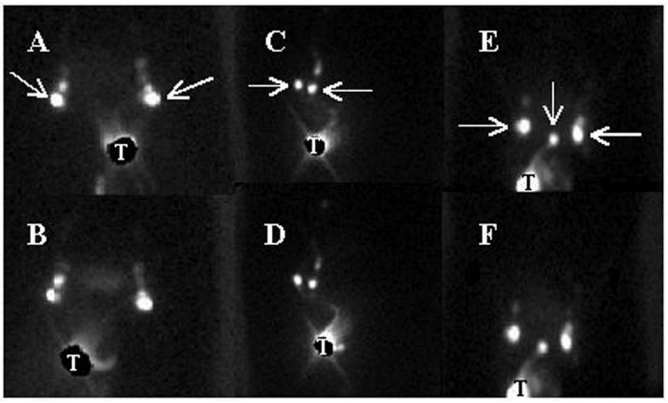

FIG. 1. Scintigraphic images in 3 paired sets demonstrate lymphatic drainage from primary tumor (T) to same nodal basins and same sentinel nodes. *A* and *B* (2-hour images obtained in 83-year-old man), bilateral drainage to 1 inguinal sentinel node in left groin and 1 sentinel node in right groin (arrows in *A*). In addition to sentinel nodes 2 second echelon nodes in right groin and 3 second echelon nodes in left groin are visualized. *C* and *D* (15-minute images obtained in 84-year-old man), unilateral drainage to 2 sentinel node (arrows in III) and 1 second echelon node in right groin. *E* and *F* (2-hour images obtained in 52-year-old man), 1 sentinel node in right groin, 1 sentinel node in left groin and 1 prepubic sentinel node (arrows in V). In addition to 3 sentinel nodes, 1 second echelon node in left groin and 1 second echelon node in right groin are visualized.

Radioactive count rates could be obtained for all 56 sentinel nodes. All hotspots visualized during the first lymphoscintigram showed an increase in radioactivity after the second injection of the radiolabeled colloid (fig. 2). The paired count rates for each hotspot are displayed in figure 3. The Pearson correlation coefficient for the count rates at the first and the second scintigraphic examinations was 0.69 ($p < 0.0001$). The differences in count rates between the first and second scintigraphic examinations were plotted against the means after logarithmic transformation according to the Bland-Altman method (fig. 4). The mean difference of the antilogs was 1.07 (95% CI 0.16–7.0). This means that for about 95% of the cases the count rate of the second measurement will be between 0.16 and 7 times the first measurement.

DISCUSSION

Variability in lymphatic drainage patterns might explain false-negative results in sentinel node biopsy. However, in the present study this assumption is enervated by the 100% concordance of the 2 lymphoscintigrams for the depiction of nodal basins, number of sentinel nodes and sentinel node location. Moreover, all hotspots that were visualized during the first lymphoscintigram showed an increase in radioactivity after repeat injection of the radiolabeled colloid, and the correlation of the count rates at first and second scintigraphic examinations was significant. Nevertheless, it is noteworthy that in 2 nodes (in 2 different patients) the uptake of the radiolabeled colloid at the first and second lymphoscintigrams was not equal. Both nodes were clearly hotter in the first study. This variability, probably caused by differences in the lymphatic flow, may result in scintigrams that are not reproducible when the uptake of the radiolabeled colloid is too low to be perceived.

In contrast to the excellent reproducibility of lymphoscintigraphy, variations between lymphatic mapping with radiolabeled colloid and mapping with blue dye occur fairly often, in our series in 30% of cases.[7] This may be caused by differences in the characteristics of the 2 tracers, the site of injection, and the difference in injected volume. For instance, blue