Lymphoscintigraphy in the Sentinel Lymph Node Technique for Breast Tumor: Value of Early and Late Images for the Learning Curve

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Key Words

Breast cancer · Lymphatic mapping · Sentinel node

Abstract

As the performance of early (H+1 to H+4) and late (D1) lymphoscintigraphic images raises organizational problems in outpatient surgery for breast cancer, only early images are generally obtained. The present study evaluated whether two series of images are better than one and defined the advantages of both methodologies. One hundred and eighteen patients with infiltrating breast carcinoma (T₀, T₁ and T₂) were included in the study: 87 in group A (early and late images) and 31 in group B (only early images). All patients received two peritumoral injections of ^{99m}Tc-sulfur colloid, 15–18 MBq (group A) and <15 MBq (group B). During the operation, the patent blue dye technique was associated with radioactivity detection. The two groups were comparable for histological type and tumor size and localization. Successful localization of sentinel nodes on early lymphoscintigraphic images was significantly greater for group B. The identification of a sentinel node focus on early lymphoscintigraphy increased by 10% during the study. Sentinel node detection by the isotopic method alone, or the two methods combined, was comparable for both groups. In radioactivity detection, the count rate for sen-

tinel nodes versus background (contralateral breast) was similar for the two groups. During the learning phase, two series of images gave a definite advantage. Subsequently, lymphoscintigraphy performed at +2 h was sufficient (the results for the two groups became indistinguishable).

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Introduction

Breast cancer screening has led to the treatment of an increasing number of subclinical cancers, but many axillary resections have proved negative because 75% of small tumors (<2 cm) are free of axillary metastases [1]. Nonetheless, the presence of an axillary node metastasis is a major prognostic factor in therapeutic strategy, and node status can only be determined by axillary resection and histopathological analysis of the nodes removed. Yet axillary resection, though essential to initial staging [2], can lead to postoperative morbidity, both immediately (lymphoceles) and subsequently (pain and lymphedemas). Given these circumstances, pre-and intraoperative sentinel node (SN) detection would seem to be an attractive alternative.

The SN concept was introduced in 1977 by Cabanas [3] for cancer of the penis and then applied to the staging

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of melanoma, with detection by vital stains [4]. The excellent results obtained in these studies rapidly led to promising applications of these techniques to breast cancer, through injection of a labeled colloid and detection by an intraoperative probe [5, 6]. With this approach, scintigraphic imaging is generally performed within 4–24 h after injection. If early images do not visualize the SN, late images are recorded [7, 8]. However, the development of outpatient surgery, with the organizational constraints involved [9], has tended to limit imaging to a single series performed 1–2 h after injection of the radiopharmaceutical.

The purpose of this study was to determine whether two series of images are preferable to a single series and to define the advantages of the two methodologies.

Materials and Methods

One hundred and eighteen patients with infiltrating breast carcinoma (T₀, T₁ and T₂) were included in the protocol from June 1999 to January 2001. This prospective study was approved by the ethics committee in 1999. For 87 patients (group A), the radiopharmaceutical was injected on the day before surgery, and for the other 31 (group B) on the day of surgery. All patients received two injections of rhenium sulfide (Nanocis®, Shering Cis Biointernational) performed peritumorally. Each syringe contained an activity of 15–18 MBq of technetium-treated Nanocis for group A and less than 15 MBq (10.5–15) for group B. Injection volume for both groups was 0.1 ml. For group A, images centered on the breast (included axilla, internal mammary and supraclavicular lymph nodes) were performed early (H+1 to H+4) and late (H+20); for group B, only early acquisition was performed just before surgery (H+1 to +1.5 h). All images (128 × 128 matrix) were in anterior incidence and in external profile of the breast studied; set imaging was 10 min. No shielding was performed for the injection sites. In the operating room, 10–15 min before surgery, about 2 ml of patent blue was injected peritumorally into all patients. The surgeon was guided by data from lymphoscintigraphy (LS). All surgeons were experienced in using detection probe. After tumor resection, the SN region was explored with a detection probe (Navigator, Tycon). Isolation of the SN for isotopic localization required a count rate equal to or twice that of the contralateral breast and/or the bluish appearance of a node rated at least ++ on a scale of 0 to +++ for the staining method. All patients underwent classical axillary resection (Berg stage I and II). Group assignment was not randomized, but based on whether a patient desired outpatient surgery (group B) or not (group A). In medical or surgical practice, a learning period is required before a new technique can be used routinely. All patients must be assured that results at least equivalent to those provided by the classical technique can be obtained in complete safety. In medical imaging, the same considerations apply for interpretation of a new examination, which requires a learning phase for optimal performance. During this period, the incidences used are not those adopted at the end of the study by an experienced observer, but those intended to allow optimal interpretation for an inexperienced observer.

The two groups (A and B) were compared for qualitative variables by the χ^2 test (or Fisher's test in case of a limited number of patients), and for quantitative variables by Student's t test (or the Mann-Whitney test in case of a limited number of patients); $p < 0.05$ was considered significant.

Results

Although the groups of patients were not randomized, they were comparable in age and in the histological type, size and localization of their tumors (table 1). A comparable proportion of patients had positive LS (74.7 and 77.4%, $p = \text{NS}$). During probe detection in vivo in the operating room, the count rate of the SN versus background (controlateral breast) was similar in the two groups: median 5.2 (1.2–110) for group A and 9.1 (0.92–245) for group B.

The success rate for SN localization in early images was significantly higher for group B (a single series of images) than for group A ($p = 0.03$, table 2). No difference

Table 1. Study population

Parameters	Group A	Group B
Patients	87	31
Mean age, years	57 ± 10.4	59.1 ± 14.9
Mean tumor size, mm	21.2 ± 2.3	17.9 ± 2.6
Histopathology ¹		
Ductal	67	23
Lobular	9	5
Other	11	3
Positive lymphoscintigraphy (%)	65 (74.7%)	24 (77.4%)
Tumor localization		
Upper external quadrant	47	17
Upper internal quadrant	16	4
Lower external quadrant	11	4
Lower internal quadrant	11	5
Central	2	1

¹ Exclusively invasive component.

Table 2. Success rate for localization of the SN by lymphoscintigraphy

Images	Group A	Group B
Early (H+1 to H+4)	48 (55%)	24 (77.4%)
Late (H+20)	62 (71%)	not applicable

Fig. 1. A, B Early images at H+2. C, D Late images at H+20. Anterior view (A, C) and left lateral view (B, D). Visualization of injection points on the left breast and uptake for the left axillary SN (seen only on late images).

Table 3. Success rate for detection of the SN (isotopic/patent blue)

SN localization	Group A	Group B
Isotopic method (%)	55/68 (81%)	21/27 (78%)
Patent blue method (%)	36/68 (53%)	16/27 (59%)
Both methods combined (%)	62/68 (91%)	23/27 (85%)

Table 4. Comparison of the success rate for SN localization by LS and surgery

	Positive LS	Negative LS	Total
Positive surgery	81	26	107
Negative surgery	8	3	11
Total	89	29	118

was noted between lymph nodes detected by early images and SN detected on delayed images. However, SN visualization for the latter group was significantly improved on late images (from 55 to 71%, $p < 0.05$). Figure 1 shows an illustrative case in which the axillary SN was only visualized late both anteriorly and laterally. Changes in the identification of an SN focus of both early and late lymphoscintigraphic images indicated that the diagnostic value of late images decreased during the study (fig. 2). In fact, the negative rate for LS decreased by 10% during the study (fig. 3).

SN detection was comparable for the two groups with the isotopic method (81 and 78%, $p = \text{NS}$) and also in the combined use of isotope and patent blue (91 vs. 85%, $p = \text{NS}$, table 3). The staining method was significantly less efficient, especially as compared to the combined use of isotope and patent blue dye (53 vs. 91% for group A and 59 vs. 84% for group B, $p < 0.001$). For the 118 patients in

Fig. 2. Lymphoscintigraphic learning curves: changes in sensitivity. A period corresponds to a 6-month interval with 40 patients for each group. Se 1 = Identification of an SN focus on early images; Se 2 = identification of an SN focus on late images.

the study, the concordance between SN visualization by LS and intraoperative detection (isotope and/or patent blue) was 71.2% (table 4). Intraoperative detection localized SN in 24% (26/107) of cases for which LS was negative. Surgery was negative in 11 cases, including 8 for which LS was positive.

Discussion

The search for SN in breast cancer is a recent and rapidly developing concept, which some authors consider to be the most significant therapeutic advance made within the last 10 years [10]. As outpatient surgery for this pathology has developed successfully in recent years [11], it would seem appropriate to adapt this detection technique to ambulatory conditions, if patients so desire.

Nanocis (Schering CIS Bio International), the tracer used in our study and the only one approved to date by the French drug administration, consists of rhenium sulfide colloids with a mean diameter of around 100 nm. Labeling is easy to perform and is reproducible. The tracer was injected peritumorally at two sites. The best choice of anatomical site remains controversial, and the options are intratumoral, peritumoral, subareolar, subcutaneous or intradermal. Most authors consider that the intratumoral site is unreliable because of possible tracer sequestration. The other injection modes have all provided excellent results, and no truly comparative studies have been con-

Fig. 3. Changes in negative detection rate in LS. A period corresponds to a 6-month interval.

ducted to show that one of these sites is preferable [12–14].

A small amount of tracer was injected into two peritumoral sites. There are two schools of thought concerning the injection volume required. American teams recommend the injection of a large volume (4–6 ml) to dilate the lymph ducts and open up the drainage to the SN. This choice increases of SN detected [10]. The activity of these nodes is then greater, which seems to facilitate intraoperative detection. European teams advocate the injection of a small volume (0.1–0.4 ml) of a sufficiently concentrated product in association with light massage of the injection area. This procedure is considered to respect physiological conditions to best advantage [15]. As published results for the two techniques are excellent, the debate remains open.

There is less controversy in the literature concerning the activity injected. The studies generally recommend 15–30 MBq (range 1.8–370) of Nanocis, depending on the interval between injection and surgery [16]. Some authors [17] feel that two injections (one the day before surgery and the other just before the intraoperative detection) are necessary if detection is performed on the day after injection. Our group A received only a single injection, with administration of increased activity. The SN count rates in vivo indicated that the increased activity was sufficient, as the percentage of successful SN detection was the same for both groups. For group A, which received additional activity, the SN count rate tended to be higher than

for group B (but the difference was not statistically significant). However, the confidence intervals overlapped considerably, which limited the statistical impact of this difference.

The proportion of positive LS (~70%) for both groups is in good agreement with the range in the literature (66–85%). No particular factors appear to account for the differences within this range [18].

The percentage of early positive LS differed significantly between the two groups, essentially because ‘doubtful’ results for group A were classified as negative prior to performance of the second series of images. This effect was particularly notable at the beginning of the study because of the learning phase required for interpretation of the images and the assurance that the patients would undergo a second imaging. The experience required, which parallels that necessary for the surgeon to obtain optimal results in intraoperative detection, involves around 20 patients [19, 20]. An analysis of figures 2 and 3 confirms the importance of the learning process, as the benefit of a second series of images was reduced with time. Negative results with LS decreased by 10% between the beginning and end of the study.

In our series, the isotope-patent blue association gave the best results, which confirms the consensus in the literature that a combination of three approaches (preoperative LS, dye injection and intraoperative probe detection) is most efficient for localizing and isolating SN [21, 22]. The results for the staining method alone show an SN detection rate of 66–93%. However, this method is not recommended for patients susceptible to atopy. The isotopic method alone is a more efficient method (a detection rate of 71–98%). Techniques combining scintigraphy with intraoperative probe detection and the staining method give an SN detection rate of 83–100% and a negative detection rate of 0–15% [4]. In fact, false-negative results with the SN procedure correspond to patients with noninvasive SN, but with histological involvement of the nodes removed by axillary resection. A combination of the staining technique with intraoperative probe detection gave a rate of 94% for SN and of around 0% for false-negatives [5].

In view of the good results obtained with probe detection and the staining method, some authors feel that LS is unnecessary [23]. Moreover, in our study, surgical excision of the SN was achieved in 24% of cases for which LS was negative. However, in some cases scintigraphic assessment is useful for other reasons. First of all, it can provide information on different drainage routes (internal mammary, supraclavicular). In fact, a decreasing order of

frequency has been determined for colloid transport by the external mammary system (85%), the transpectoral route (10%) and the internal mammary route (5%) [24]. This information could be of importance for postsurgical (notably radiotherapeutic) treatments. Furthermore, a recent study [25] found that 26.8% (11/41) of internal mammary metastases were LS-positive in this location, including 7.3% (3/41) for which internal mammary invasion was not associated with axillary involvement. However, the clinical impact of these observations seems limited, given the low recurrence of the disease in the internal mammary lymph nodes [26]. Less successful identification of SN has been reported when LS was not performed (98% with LS vs. 92% without) [23]. LS also provides more precise guidance for the surgeon, particularly for SN with a slightly atypical axillary topography (our of the typical axillary dissection area), allowing more rapid and reliable surgical exploration [27]. In a few cases, probe detection may fail to detect the SN despite LS positivity. In our study, the use of cutaneous landmarks for SN detected by LS might have helped account for the localization difficulties experienced by the surgeon. In the literature, these discordant cases have been attributed to the learning process for the surgical technique, especially for probe detection [20].

The recording of dynamic scintigraphic images at the time of injection is of definite value for localization of SN in melanoma. Indeed, the possibility, in melanoma, of an unforeseeable localization in a vast anatomical region requires images that are delocalized from the initial injection site. The usefulness of this procedure is less certain in breast cancer. Most authors deny any need for dynamic imaging [23] because the drainage area is more limited and quite predictable. However, the use of a large-field camera allows all possible drainage areas to be covered. The optimal interval between injection and imaging would appear to be 2 h, as no significant increase in the number of positive LS was obtained beyond that time point [28]. In our study, the significant decrease in the diagnostic value of late images over time tends to corroborate this observation. However, a considerable scatter effect can persist during early LS and hinder image interpretation. Indeed, the SN may be very difficult to detect because it is situated along the path of the artefact. In this case, late images can allow improved interpretation. However, experience tends to minimize these difficulties. On the other hand, a shorter interval between injection and imaging (<2 h) increases the number of negative LS and limits the possibility of localizing extra-axillary drainage [29].

Conclusion

A learning phase is important not only for surgical detection of sentinel nodes in breast cancer, as emphasized in the literature, but also for the practice of LS in nuclear medicine. During the period in which experience is being acquired, two series of LS images tend to improve interpretation. Subsequently, a single image performed

optimally 2 h after injection seems sufficient. LS, though considered unnecessary by certain authors and sometimes not performed, has various advantages, particularly in increasing the intraoperative detection rate significantly and in guiding the surgical act. The detection of SN in outpatient surgery requires an adaptation of the nuclear medicine facility to allow patients to benefit fully from the technique.

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