
Prospective Comparison of 3 γ -Probes for Sentinel Lymph Node Detection in 200 Breast Cancer Patients

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Previous reports have shown that axillary sentinel lymph node (ASLN) radiodetection allows accurate axillary staging for patients with early breast cancer. Radioguided surgery implies the use of a γ -probe to count the emitted radioactivity of marked ASLNs. Several γ -probes are commercially available, each with its own properties. The clinical impact of the type of γ -probe used for ASLN radiodetection remains to be evaluated. **Methods:** Three commercially available γ -probes were evaluated: a scintillator with a bismuth germanate crystal (probe A), a semiconductor with a cadmium telluride crystal (probe B), and a semiconductor with a cadmium zinc telluride crystal (probe C). Two hundred patients with early breast cancer were prospectively enrolled to undergo ASLN radiodetection and axillary lymphadenectomy. ASLN mapping consisted of injecting ^{99m}Tc-sulfur-colloid around the tumor. For each patient, sentinel lymph nodes were counted successively with the 3 probes and the sensitivity of each γ -probe was determined from ASLN residual activity. The results of detection rates and false-negative rates for each probe were compared. **Results:** Mean residual ASLN activity was 52 kBq (range, 0.07–189 kBq). Sensitivity was compared among the 3 probes and found to be best for probe A. The detection rate of probe A was significantly better than that of probe B (93% vs. 86%, $P = 0.05$) but not different from that of probe C (93% vs. 90%). No differences in false-negative rates were observed among the 3 probes. **Conclusion:** ASLN detection rate depends on the type of γ -probe used. Because failure to detect the ASLN leads to complete axillary lymphadenectomy, involving local morbidity and other sequelae, the type of γ -probe must be considered important for sentinel lymph node radiodetection.

Key Words: breast cancer; sentinel lymph node; γ -probe

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The sentinel lymph node concept, first described for penile cancer and melanoma, has recently been applied to early breast cancer staging (1–3). Axillary lymph node status currently remains one of the most important prognostic indicators in early breast cancer (4,5) and is of particular value in the choice of adjuvant therapy (6). If an axillary sentinel lymph node (ASLN) is detected, excised, and free of pathologic metastatic involvement, the patient is spared the morbidity of conventional axillary lymphadenectomy (7,8). Morbidity related to ASLN excision is significantly less than that related to axillary lymphadenectomy (9–11).

The ASLN may be detected using peritumoral or periareolar injection of lymphotropic products, stains, or radiotracers that map the regional lymph network of the tumor (12,13). The radiotracer approach involves the injection of a colloidal or other lymph node-avid agent labeled with a γ -emitter such as ^{99m}Tc to radioactively label the ASLN in situ. The ASLN can then be detected at surgery with a hand-held γ -probe (14).

The main criteria used to evaluate the ASLN technique are detection and false-negative rates (12,13). Detection failure leads to axillary lymphadenectomy and potential axillary morbidity (15,16). A false-negative result means the apparent lack of involvement of the ASLN in the presence of actual involvement of the ASLN or other lymph nodes. False-negative results can lead to inadequate treatment and, ultimately, to a risk of cure failure (17). The false-negative rate can be evaluated most definitively by concomitant ASLN detection and axillary resection (18).

Several types of γ -probes are commercially available and characterized according to their principle of detection (scintillators exploiting excitation phenomena and semiconductors exploiting ionization phenomena) and their collimation (19). The basic physical performance of a γ -probe can be described by its spatial resolution, sensitivity, and counting

rate linearity (20). Spatial resolution indicates the capacity of a probe to discriminate between target and background activity (21). Sensitivity characterizes the ability of a γ -probe to count a low activity (20). In the particular case of sentinel lymph node radiodetection, laboratory simulations found that the sensitivity of the γ -probe was the dominant performance factor (22).

To date, no published study has considered the impact of γ -probe sensitivity in the context of ASLN detection of early breast cancer clinically, rather than in laboratory simulations. Our working hypothesis was that the results relative to ASLN radiodetection do not differ as a function of the type of γ -probe used. We compared 3 commercially available γ -probes: a scintillator and 2 semiconductors. We first used ASLN residual activity to compare the sensitivity of these 3 probes and then tested our hypothesis on a prospective clinical series of 200 patients with invasive early breast cancer, in accordance with the legal recommendations relative to the rules of clinical research.

MATERIALS AND METHODS

γ -Probes

The 3 probes tested were Modelo 2 (probe A; Damri), a scintillator with a bismuth germanate (BGO) crystal, and the 2 semiconductors Navigator (probe B; Tyco), with a cadmium telluride (CdTe) crystal, and Neoprobe (probe C; Breast Care), with a cadmium zinc telluride (CZT) crystal. The main features of these probes are indicated in Table 1.

Clinical Series

From June 1999 to September 2001, a prospective series of 200 patients treated for invasive early breast cancer underwent ASLN detection with the 3 probes and concomitant complementary axillary lymphadenectomy. Each patient gave signed informed consent, in accordance with the legal recommendations relative to the rules of clinical research. The inclusion criteria were preoperative diagnosis of invasive early breast carcinoma, clinical tumor size of less than 3 cm (T0, T1, T2 < 3 cm), no palpable axillary node (N0), an indication for initial surgical treatment, and the signed informed consent form. Exclusion criteria were pregnancy, lack of preoperative diagnosis, and previous tumor excision or neoadjuvant chemotherapy.

The radiodetection method consisted of the injection of unfiltered ^{99m}Tc -labeled rhenium sulfur colloids (Nanocis; CIS Bio

International) superficially within the parenchyma around the tumor. An activity of 30–40 MBq in 2×0.1 mL of physiologic serum was used if the injection was performed on the evening before surgery, or 20–30 MBq in 2×0.1 mL if performed on the morning of surgery. Intraoperative detection was performed with the 3 tested probes: probe A and probe B for all patients plus probe C for the last 140 patients. The probes were always used in the same order: A, then B, then C. Probes A and C were used with an external detachable collimator, and probe B had an internal integrated collimator. The intraoperative detection protocol included successive counts of the chest wall (defined as background) and counts of each ASLN with each of the 3 probes.

The surgical technique systematically involved breast tumor excision, followed by a horizontal axillary incision to detect and remove 1 or more ASLNs, and a complementary functional axillary lymphadenectomy of the first 2 Berg levels.

A positive finding of an ASLN was defined as the intraoperative detection of a number of counts per second that was at least twice the background level.

The sensitivity of a probe is defined as the number of counts recorded by the probe per unit of source activity and is expressed in counts per second per kilobecquerel (20). To evaluate the sensitivity of the 3 γ -probes tested, immediately after surgical resection we used a scintillation well counter (COBRA II model 85003; Packard) calibrated with a ^{99m}Tc source to measure the residual activity of 72 ASLNs previously counted with the 3 probes. The ASLN activity used to calculate the probe sensitivities was decay corrected in accordance with the technetium period. Residual activity was expressed in counts per minute per kilobecquerel. Direct measurement of ASLN activity in a scintillation well counter allowed determination of the amount of residual activity in the ASLN relative to the injected dose. The sensitivity of each probe was determined by comparing the number of counts obtained with each probe during surgery with the residual activity of each ASLN. The results for 28 nodes from patients injected the morning of surgery and 44 nodes from patients injected the evening before surgery were considered.

Pathologic Analysis

No intraoperative histopathologic examination was performed. Each node was completely embedded in paraffin and cut into 2-mm-thick sections perpendicular to its long axis. Further analysis differed for ASLN and axillary lymphadenectomy. ASLNs were cut into ten 4- μm sections. Standard hematoxylin-phloxine-saffron staining was performed on levels 1, 4, and 7. In the absence of detectable metastasis or micrometastasis on these first sections, immunohistochemical labeling was performed on the 3 intermediary levels. A micrometastasis was defined as a metastasis less than or equal to 0.2 cm in diameter. For each node from the lymphadenectomy, one 4- μm section was cut from each block and stained with hematoxylin-phloxine-saffron but no immunohistochemistry was performed.

Definitions

The detection rate was defined as the number of patients whose ASLNs were identified by γ -probe counting relative to the total number of patients in the study. This rate was determined for each of the 3 probes. Considering only patients with at least 1 detected ASLN, the false-negative rate was defined as the ratio of the number of patients whose ASLNs were not involved but who had 1 or more involved nonsentinel axillary nodes in concomitant axillary lymphadenectomy, to the number of patients with 1 or

TABLE 1
Main Features of the 3 γ -Probes

Feature	Probe A	Probe B	Probe C
Probe	Modelo 2	Navigator	Neoprobe
Manufacturer	Damri	Tyco	Breast Care
Principle	Scintillator	Semiconductor	Semiconductor
Detector	BgO	CdTe	CZT
Collimator	Detachable	Integrated	Detachable
Diameter of the detector (mm)	5	14	14
Spatial resolution (cm)	0.6	1.3	0.3

TABLE 2
Clinical Characteristics of the 200 Patients

Clinical characteristic	Finding
Mean age	56 y
Clinical size of tumor, by TNM stage	T0 = 38 (19%); T1 = 91 (45.5%); T2 = 71 (35.5%)
Tumor site	
External upper quadrant	74 (37%)
Internal upper quadrant	21 (10.5%)
External lower quadrant	26 (13%)
Internal lower quadrant	8 (4%)
Union of external quadrants	23 (11.5%)
Union of internal quadrants	14 (7%)
Union of upper quadrants	32 (16%)
Union of lower quadrants	2 (1%)
Histologic size of tumor	12.14 mm (range, 3–30 mm)
Mean number of nodes removed	9.3 (range, 3–22)
Mean number of ASLN removed	2.2 (range, 0–7)

more lymph nodes involved, whether sentinel or not. This rate was determined for each of the 3 probes.

Statistical Method

The χ^2 test was used, with an α -risk of 5%, to compare detection and false-negative rates for the 3 probes.

RESULTS

Population Characteristics

The characteristics of the patients are indicated in Table 2. The T of TNM staging was used to distinguish the groups by clinical size of tumor.

ASLN Residual Activity and γ -Probe Sensitivity

The mean ASLN activity was 52 kBq (range, 0.07–189 kBq), as indicated in Table 3. Whether injection was performed the morning of the operation or the evening before, the percentage of injected activity in the ASLN was 0.15% of the injected dose (Table 3). The sensitivity of the probes is indicated in Table 4. Sensitivity was comparable for probes B and C. The sensitivity of probe A was 6-fold higher than that of probe B or probe C when injection was

TABLE 3
Residual Activity in ASLNs as Function of Dose Injected Around Breast Tumor

Parameter	Time of ^{99m}Tc injection	
	Evening before surgery (<i>n</i> = 28 ASLNs)	Morning of surgery (<i>n</i> = 44 ASLNs)
Mean injected activity (MBq)	34 (19.5–50)	33.8 (26.5–40)
Mean time from injection to intraoperative counting (h)	22 (17.5–23.25)	2 (1.5–6)
Mean ASLN activity (kBq)	52.6 (0.12–189)	52.37 (0.07–189)
Mean percentage of injected activity	0.15 (0.008–0.7)	0.15 (0.002–0.4)

Ranges are indicated in parentheses.

TABLE 4
Count Efficiency of the 3 γ -Probes as Function of Time Between Injection and Surgical Incision

Time of injection	Count efficiency (cps/kBq)		
	Probe A	Probe B	Probe C
Morning of operation	79 (0.6–285)	11.8 (2–973)	16.3 (1.8–91)
Evening before operation	16.02 (0.2–36)	4.43 (0.2–60)	4.26 (0.01–45)

Ranges are indicated in parentheses.

performed the morning of the operation and 4-fold higher when performed the evening before (Table 4).

Detection Rate

The radiodetection rates per probe are indicated in Table 5. The detection rate was significantly better with probe A than with probe B (93% vs. 86%, respectively; $P < 0.05$) (Table 5).

False-Negative Rate

Table 6 indicates the false-negative rate for each probe. No significant differences in false-negative rates were found among the 3 γ -probes tested (Table 6). For each patient with at least 1 ASLN detected and at least 1 lymph node involved, whether sentinel or not, the hottest ASLN was not involved in 12 cases with probe A or B and in 6 cases with probe C. Table 7 indicates the false-negative-rate for each probe if, with the same ASLN definition, only the hottest ASLN was analyzed (Table 7).

DISCUSSION

In the current study, a clinical comparison of 3 γ -probes (BGO scintillator and CZT and CdTe semiconductors) showed that they differ in sensitivity and detection rates for sentinel lymph nodes.

Whereas a radioactive source emits its γ -rays in a 4π solid angle, a γ -probe detects only a small fraction of them along its axis. Sensitivity, which indicates the efficiency of

TABLE 5
Radiodetection Rates with the 3 γ -Probes

Probe	No. of patients	No. of ASLNs detected	χ^2
A	200	186 (93%)	A vs. B, $P < 0.05$
B	200	172 (86%)	
C	140	126 (90%)	

a probe in detecting and counting radiation, corresponds to the number of counts per second per unit of source activity expressed in kilobecquerels. Our results showed that residual activity in the ASLN was approximately 50 kBq, corresponding to 0.15% of the injected dose (Table 3). It has been shown that the sensitivity of a scintillator is better than that of a semiconductor (23–25) and that the sensitivity of a CZT semiconductor is better than that of a CdTe semiconductor (21). In our experiment, the BGO scintillator (probe A) counted 4 times as much radioactivity as did the 2 semiconductors (probes B and C) for patients injected the evening before and 7 times as much for patients injected the morning of the operation (Table 4).

Spatial resolution and sensitivity differ depending on whether the probe is collimated. The purpose of collimation is to maintain maximum precision for axial localization of the target by counting only radiation from the target itself (25,26). Generally speaking, collimation improves spatial resolution but reduces sensitivity (20–23). For our comparisons, we used 3 commercially available collimated γ -probes without any modification: a scintillator with a BGO crystal, a semiconductor with a CdTe crystal, and a semiconductor with a CZT crystal (Table 1).

Our results showed that the sensitivity of the 3 γ -probes differed. On the basis of a prospective clinical series of 200 patients, these differences in physical performance were determined to have a clinical impact on the detection rate of ASLNs. The detection rate was 93% with the collimated BGO scintillator, 90% with the collimated CZT semiconductor, and 86% with the CdTe semiconductor (Table 5). This difference between the BGO scintillator and the CdTe semiconductor was statistically significant ($P < 0.05$) and may be an unrecognized cause of different success rates for ASLN detection. This is an important consideration, as detection failure implies that the patient will undergo axil-

TABLE 6
False-Negative Rates for the 3 γ -Probes

Probe	No. of patients	False-negative rate (γ -detection)	χ^2
A	200	6.7% (4/58)	NS
B	200	11.1% (6/54)	NS
C	140	14.3% (4/28)	NS

NS = not statistically significant.

TABLE 7
False-Negative Rates for the 3 γ -Probes If only Hottest ASLN Was Excised

Probe	No. of patients	False-negative rate (γ -detection)	χ^2
A	200	20.7% (12/58)	NS
B	200	22.2% (12/54)	NS
C	140	21.4% (6/28)	NS

NS = not statistically significant.

lary resection and thereby have a lower quality of life than will a patient undergoing only ASLN excision. This consideration is of particular importance for inexperienced surgeons, for whom the best of sensitivity is required to ensure detection of low-activity ASLNs.

In the current study, a comparison of the 3 probes showed no significant differences in false-negative rates (Table 6). Analysis of the relative impact of the choice of γ -probe for ASLN detection on the risk of a false-negative result would require investigation of a larger series because of the infrequency of this event (27). Isotopic activity counted in ASLNs is not predictive of metastasis (28,29). In the current study, the ASLN with the highest count was not the involved node in 20% of patient with at least 1 ASLN detected, whatever the γ -probe used (Table 7). Furthermore, a recent study has shown that false-negative results have little impact on the definitive choice of complementary treatment (30).

CONCLUSION

In summary, this study showed that the performance of γ -probes tested clinically affected ASLN detection rates. Among the γ -probes tested, the scintillator showed the best sensitivity and the best detection rate for ASLNs. The rate of ASLN detection depends not only on the skill and experience of the surgeon but also on the performance of the γ -probe. Given the low residual activity in the ASLN, sensitivity seems to be the main criterion for the choice of a γ -probe. In the current context of an international validation of ASLN detection in the surgical management of early breast cancer, it is important to consider the relative efficiency of γ -probes.

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