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Surgical sentinel lymph node biopsy in early breast cancer. Could it be avoided by performing a preoperative staging procedure? A pilot study

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: The aim of this pilot trial was to study the feasibility of sentinel node percutaneous preoperative gamma probe-guided biopsy as a valid preoperative method of assessment of nodal status compared to surgical sentinel lymph node biopsy.

Material/Methods: This prospective study enrolled 10 consecutive patients without evidence of axillary lymph node metastases at preoperative imaging. All patients underwent sentinel node occult lesion localization (SNOLL) using radiotracer intradermic injection that detected a "hot spot" corresponding to the sentinel node in all cases. Gamma probe over the skin detection with subsequent ultrasonographically guided needle biopsy of the sentinel node were performed. The percutaneous needle core histopathological diagnosis was compared to the results of the surgical biopsy.

Results: Preoperative sentinel node identification was successful in all patients.

Conclusions: The combination of preoperative gamma probe sentinel node detection and ultrasound-guided biopsy could represent a valid alternative to intraoperative sentinel node biopsy in clinically and ultrasonographically negative axillary nodes, resulting in shorter duration of surgery and lower intraoperative risks.

key words: **Sentinel Lymph Node Biopsy (SLNB) • Sentinel Node Occult Lesion Localization (SNOLL) • preoperative axillary node core needle biopsy**

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Background

Lymph node involvement is an important prognostic factor for patients with breast cancer. The sentinel node is defined as the first tumour-draining lymphatic filter, and its involvement by metastatic disease should predict the global nodal status of the specific patient. Skip metastasis in the context of a normal sentinel node is described as a very rare event [1].

In patients with clinically node-negative disease, sentinel lymph node biopsy (SLNB) had become the gold standard staging procedure, followed by axillary lymph node dissection (ALND) performed selectively in patients with previously proven (by SLNB) sentinel node metastases [2].

Considering the therapeutic consequences, involvement of the sentinel node by metastatic disease in breast cancer patients is of great interest to the breast surgeon in order to plan the surgical approach.

Unfortunately, the physical examination of the axillae can be inaccurate in identifying pathologic lymph nodes [3]. The same is also true for the pre-treatment imaging (with or without interventional procedures on the axillary node), characterized by a poor negative predictive value [4–8].

Using gamma probe combined with ultrasound- (US) guided percutaneous core needle biopsy (CNB) could increase the accuracy of identifying the sentinel node and allow a proper histopathologic diagnosis in order to avoid further SLNB.

The purpose of this pilot study was to assess this new preoperative diagnostic approach.

Material and Methods

This was a prospective, single arm, uncontrolled study. Consecutive patients with histologically confirmed invasive breast cancer were enrolled in the study. Main inclusion criteria were: women ⩾18 years old, invasive breast carcinoma, with no clinically positive axillary node and no history of any other malignancy. Multicentric cancer and previous excisional biopsy were exclusion criteria. The Sentinel Node Occult Lesion Localization (SNOLL) was performed in all patients the day before surgery. A dose of 5–10 (generally 7) mBq of technetium 99^{m}-labelled human albumin nanocolloid particles in 0.3 mL saline were administered by US-guided percutaneous injection in the area immediately surrounding the breast lesion, followed by injection of 0.2 mL saline using a 22 G needle. We used nanocolloid particles with a size range of 5–100 nm (Nanocoll®, GE Healthcare). After injection, antero-posterior and lateral lymphoscintigraphic projections were obtained to identify the presence of a sentinel node and to define whether the radiocolloid has shifted to other possible sites of drainage, such as the internal mammary, intramammary, contralateral axillary or supraclavicular nodes.

The hot spot was identified over the skin by the handheld gamma probe (Navigatog gps® RMD) and was examined using ultrasound Logos HI Vision Gold® (Hitachi) using a breast-dedicated linear array transducer.

The radiologist performing the US-guided biopsy established which lymph node corresponds to the hot spot under gamma probe guidance. We evaluated suspect US findings such as cortical thickening, especially if focal, markedly hypoechoic cortex, absence of the fatty hilum, large expansion, irregular shape, round shape, extracapsular tumoral extension or increased peripheral blood flow at Power Doppler. Lymph nodes with at least 2 of these criteria were considered pathologic, and we excluded suspicious lymph nodes.

Patients were placed in a supine or contralateral-side-down oblique position on the table, with the ipsilateral hand placed behind the head. Biopsies were performed in all patients by a single radiologist with more than 10 years experience in ultrasonography. CNB was performed with an automatic 18 G needle (Bard core biopsy Instrument®, Tempe, USA) after local anesthesia with 2% mepivacaine. All biopsies with a free-hand technique were performed under US guidance with direct visualization of the needle entering into the cortex of the node to confirm position of the needle tip in the appropriate location. Only 1 pass was made during sampling for each CNB of the hot spot node. The percutaneous biopsy was performed only if the lymph node corresponded to the hot spot.

We considered the biopsy procedure to be successful when the obtained sample contained a large portion of solid nonfatty tissue and/or sank in formalin to be stained with haematoxylin and eosin. The skin above the first radioactive node was marked by the radiologist with an indelible ink tattoo to assist the surgeon. The puncture zone was compressed and the presence of complications such as local pain or hematoma was evaluated.

The next day, in the operating room, radioactive lymph nodes were detected in all cases using the same gamma probe that was used to detect the hot spot for the US-guided preoperative imaging. Residual radioactivity was checked after surgery. Surgical SLNB was performed in all cases, followed by ALND in cases of positive percutaneous biopsy. The surgeon was able to recognize the sentinel lymph node biopsy marked by the radiologist with the skin mark and correlate with the results of the standard SLNB (validate the ability of the preoperative diagnostic method to correctly identify the sentinel node). Because the most frequent tumor site is the upper-outer quadrant of the breast, the surgeon generally used the same type of incision of the breast to identify the sentinel node using the gamma probe guide when the conservative surgery was performed. In different cases, the surgeon used a separate incision guided by the skin marker performed by the radiologist.

Removed sentinel lymph nodes were sent for immediate frozen-section analysis. The final histopathological diagnosis of SLNB was compared with the results of the CNB of the sentinel node. Both specimens were examined routinely by single-section and haematoxylin-eosin staining. The accuracy of percutaneous biopsy guided by US and gamma probe over the skin in the pre-operative staging was correlated with final pathologic reports of SLNB. Information on histological type and grade and biological characteristics (eg, receptor status or peritumoral vascular invasion of the primary carcinoma) were obtained from the pathology report of the breast specimen. For the pathological staging of the axillae, this study used the guidelines and terminology proposed by the seventh edition of the American Joint

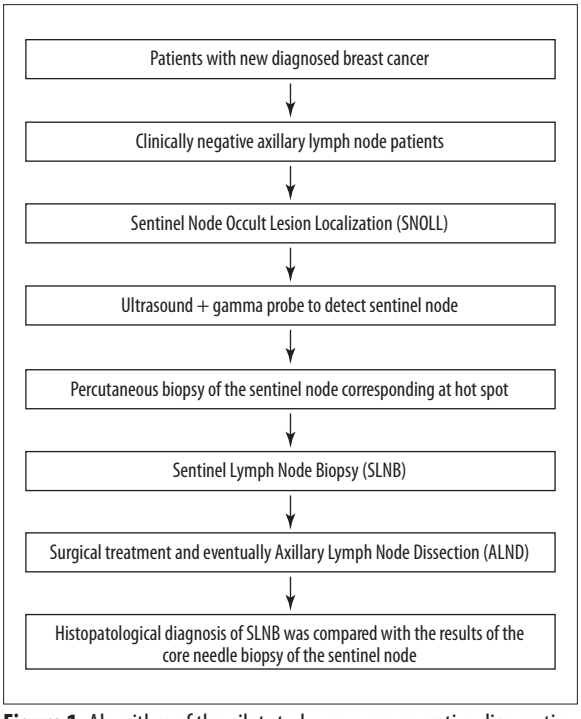

Figure 1. Algorithm of the pilot study: new pre-operative diagnostic approach using US and gamma camera probe over the skin to evaluate the axillary sentinel node.

Committee on Cancer staging manual. Figure 1 shows a simple algorithm of this pilot study.

Results

A total of 10 consecutive patients were enrolled in this study. The results are summarized in Figure 2.

Main patient characteristics are shown in Table 1 and include age, type of surgery, location of primary breast cancer, nodal stage at percutaneous biopsy, pathological nodal stage, and biological features of the breast tumor.

Sentinel node identification was successful in all patients, although there were no suspicious nodes at US examination. The hot spot was detected over the skin by gamma probe in all 10 patients, and was examined using US-guided CNB in all patients. Each of the patients had malignant lymphatic spread only into 1 axillary sentinel node. Multiple sentinel nodes were not detected and no patient had the sentinel node draining to different possible sites.

There were no major complications (eg, clinically important bleeding, nerve injury, or infection) related to the CNB procedure. One patient experienced a small amount of bleeding, which was stopped by simple local compression; this was considered a minor complication. In all patients, the samples obtained at CNB contained a sufficient amount of tissue for histopathologic analysis. There was no positive CNB for the detection of metastases.

Nodal metastases were found at final diagnosis in 2 of 10 patients (Table 1). ALND was performed in these 2 patients. In 1 patient the definitive histopathological report of SLNB expressed the presence of 1 micrometastasis that was not observed in the frozen section at the extemporary analysis. In the second patient, micrometastases were observed in the para-sentinel node at SLNB, but no macrometastasis in the sentinel node were found. The remaining 8 patients had both negative preoperative CNB and SLNB results. In all the surgically excised sentinel lymph nodes, the pathologist documented the sign of the previous core needle biopsy, verifying that the biopsied lymph node was really the sentinel node.

Discussion

In women with early breast cancer, SLNB has proved to be a safe and accurate method for evaluating axillary disease, and is associated with less morbidity than complete ALND [2].

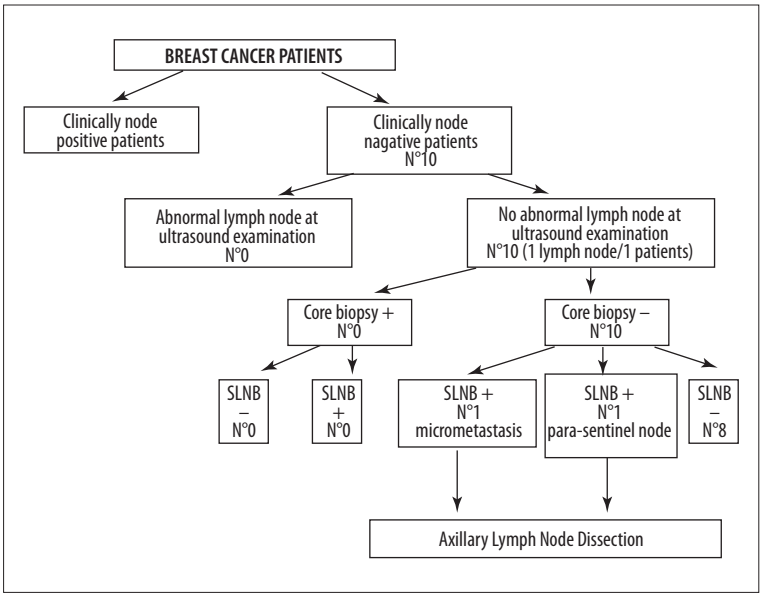

Figure 2. Flow chart representing axillary US, results of needle core biopsy and results of final pathological sentinel lymph node mnbiopsy (SLNB).

Table 1. Patient data and histopathologic results (sentinel node CNB and standard SNLB).

Patient	Age	Tumour location	Surgery	Status lymph node imaging	Sentinel node percutaneous biopsy	Sentinel node specimen	Sentinel node final staging	Tumour size staging	M+	Histo-type	Grade	Hormone receptor status	Her-2-neu	Peri-tumoral vascular invasion
1. LP.F.	46	Right lateral upper quadrant	QUAD	–	–	–	+ NIa (1/24)	T2 3.4 cm	–	Lobular	G2	Yes	No	No
2. B.D.	27	Right lateral upper quadrant	QUAD	–	–	–	N0	T1 1.5 cm	–	Ductal	G2	Yes	Yes	No
3. C.T.	56	Left internal lower quadrant	CT + QUAD	–	–	–	N0	yT1c 1.4 cm	Lung	Ductal	G3	Yes	Yes	Yes
4. B.M.	68	Right lateral upper quadrant	QUAD	–	–	–	N0	T1c 1.2 cm	–	Ductal	G2	Yes	No	No
5. P.L.	68	Left lateral lower quadrant	QUAD	–	–	–	N0	T1c 1.6 cm	–	Ductal	G2	Yes	No	Yes
6. S.A.	45	Right lateral upper quadrant	QUAD	–	–	–	N0	T1b 1.0 cm	–	Ductal	G2	Yes	No	No
7. T.E.	48	Left	Maste-ctomy	–	–	–	N0	T1c 1.7 cm	–	Ductal	G2	Yes	Yes	Yes
8. R.S.	38	Left lateral upper quadrant	QUAD	–	–	–	N0	T1c 1.8 cm	–	Ductal	G3	No	Yes	No
9. B.G.	81	Right lateral upper quadrant	QUAD	–	–	–	N0	T1c 1.1 cm	–	Ductal	G2	No	No	No
10. M.A.	50	Left	Maste-ctomy	–	–	–	+ Nmi (1/11)	T2 2.1 cm	–	Ductal	G2	No	Yes	No

"–" – negative result.

Nevertheless, SLNB is not a problem-free procedure. Patients with documented lymph node involvement at the SLNB usually require further ALND as a second step during the same surgical procedure, favoring scar tissue formation and edema, and increasing the rate of complications and the surgery time [7]. Hospital stays are also increased in case of SLNB + ALND compared with ALND alone as suggested by Goyal et al. [9].

Pre-operative knowledge of an axillary metastatic sentinel lymph node could avoid the intraoperative SLNB. In fact, in cases with positive preoperative lymph node CNB, a complete ALND can be performed directly as a primary procedure. The obvious advantages of this approach are suggested by several authors that used different methods to localize the abnormal lymph node before surgery. Altomare et al. [4] had avoided SLNB in 30% of patients with a final pathology of metastatic lymph node by performing fine needle aspiration cytology (FNAC) of the abnormal sonographic axillary node. Sever et al[10] proposed the use of intradermal peritumoral microbubble US contrast agents injection and lymphatic imaging to identify and localize the sentinel node in the preoperative stage.

Many studies [4,6,8,11] report a moderate diagnostic sensitivity of the percutaneous biopsy of a morphologically abnormal axillary lymph node and an even lower sensitivity in cases where the biopsied lymph node has an unaltered appearance and the procedure is performed randomly [12]. But how can you differentiate the sentinel node from a regular lymph node especially when the pathological sentinel node is not always the largest one or the morphologically abnormal one? Britton et al. [13] found metastatic involvement in 12% of the lymph nodes with normal sonographic appearance, and declared that US-guided biopsy would miss the sentinel node in 36% [14] of the cases, resulting in false-negative axillary CNB, partly due to failure to identify the lymph node or the abnormal region of the lymph node to biopsy. Furthermore, there is little information in the literature regarding the accuracy criteria for performing an axillary US [15]. Adding gamma probe over the skin could increase the sensitivity of percutaneous US-guided biopsy, providing a good approximation of detection of "true" sentinel lymph node.

Theoretically, it is well established that a negative sentinel lymph node is currently equivalent to disease-free axillae. The majority (about 70%) of women with clinically negative axillae will prove to be microscopically negative as well [16]. On the other hand, it is also documented that a certain percentage of the false-negative sentinel node CNBs are for micrometastases or isolated tumor's cells [5,17]. There is no current evidence showing that submicroscopic metastases predict an adverse outcome or that they require treatment [2,16]. Several authors [18–20] demonstrated the absence of axillary recurrence during long-term follow-up in patients with sentinel node micrometastasis in which ALND was not performed.

Micrometastases are often associated with false-negative sentinel node biopsies. Several studies were done, and one of the most recent addressing this question participated in an IBCSG trial that compared complete ALND (used in cases with positive SLNB) to follow-up (in patients with node-free macrometastasis disease) [21]. Similarly, we speculate that patients with micrometastases and false-negative sentinel node proved by CNB, gamma probe and US-guided biopsy, may not need intraoperative SLNB, particularly since follow-up with ultrasonography, and eventually PET, could detected early axillary disease that can be adequately treated later by therapeutic axillary dissection.

Nevertheless, avoiding the morbidity of SLNB must be weighed against the risk of harboring axillary micrometastases that may potentially seed occult metastatic disease after a percutaneous biopsy. In the clinical context, considering a patient's expected life span and associated health problems, this situation might be defined as a "minimal acceptable risk". SLNB has also a false-negative rate (5% according to Veronesi et al. [21]) and this is the reason why these patients are generally subject to regular follow-up with clinical and US examination of the axilla. We also suggest that cases with negative sentinel node percutaneous gamma probe and US-guided biopsy should be similarly monitored.

Several studies reported that the sensitivity of US in identifying axillary adenopathy has been increased by cytology sampling of the suspicious lymph node; the approach is limited by the high rate of false-negatives results of the aspiration tecnique [22,23].

In other words, the unacceptably high rate of false-negatives results makes nodal FNAC an unreliable method that cannot be used to avoid intraoperative SLNB. As known, there are a number of possible reasons for a false-negative result at FNAC: inadequate specimen sampling, a low number of metastatic lymph nodes, small-sized metastasis, and failure to visualize "true" sentinel lymph node during the US examination of the axilla. The latter, in our opinion, is the cornerstone of our pilot study.

The aim of this study was to verify the feasibility of this innovative method to detect and to biopsy the sentinel node in order to improve confidence in identification of the metastatic lymph node in the preoperative phase. In our opinion, there are 2 important elements to be considered.

First, the CNB allows collection of more tissue than does FNAC. The decision to use large CNB rather than FNAC was made because the amount of tissue taken is greater than with the latter, providing a high negative predictive value. It is reasonable that increasing the volume of tissue obtained from 1 step by CNB can be more effective than multiple samples of FNAC to obtain a final diagnosis. The sensitivity of the method could be increased by performing several CNBs (2–3 or 3–5 samples according to Garcia-Ortega [24]) from the cortex of the presumed sentinel node.

Moore et al. [22] do not recommend the use of CNB because of the potential complications of this procedure (eg, bleeding and nerve damage); previous reports have shown that such interventional procedures in all breast cancer patients are not cost-effective.

On the other hand, complications can be reduced if the procedures are performed by an experienced, dedicated breast radiologist (within the Breast Unit). Another reason for preferring the CNB to FNAC is less operator dependence. As described [4,24,25], CNB has a higher sensitivity in detecting lymph node macrometastases. This feature is of major importance because, in early the stage, the lymph nodes usually have normal findings at US, and they are frequently small in size. Consequently, the cutting needle must be sampling only the cortical layer if performed in a technically adequate way.

The second element is identification of the axillary sentinel lymph node preoperatively using the gamma probe over the skin.

Combining the use of the gamma probe, with which the "true" sentinel node can be identified with reasonable confidence, and the US-guided CNB that can avoid the sampling error dictated by the reasons mentioned above (in case of FNAC), the diagnostic sensitivity should, theoretically, increase.

As a minimally invasive staging procedure, US-guided lymph node biopsy under percutaneous gamma probe surveillance seems attractive because it provides information during the preoperative period that could allow avoidance of intraoperative SLNB if the sentinel node is negative, and hence, avoid ALND in case of micrometastasis or isolated tumor's cells.

The most relevant predictive factor for sentinel node metastases is the primary carcinoma peritumoral vascular invasion. It could be suggested that whenever this pathology (or other findings [26]) finding is found in association with a negative percutaneous sentinel node biopsy performed under US gamma probe guidance, intraoperative SLNB should be mandatory.

Only 2 studies in the literature – Motomura et al. [27] and Hollerweger et al. [12] – have reported the pre-operative use of gamma probe over the skin to detect axillary sentinel node under US guidance. The latter had evaluated the sentinel node's location using the gamma probe and then marked it with a hook wire, while Motomura [27] used the gamma probe combined with FNAC to obtain the sample.

To our knowledge, no other published study evaluated gamma probe-assisted sonographic localization combined with CNB of the presumed sentinel node as a "one -step" procedure in the pre-treatment phase of breast cancer patients.

Of course, there are several obvious limitations of this study. First, this is a pilot study that analyzed the feasibility of a new pre-treatment method proposed for detecting the sentinel node. Second, the patient population is small because this is a pilot study, hence the results do not have a statistical impact. However, the concepts presented could improve the quality of lymph node sampling, particularly in early breast cancer patients. This could be particularly useful in cases that need SLNB before neoadjuvant chemotherapy [28].

The pre-treatment sentinel node evaluation technique described in this pilot study had shown a perfect concordance with the histological findings, even if the number of subjects enrolled in this study was relatively low. The accuracy and the clinical implications of the method must be confirmed by larger studies.

Conclusions

In conclusion, gamma probe-assisted sonographic localization associated with CNB of the sentinel node in early breast cancer patients could be a feasible and accurate new method. Further studies should investigate the definitive role of this method in pre-treatment breast cancer staging. Particularly, it is necessary to investigate the clinical impact of this method in avoiding SLNB, especially in cases when percutaneous sentinel node CNB is negative, without primary carcinoma peritumoral vascular invasion, in clinically node-negative breast disease patients.

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Conflict of interest statement

This research was not supported by any organization and none of the authors has a financial relationship that would represent a conflict of interest.

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