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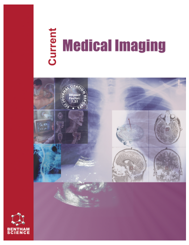

RESEARCH ARTICLE

The Sentinel Node and Occult Lesion Localization (SNOLL) Technique Using a Single Radiopharmaceutical in Non-palpable Breast Lesions

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Abstract:

Background:

In order to perform a full surgical resection on non-palpable breast lesions, a current method necessitates correct intraoperative localization. Additionally, because it is an important prognostic factor for these patients, the examination of the lymph node status is crucial.

Objective:

The aim of this study was to evaluate the efficiency of the sentinel node and occult lesion localization (SNOLL) technique in localizing non-palpable breast lesions together with sentinel lymph node (SLN) using a single radiotracer, that is, nanocolloid particles of human serum albumin (NC) labeled with technetium-99m (^{99m}Tc).

Methods:

39 patients were included, each having a single non-palpable breast lesion and clinically no evidence of axillary disease. Patients received ^{99m}Tc-NC intratumorally on the same day as surgery under the guidance of ultrasound. Planar and single-photon emission computed tomography/computed tomography lymphoscintigraphy were performed to localize the breast lesion and the SLN. The occult breast lesion and SLN were both localized using a hand-held gamma-probe, which was also utilized to determine the optimal access pathway for surgery. In order to ensure a radical treatment in a single surgical session and reduce the amount of normal tissue that would need to be removed, the surgical field was checked with the gamma probe after the specimen was removed to confirm the lack of residual sources of considerable radioactivity.

Results:

Breast lesions were successfully localized and removed in all patients. Pathological findings revealed breast carcinoma in 11/39 patients (28%) and benign lesions in 28 (72%). Axillary SLNs were detected in 31/39 (79.5%) patients. The metastatic involvement of SLN was only seen in two cases.

Conclusion:

While the identification rate of the SNOLL technique performed with an intratumoral injection of ^{99m}Tc-NC as the sole radiotracer in non-palpable breast lesions was great, it was not fully satisfactory in SLNs.

Keywords: Lymphoscintigraphy, Non-palpable breast lesion, Radio-guided surgery, Radiotracer, Sentinel lymph node, SNOLL.

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1. INTRODUCTION

Breast lesions can now be discovered very early on before they become clinically palpable, thanks to the widespread use of mammography and ultrasound for the early detection of breast cancer, and the fact that a lot of asymptomatic women now routinely carry out breast screening [1 - 4].

The constant increase of early, non-palpable breast cancer diagnosis requires a comprehensive approach in order to achieve optimal surgical treatment. The main challenge with non-palpable breast lesions is that they must be localized precisely enough to allow an acceptable appropriate excision to be performed in a single surgical session, avoiding excessive removal of healthy tissues. It is for this reason that efforts are being made to create an ideal technique that will enable this

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level of exact localization [5, 6]. At the European Institute of Oncology, Milan, Italy in 1997, radio-guided occult lesion localization (ROLL) was initially proposed [7]. The technique enables preoperative localization of non-palpable breast lesions. Sentinel lymph node (SLN) biopsy candidates typically have early-stage breast cancer and a status of no suspicious lymph nodes. The sentinel node and occult lesion localization (SNOLL) technique was developed as a result of combining ROLL and SLN biopsy in a single surgical procedure [5 - 7].

The purpose of this study was to evaluate the efficiency of the SNOLL technique for simultaneous non-palpable breast lesion and SLN localization using a single radiotracer, that is, nanocolloid particles of human serum albumin (NC) labeled with technetium-99m (^{99m}Tc).

2. MATERIALS AND METHODS

2.1. Patients

All patients provided a written informed consent prior to their individual clinical findings being used for research in this single-center prospective study, which was given local ethics committee approval. The study included a total of 39 consecutive individuals with a mean age of 47.2 ± 12.2 years (range 19-77 years) who had single, non-palpable, and suspected malignant breast lesions as detected by ultrasound (US) and/or mammography. Clinical evidence of axillary disease was not present in any of the patients. Following US, mammography, or both, they were programmed for surgery and SLN biopsy. Clinical or radiological manifestations of metastatic disease, which are the existence of multicentric lesions or diffuse microcalcifications, palpable axillary lymph nodes, previous breast surgery, radiotherapy, pregnancy, and lactation, comprised the exclusion criteria.

2.2. The SNOLL Technique

The SNOLL procedure was carried out in a one-day protocol with scheduled surgery. In this study, a single radiopharmaceutical, that is NC (Nanocoll, Nycomed Amersham Sorin, Saluggia, Italy) with a size range of 10-80 nm, was used. NC was labelled with a ^{99m}Tc. On the same day of surgery, every single dose of ^{99m}Tc-NC containing 8-15 MBq of ^{99m}Tc in a volume of 0.2 ml was injected intratumorally under US guidance using a high-resolution linear probe with a frequency of 7.5-12 MHz (Toshiba Aplio 500, Toshiba Medical Systems Co. Ltd., Otawara, Japan) (Fig. **1**). After the radiopharmaceutical administration, the injection site was gently massaged to improve drainage of the radiopharmaceutical. Planar scintigraphy and single-photon emission computed tomography/computed tomography (SPECT/CT) were performed using a dual-head SPECT/CT system (GE Infinia Hawkeye 4, GE Healthcare, Buckinghamshire, UK) equipped with low-energy high-resolution parallel-hole collimators (Fig. **2**). Planar acquisition consisting of the anterior projection obtained with the patient lying supine and the lateral projection obtained with the patient's arm on the same side as the lesion in abduction was acquired 15-30 min and 3h after the radiopharmaceutical injection with a 256 × 256 matrix and zoom factor 1.0. SPECT/CT was started following the acquisition of delayed planar images. A step-and-shoot technique of 25 seconds per frame for a total of 64 frames was used to obtain SPECT images in a 128×128 matrix. An iterative reconstruction algorithm was used to recreate the SPECT data, with 2 iterations and 10 subsets of parameters. To be used for attenuation correction and anatomical localization, the CT component of the imaging was obtained promptly after the SPECT acquisition using the following parameters: a slice step of 10 mm, a current of 2.5 mA, and a voltage of 140 kV. After

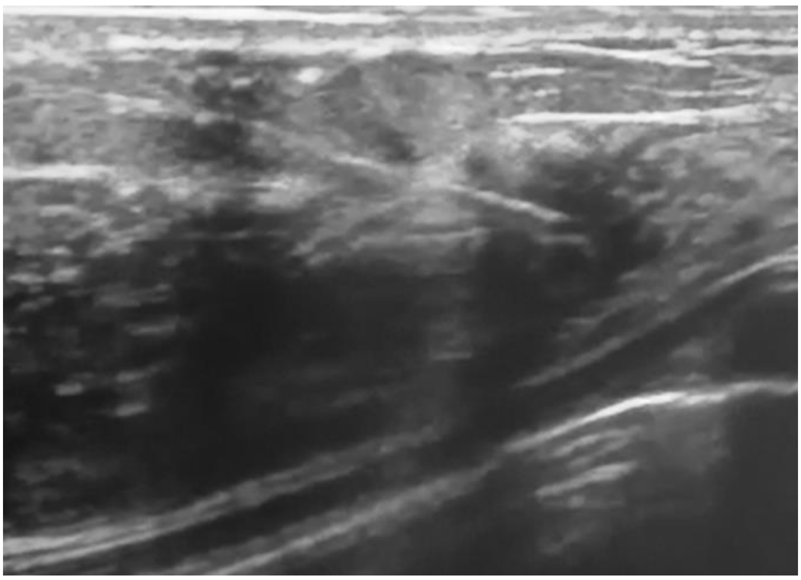

Fig. (1). Nanocolloid particles of human serum albumin labeled with ^{99m}Tc were injected intratumorally under US guidance using a needle.

completing the preoperative diagnostic imaging studies, the patient was placed in a supine position with the arm extended laterally at 90 degrees to the body. The cutaneous projection of the SLN was then marked on the skin using permanent ink.

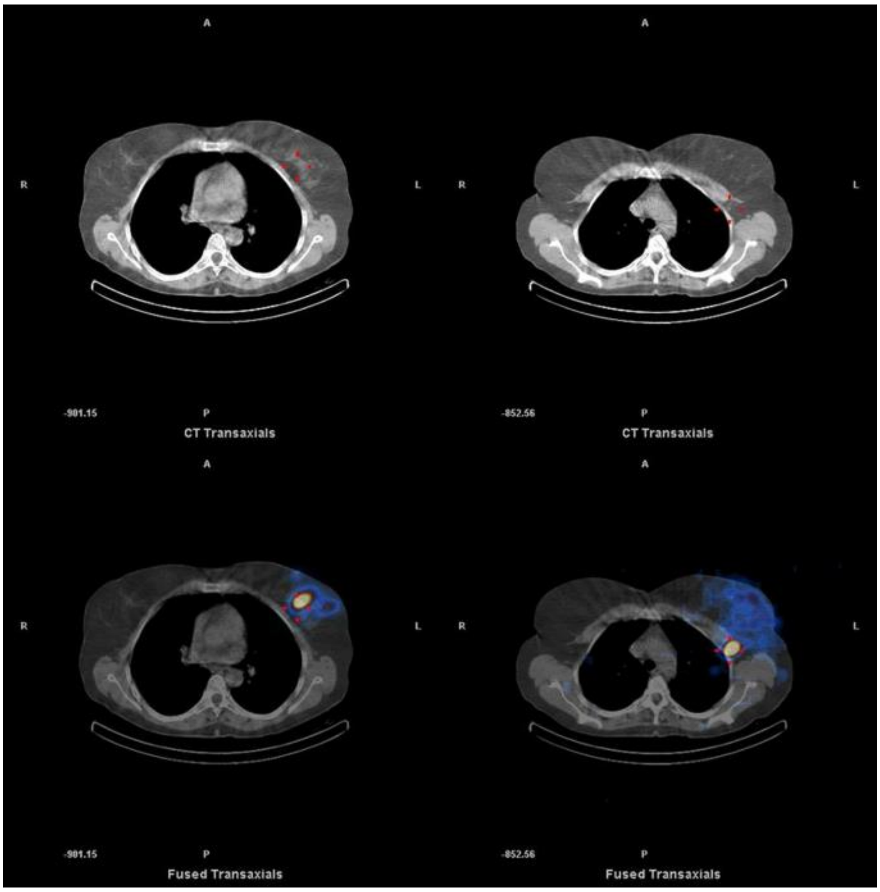

Fig. (2). Axial CT and fused SPECT/CT images revealed the left breast lesion as well as the axillary sentinel lymph node.

Fig. (3). Intraoperative breast lesion localization under gamma probe guidance.

2.3. Surgery

The breast lesion of each patient was surgically excised under general anesthesia, with a gamma-probe guidance (Europrobe, EuroMedical Instruments, Le Chesnay, France) (Fig. **3**). After excision, the specimen was checked with a gamma-probe once removed from the surgical bed, and then the surgical bed was reexamined using a gamma probe to check for any residual radioactivity. The gamma probe was likewise used in the identification and removal of the SLN. To ascertain whether the surgical specimen was malignant, an intraoperative frozen section examination was carried out promptly. If an invasive carcinoma was diagnosed, an SLN biopsy was then performed. The resected specimen of the SLN was also subjected to intraoperative examination. If metastatic involvement of the SLN was found, axillary dissection was performed immediately. All surgical specimens were examined in serial sections using haematoxylin-eosin staining and immunohistochemistry using anti-cytokeratin antibodies to determine the existence of macrometastases, micrometastases, or isolated tumor cells.

3. RESULTS

In all 39 individuals, non-palpable breast lesions were successfully localized and removed (Table **1**). A carcinoma was found in 11/39 (28.2%) patients' surgically excised breast lesions, while benign lesions were found in 28/39 (71.8%) patients, according to the final histopathological analysis. All of the histopathological findings are shown in Table **2**. The average size of a localized lesion was 10.1 ± 5.7 mm (range 4.5-38 mm). Breast lesions were excised with negative surgical margins in 31/39 (79.5%) of the cases. Eight patients had involved margins of invasive carcinomas in 2 cases and benign lesions in 6 cases.

Table 1. The clinical characteristics of all patients in the study.

Parameter	Value (%)
Patients	39
Age (y)	-
Mean ± SD	47.2 ± 12.2
Range	19-77
Radiological classification	-
BI-RADS 4	36 (92)
BI-RADS 5	3 (8)
Lesion localization	-
Upper outer quadrant	22 (56)
Lower outer quadrant	7 (18)
Upper inner quadrant	6 (15)
Lower inner quadrant	4 (11)

Table 2. Histopathological findings of the surgically removed breast lesions.

Histopathology	Value (%)
Benign lesions	28 (72)
Fibrocystic disease	10 (26)
Fibroadenoma	8 (21)
Adenosis tumor	1 (3)
Others	9 (22)
Carcinoma	11 (28)
Non-invasive	-
Ductal carcinoma *in situ*	1 (3)
Invasive	-
Invasive ductal carcinoma	9 (22)
Invasive cribriform carcinoma	1 (3)
Dimensions (mm)	-
Mean ± SD	10.1 ± 5.7
Range	(4.5-38)
Margins (mm)	-
>10	1 (3)
5-10	11 (28)
1-4	19 (48)
0 (involved)	8 (21)

Table 3. Sites and status of removed sentinel lymph nodes.

-	Value (%)
SLN location	-
Axilla	40 (98)
Axilla plus IMC	1 (2)
SLN status	-
Metastatic SLNs	2 (5)
Non-metastatic SLNs	39 (95)

Abbreviations: IMC, internal mammary chain; SLN, sentinel lymph node.

Table **3** summarizes the results of lymphoscintigraphy. It was possible to identify axillary SLNs in 31 of 39 (79.5%) patients, including those who did not need SLN biopsy because the breast lesion was revealed benign in the intraoperative frozen section examination. The mean number of SLNs identified was 1.3 ± 0.6 (range 1-3). Internal mammary chain SLNs, one of the nodes located outside the axilla, were detected in 1/39 (2.6%) patient. SLN biopsy was carried out in 11/39 (28.2%) patients with diagnosed breast carcinoma. A total of 41 SLNs were removed. A complete three-level lymphadenectomy was performed on two individuals (18.2% of the 11 breast cancer patients) who had metastatic disease.

All patients tolerated the complete SNOLL process without any problems being noted.

4. DISCUSSION

The results of the present study confirm the data of previous studies that the SNOLL technique is reliable for locating and removing non-palpable breast lesions [4 - 7].

A method that aims to both accurately intraoperatively localize occult neoplastic lesions and reliably identify SLN is necessary given the increased incidence of non-palpable breast tumors, which are known for having low risk of metastatic lymph nodes upon detection [4, 8]. For this purpose, a number of techniques are currently in use, such as intra-operative US, carbon localization, skin tagging with US, and the commonly applied wire-guided localization.

Combining the ROLL with SLN biopsy, SNOLL is a method that precisely detects and eliminates a non-palpable occult breast lesion, avoiding all the disadvantages of more conventional approaches [5, 9 - 11]. It is also quick and patient-friendly due to its low invasiveness. In addition to enhanced convenience of use and the resection special control provided by a hand-held gamma-probe, it delivers a higher rate of clean margins of resected specimens, resulting in a reduced rate of reoperation [12]. Finally, the cosmetic outcome is much improved by the smaller volume of the resected breast gland [6, 13].

Several studies comparing the ROLL and wire-guided methods have been carried out [11, 13, 14]. The ROLL method has significantly decreased the rate of reoperations in terms of resection radicality [10]. According to Nadeem *et al*.'s research, 83% of patients treated with ROLL had clean margins, compared to 57% of those treated with wire-guided localization [13]. Proportions of 87.5% and 62.5%, respectively, for the ROLL and wire-guided methods were reported by Medina-Franco *et al*. [15]. Van Esser *et al*.'s multi-center, randomized clinical research revealed a 15% advantage in the clean margin rate obtained using ROLL [16]. Also compared was the cosmetic effect following surgery. In contrast to wire-guided localization patients, who assessed the effect as good at 46% and very good at 54%, ROLL patients rated it as good at 25% and very good at 75% [13, 15].

Two different types of ^{99m}Tc carriers are used in the original SNOLL approach created by the European Institute of Oncology in Milan [17]. A non-palpable breast lesion can be easily identified by macroaggregates of human serum albumin, which include particles large enough not to be evacuated by lymph vessels surrounding the tumor and instead remaining at the site of injection. Smaller nanocolloid particles can then easily enter lymphatic vessels and flow freely to the SLN, where they build up to make it identifiable [5, 7, 14].

The authors of previous studies have emphasized that applying the SNOLL approach with a single radiotracer can save time and cost, as well as simplify the procedure [10, 17, 18]. For the simultaneous performance of ROLL and SLN detection, Feggi *et al*. suggested using a ^{99m}Tc-NC intratumorally and superficially. Both the excision of occult breast lesions and the localization of the SLN were successfully accomplished by the technique, with a success rate of 100% and 97.3%, respectively [17]. Lavoue *et al*. came to similar conclusions after injecting ^{99m}Tc-NC just peritumorally above and below the tumor [10]. While non-palpable breast lesions were excised from all patients, the 90% SLN recognition rate was not entirely satisfactory, indicating the need for additional technique development. De Cicco *et al*. reported a high rate of localization of lesions and SLN with intratumoral injection of ^{99m}Tc-NC (94.7% and 88.6%, respectively) [7]. In the present study, the SNOLL technique, characterized by US-guided intratumorally injection of ^{99m}Tc-NC, showed an excellent localization rate of occult breast lesion in 100% of cases. The findings of this series demonstrate that SNOLL has a high rate of success, which is consistent with the findings of earlier research [4 - 7, 10, 17, 19]. In SLN localization, we achieved a lower rate of 79.5% using this technique compared to previous studies [7, 10, 17]. One of the reasons for the lower detection rate of SLN in our population may be the small sample size. Other potential explanations include the varying structure and size of the breast, blockage of a lymphatic channel, or a significant invasion of cancerous cells into the lymph node. Despite the proper application of the procedure, the SLN is undetected in a tiny proportion of patients because some of these potential factors are uncontrollable [6, 20].

Given the possible advantages of preoperative scintigraphic mapping over intraoperative gamma-probe guiding alone in terms of accuracy improvement and morbidity reduction, it is strongly advised. Conventional planar imaging, however, may not always offer a precise anatomic localization of the identified nodes prior to surgery. SPECT/CT is an integrated system that provides a combination of functional and anatomical information, increasing the diagnostic value of the procedure [21]. Lerman *et al*. also provided evidence of the benefits of SPECT/CT over planar imaging [22]. The planar approach had a SLN detection rate of 84% and hybrid imaging had a detection rate of 90% among 157 individuals with early-stage breast cancer. In 44/142 (30%) of the patients with negative planar imaging in a multicenter trial by Jimenez-Heffernan *et al*. [23], SLN was detected by SPECT. According to one study, SPECT/CT may detect SLN in up to 53% of patients with negative planar imaging [24].

The assessment of false-negative/positive planar results that may occur as a result of uptake from extranodal foci, such as lymphoedema, skin contamination, or vascular uptake, has become possible *via* hybrid imaging [25]. The "shine-through" effect might be the root of results from planar scans that are falsely negative. Lerman *et al*. [22] speculate that this effect may be to blame for 50% of the instances where SLN is missed by 2D imaging. Husarik *et al*. reported a "shine-through" effect as the cause of undetectable SLNs in 14% of patients, which were detected on SPECT/CT [26]. In our study, SPECT/CT identified SLNs, 2 of which were located extra-axillary, which were missed in planar imaging in 23.07% of the patients. On the other hand, some authors have reported that 2-15% of false-positive planar data were identified by SPECT/CT as non-nodal sites of uptake foci, the most common cause of which was skin contamination [22, 24, 26, 27]. In 10.26% of our patients, SPECT/CT enabled the identification of false-positive planar results, often interpreted as contamination.

Several limitations of this study should be acknowledged. One of these limitations is the small sample size. Another limitation of the study is the lack of any postoperative cosmetic evaluation. The last of the limitations is that the study was conducted in a single institution, requiring a multicenter study to generalize the results.

CONCLUSION

In conclusion, the easy-to-perform SNOLL technique with US-guided intratumoral injection of ^{99m}Tc-NC as the sole radiotracer represents a useful and feasible choice for the localization of non-palpable lesions of the breast. However, the lower SLN identification rate compared to different approaches necessitates studies with a larger sample size. Besides these, combining SPECT/CT with the conventional imaging approach for lymphatic mapping and SLN localization in breast cancer patients seems to increase the detection and anatomical localization of sentinel nodes, but further research is necessary to reveal the potential advantages of preoperative scintigraphic mapping against intraoperative gamma-probe guidance alone.

LIST OF ABBREVIATIONS

SPECT/CT	=	Single-photon Emission Computed Tomography/computed Tomography
SNOLL	=	Sentinel Node and Occult Lesion Localization
ROLL	=	Radio-guided Occult Lesion Localization

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Clinical Research Ethics Committee of the Ankara Numune Training and Research Hospital (registration number: E-17-1489).

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committee, and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

Informed consent was obtained from all participants.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data and supportive information are available within the article.

FUNDING

None.

CONFLICT OF INTEREST

Dr. Bedri Seven is on the editorial advisory board of the journal Current Medical Imaging.

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