Radio-guided occult lesion localization for nonpalpable suspicious breast lesions: A novel technique

S. P. Somashekhar, Shabber S. Zaveri, K. Venkatachala, Parmeshwaran*, Raveesh, Siddappa****

*Departments of Surgical Oncology, *Nuclear Medicine and **Radio-diagnosis, Manipal Comprehensive Cancer Center, Manipal Hospital, Bangalore, India*

For correspondence:
Dr. S. P. Somashekhar, Department of Surgical Oncology, Manipal Comprehensive Cancer Center, Manipal Hospital, Airport Road, Bangalore - 560 017, India. E-mail: somusp@yahoo.com

ABSTRACT

Background: Breast screening programs and increased self-awareness has led to increased identification of early breast cancers. Up to 25% of mammographicaly identified lesions are nonpalpable, which require a precise technique to localize and excise completely. Radio-guided occult lesion localization (ROLL) is a technique, which uses hand held gamma probe to accurately localize and completely excise occult beast lesions. ROLL can also be combined with sentinel lymph node biopsy (SLNB) for early breast cancers. This is a minimally invasive approach with least morbidity and better patient compliance. **Materials and Methods:** 25 cases underwent ROLL for nonpalpable breast lesions. ^{99m}Tc-sulphur colloid was injected into the center of the lesion under ultrasound guidance preoperatively. No guidewire localization was performed. Under general anesthesia, surgical excision of the lesion was carried out using the hand-held gamma probe. Fifteen patients were diagnosed with early breast cancer with clear margin status. These patients also underwent SLNB at the same procedure. **Results:** Fifteen out of 25 cases were found to harbor invasive breast cancer. The pathological margins were clear of tumor in all of these patients. The sentinel node was identified in all cases. In four out of the 15 cases, sentinel node harbored occult metastases. **Conclusion:** ROLL is a useful method for precise, three-dimensional localization of impalpable breast tumors with results comparable to those achieved by surgery of palpable lesions. Furthermore, ROLL is feasible in connection with sentinel node biopsy in the same setting. It is performed as a day-care procedure with good cosmesis.

Key words: Breast cancer, localization, nonpalpable breast lesions, radio-guided occult lesion localization

How to cite this article:
Somashekhar SP, Zaveri SS, Venkatachala K, Parmeshwaran, Raveesh, Siddappa. Radio-guided occult lesion localization for nonpalpable suspicious breast lesions: A novel technique. Indian J Surg 2007;69:57-61.

INTRODUCTION

The widespread use of breast imaging techniques as well as mammographic screening has remarkably increased the proportion of nonpalpable invasive and preinvasive lesions detected during the last 10 years. Breast screening programs and increased self-awareness has led to increased identification of early breast cancers. Up to 25% of mammographicaly identified lesions are nonpalpable.[1] Precise localization of the clinically occult lesion is critical in order to perform breast conserving surgery without jeopardizing sufficient free tissue margins and to optimize the cosmetic outcome. This can be achieved by accurate localization of the occult lesion, appropriately planned surgical incision and excision of an adequate volume of breast tissue compatible with complete surgical excision of the tumor.

Detecting, diagnosing and treating these tumors is a surgical challenge. Traditionally, the localization of the tumor is done by guidance of a wire inserted

Paper Received: August, 2006. **Paper Accepted:** February, 2007.
Source of Support: Nil. **Conflict of Interest:** None declared.

under radiographic control [Wire Guided Localization (WGL)].[2,3] The insertion of a wire may be technically difficult leading to an imprecise wire placement. Migration, displacement or transection of the wire may occur. Furthermore, the procedure is uncomfortable for the patient and the wire may also harm a member of the surgical team or the pathologist examining the resection specimen.

Other techniques for preoperative localization of nonpalpable breast abnormalities include needle localization biopsy (NLB), dye injection under radiological guidance, perforated grids or stereotactic methods. Ultrasonography, computed tomography and magnetic resonance imaging have also been used for localization of such lesions.

Radioguided occult lesion localization (ROLL) has emerged as a novel technique in surgery of impalpable breast lesions inspired by sentinel node biopsy (SNB).[4] In ROLL, radioisotope injection adjacent to or into the lesion is performed under ultrasonographic or stereotactic guidance preoperatively. Intraoperative tumor localization is carried out searching for the maximal radioactivity by gamma-probe designed for sentinel lymph node localization.

The technique was pioneered by Dodd *et al* in 1996 at the European Institute of Oncology, Milan, applying an intratumoral injection of ^{99m}Tc-labelled human albumin colloid with particle size large enough to retain at the injection site (macroaggregates).[5] In order to ensure the accurate placement of the injection and to assist the surgeon in localizing the lesion, breast scintigraphy superimposing has been performed to confirm the position.[6] Recently, the original technique has been simplified performing the localisation without breast scintigraphy or contrast medium injection and mammography.[7] However, it is critical that the lesion is recognizable in breast ultrasonography, when using an ultrasonographically guided radioisotope injection without breast scintigram or mammogram. ROLL has also been performed in combination with wire guidance[8] or placing a titanium seed containing iodine-125 (commonly used for the brachytherapy of prostate cancer) adjacent to the tumor.[9,10] The centering of the tumor with a hand-held gamma-probe under radioactive guidance helps the removal of the lesion with adequate free margin of healthy tissue. The tumor edges are easily controlled using a gamma-probe while the radioactivity decreases clearly outside the tumor. Furthermore, it is easy to check residual radioactivity from the wound to ensure that the tumor is excised radically. The control of margins using wire localization is more difficult because of wire displacement or migration or when the tip of the guide wire is distant from the lesion after an unsuccessful wire placement.

The aim of this study was to apply the technique of ROLL for impalpable, mammographically detected BIRADS 4 and 5 tumors at our center.

MATERIALS AND METHODS

Twenty-five consecutive cases of impalpable (occult), mammographicaly detected lesions presenting to Manipal Comprehensive Cancer Center during the period January 2002 to January 2006 were recruited into this study after approval from the Manipal Hospital Research Ethics Committee. Preoperative diagnosis of breast lesions was performed by clinical examination (to document that the index lesions were non-palpable) and mammography and sonomammography.

The ultrasound uses a system, US lexicon (U0-U6) to categorize the lesions, which is similar to BI-RADS® system (American College of Radiology) to categorize the lesions:[11,12]

BI-RADS 0/ U0- need additional imaging evaluation
BI-RADS 1/ U1- negative
BI-RADS 2/ U2- benign findings
BI-RADS 3/ U3- probably benign- short interval follow-up suggested

BI-RADS 4/ U4- suspicious abnormality- consider biopsy
BI-RADS 5/ U5- highly suggestive of malignancy
BI-RADS 6/ U6- known biopsy proven malignancy

Following written informed consent, preoperatively on the day of surgery, patients were injected with 0.1 ml (1 mCi) ^{99m}Tc- sulphur colloid into the centre of the lesion using a 25 G needle under ultrasound or stereotactic guidance (3 cases in this study). Radiographic contrast (0.1 ml urografin) was injected in the 3 cases that underwent stereotactic localization. The injection of radio-isotope was done by the consultant nuclear medicine physician in the nuclear medicine department under USG-guidance. When injections were done under mammographic guidance (three cases in our study), it was done by the same person in mammography suite. Results showed that radiation doses are low and no additional procedures are required for protection of staff, provided the usual procedures for biohazards are in place. All precautions were taken according to the recommendations of the International Commission on Radiological Protection Isotope loaded syringe was placed in a lead shield and carried in a lead coated box. The dose limit under IRR99 for employees exposed to ionizing radiation is 20 mSv per annum and clearly no member of staff will approach 10% of this (or even the 1 mSv dose limit for a member of the public). Routine whole body monitoring of staff is therefore not required.[13] Cumulative whole-body doses to

the surgeon and other personnel for 100 operations correspond, at most, to approximately 10% of the annual dose limits for the general population.[14,15]

Immediately after the injection, lateral and cranio-caudal mammograms were carried out to confirm the position of the injectate [Figure 1]. Patients localized by ultrasound also had the location of the index lesion marked on the skin. No wire localization was performed.

In the operation theatre, under general anesthesia, the lesion is localized with the help of a gamma-probe placed on the skin of the breast at the site of injection previously marked. Surgical excision (lumpectomy with 1 cm margin of surrounding tissue in all directions) of the occult lesion was carried out through a circum-areolar/ curvilinear skin incision, depending on the location of the index lesion, under guidance of a gamma-probe. The index lesion corresponds to the area of highest counts. The post-excision biopsy cavity was evaluated for any residual radioactivity. The excised specimens were marked for orientation to the pathologist and specimen radiography was performed. Further, immediate re-excision was dictated by clinical findings on intraoperative evaluation of the excision specimen with the gamma-probe, hot counts in the residual cavity wall or specimen radiography reveals the lesion to be close to the excision margins.

Frozen section analysis of the excision specimen was carried out to document the tumor histology. In case of invasive malignancy, sentinel lymph node biopsy was carried out at the same procedure using the currently accepted technique.

Histopathological examination of the specimen documented the specimen size, tumor size, tumor histology, margins status and the nearest radial margin in mms. A minimum of 10 mm radial margin is acceptable.

If a further reexcision was carried out subsequently based upon the final histology report, the procedure is termed a second therapeutic procedure.

All procedures were performed as day-care.

RESULTS

Twenty-five patients underwent ROLL at our institute for impalpable breast tumors from January 2002 to January 2006. The mean age of the patients was 52 years (range 45 to 68 years). Tumor was located in the upper outer quadrant in 15 cases, inner quadrants in five cases and outer central quadrant in five cases. The type of mammographic abnormality, pathological findings and sentinel node status are described in Table 1. Duration of the procedure ranged from 15 to 25 minutes (average 22 minutes).

Frozen section analysis of the resected specimen was carried out in all cases. None of these patients had positive or close resection margins requiring immediate re-excision. Size of the lesions ranged from 4 mm to 11 mm (average size 7.3 mm). On histological assessment, invasive ductal carcinoma was present in 14 patients, one had ductal carcinoma *in situ* and one had atypical

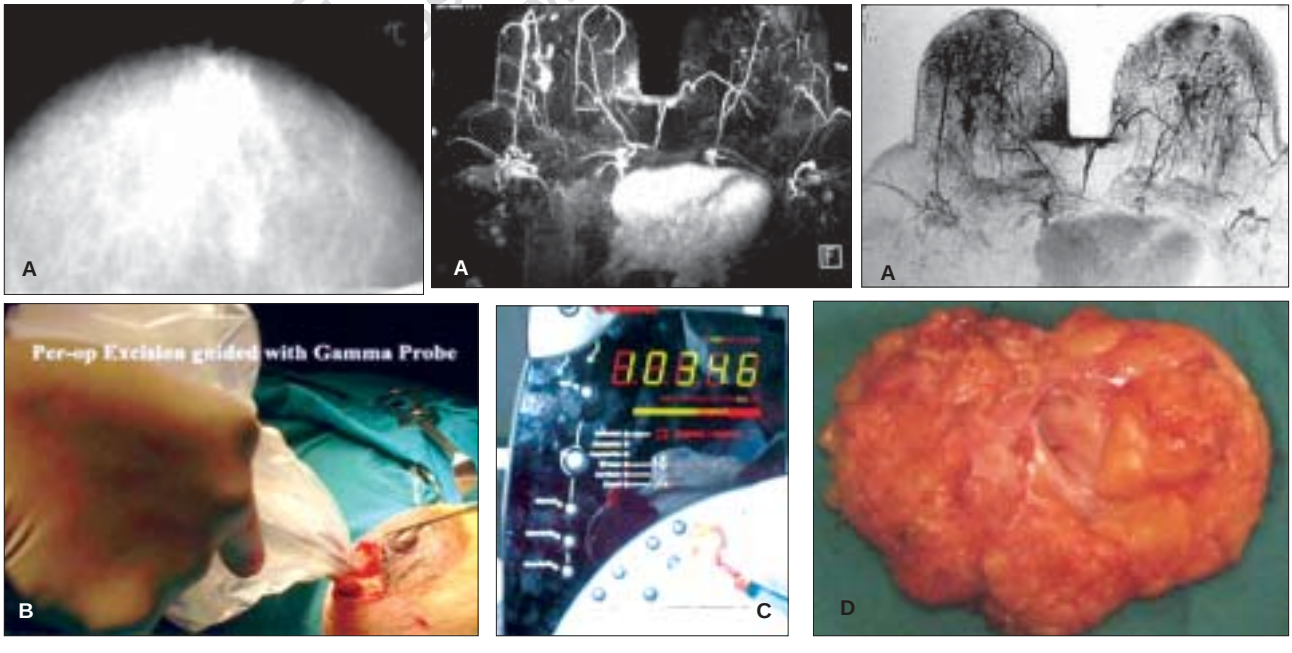

Figure 1: A. BIRADS-4 suspicious non-palpable lesion detected on Mammography. Contrast MRI shows hypervascualrity and early wash out of contrast-Suspicious for Malignancy. B. Localisation. C. Confirmation The intensity and frequency of the auditory signal are directly proportional to the radioactivity detected-Hand Held Gamma probe with Counter. D. Excised specimen after ROLL - Lesion in the centre

Table 1: Mammographic abnormality, localization, pathology and sentinel node status

Mammographic abnormality	BI-RADS score	Method of localisation	Lesion size (mm)	Histo-pathology	Sentinel node biopsy	Sentinel node status
Microcalcification	5	Ultrasound	10	IDC	Yes	Negative
Asymmetric density	4	Ultrasound	6	Fibroadenosis	No	-
Opacity	4	Ultrasound	8	Fat necrosis	No	-
Microcalcification	5	Ultrasound	5	IDC	Yes	Negative
Spiculated mass	5	Ultrasound	10	IDC	Yes	Positive
Microcalcification	5	Ultrasound	4	IDC	Yes	Negative
Opacity	4	Ultrasound	8	Fibroadenoma	No	-
Spiculated mass	5	Ultrasound	8	IDC	Yes	Positive
Asymmetric density	4	Ultrasound	5	IDC	Yes	Negative
Spiculated mass	5	Ultrasound	11	IDC	Yes	Negative
Microcalcification	5	Ultrasound	7	Ductal carcinoma ***in situ***	No	-
Spiculated mass	5	Ultrasound	9	IDC	Yes	Negative
Asymmetric density	4	Ultrasound	4	Fibroadenosis	No	-
Spiculated mass	5	Ultrasound	10	IDC	Yes	Negative
Opacity	4	Ultrasound	5	Atypical hyperplasia	No	-
Asymmetric density	4	Ultrasound	6	Fibroadenosis	No	-
Spiculated mass	5	Ultrasound	9	IDC	Yes	Positive
Asymmetric density	4	Ultrasound	8	Fibroadenosis	No	-
Microcalcification	5	Stereotactic	6	IDC	Yes	Negative
Spiculated mass	5	Ultrasound	10	IDC	Yes	Positive
Opacity	4	Ultrasound	7	Fibroadenosis	No	-
Spiculated mass	5	Stereotactic	5	IDC	Yes	Negative
Opacity	4	Ultrasound	8	Fibroadenosis	No	-
Spiculated mass	5	Stereotactic	9	IDC	Yes	Negative
Asymmetric density	4	Ultrasound	5	Fibroadenosis	No	-

BI-RADS score, Breast imaging reporting and data system, IDC - Invasive ductal carcinoma

hyperplasia. Rest nine cases had benign lesions. Breast conservation surgery was carried out with SNB using combination of radio-isotope and blue dye- ^{99m}Tc-sulfur colloid and methylene blue dye in all 14 cases with invasive carcinoma in the same setting. 1 ml methylene blue (total of 4 ml) was injected into the walls of the lumpectomy cavity. Axillary node dissection was performed only if the sentinel node is positive; if sentinel node is negative, no axillary node dissection was carried out. Four patients had occult axillary node metastasis on SNB. They underwent axillary node dissection. No second therapeutic procedure was needed for residual disease in reexcised specimen. There were no systemic reactions as a result of the radiotracer or methylene blue dye injections.

Patients with invasive ductal carcinoma received adjuvant therapy based on currently accepted guidelines. None of these patients had recurrence on a median follow-up of 18 months (range: six to 40 months).

The patients were asked to report their cosmetic results as fair/ good/ excellent (what they actually felt compared to preoperative appearance) at the end of six weeks and the results were analyzed. Twenty out of 25 patients (80%) reported that the cosmetic results were excellent and rest 20% reported it as good.

DISCUSSION

ROLL technique was first described using ^{99m}Tc-labelled human macroaggregrate albumin at the European Institute of Oncology in Milan.[5] When ROLL is combined with sentinel node biopsy using the Milan technique, two injections are needed, (i) intratumoral ^{99m}Tc-macroaggregrates of human serum albumin, (ii) subdermal ^{99m}Tc-nanocolloid. This is because ^{99m}Tc-macroaggregrates of human serum albumin localize to the tumor and ^{99m}Tc-nanocolloid is taken by the lymphatics leading to the identification of the sentinel node. In our study, we used ^{99m}Tc- labelled sulphur colloid, which localized to the primary tumor as well as the sentinel lymph node.

The localization time either using ultrasonography or stereotactic guidance has been found significantly reduced compared with guide wire placement. The length of the surgical procedure was reduced with ROLL (average time taken - 22 min). As regards to the radiation exposure, ROLL seems safe to the patient as well as to the medical staff due to the very short half-life of ^{99m}Tc of only 6h and the low dose gamma radiation used.[16]

All studies evaluating ROLL have concluded it as easy and accurate method for a surgeon to find an occult breast lesion and excise it with adequate free tissue margins. Clear margins were obtained in a significantly higher percentage of cases with ROLL as compared to WGL in several studies.[4,6-10,17-22]

ROLL has been found superior to the wire-guided resection as regards to achieve free tissue margins.

ROLL also enables reduced excision volume and better lesion centering within the specimen compared to wire localization.[17] Consequently, even the cosmetic results seem better when using ROLL. Furthermore, the results achieved by ROLL have been fully comparable to those obtained in breast conserving for palpable cancer as regards to sufficient free tissue margins as well as the size of the excised specimen related to the tumor size.[7]

This study has shown that a single intramural injection of ^{99m}Tc-sulphur colloid for ROLL and sentinel node biopsy is a feasible technique with accurate localization thereby simplifying the previous methods described. According to our experience, tumor localization has been successful in all the cases and at least 10 mm free margins have been achieved in all our cases after completion of the primary operation. The cosmetic outcome in all the patients was good/ excellent.

ROLL and simultaneous SNB

A few studies have addressed the feasibility of ROLL in connection with lymphoscintigraphy and SNB.[6,8,9,18-20] Alternatively, a subdermal injection of ^{99m}Tc-labelled small particle human albumin colloid may be used for SNB and an intratumoral injection of ^{99m}Tc colloid with the larger particle size for ROLL.[18] Furthermore, ROLL and SNB have been performed also using the same radioisotope (Nanocoll®) injecting half of the dose of intratumorally for ROLL and the other half more superficially to facilitate the transportation to the lymph nodes[6] or even applying a single intratumoral tracer injection for both ROLL and SNB.[7,8] In centers where sentinel node biopsy protocol is carried out, simultaneous performance of ROLL and SNB seems very feasible in the management of early breast cancer.

CONCLUSION

ROLL is a useful method for three-dimensional localization of impalpable breast tumors with results comparable to those achieved by surgery of palpable lesions. Furthermore, ROLL is feasible in connection with SNB in the same setting. It is performed as a day care procedure with good cosmesis.

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