Radioguided Surgery for Nonpalpable Breast Tumors Following Neo Adjuvant Systemic Therapy

Original Article

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ABSTRACT

Background: The tumor burden in the breast can be markedly decreased following Neoadjuvant chemotherapy (NAC). Nevertheless, surgical excision of the residual tumor, or the tumor bed in cases of complete response is required. Accurate intraoperative tumor localization is essential. Wire-guided localization is currently being the most commonly used, yet, with several drawbacks. As a result, localization techniques using radio-isotopes were developed, including radio guided occult lesion localization (ROLL) and sentinel-node and occult-lesion localization (SNOLL). Over the past decade, ROLL has become popular due to its numerous benefits.

Aim: To verify the efficiency of radio guided surgical management of breast cancer patients with nonpalpable residual breast lesions post-NAC.

Patients and Methods: This is a prospective cohort study undertaken at the National Cancer Institute (NCI), Cairo University between April 2021 and 2023 on female breast cancer patients with clinically nonpalpable breast lesions post-NAC.

Results: Our study included 52 female patients with breast cancer post-NAC. The highest pathological complete response rate was observed in triple-negative patients. The median scar length was 4.5 cm. The largest volume of breast tissue excised was 8×6 cm and the smallest was 3×2 cm with a median excision size of 6×4 cm. Thirty three patients were submitted to sentinel lymph node biopsy and 19 patients underwent axillary lymph node dissection. The maximum number of positive lymph nodes (LN)s in patients who underwent sentinel lymph node biopsy was 2LNs. All pretreatment clips were retrieved successfully with no major complications. ROLL positive margin rate was (3.8%).

Conclusion: ROLL is superior to wire-guided localization for nonpalpable breast lesion localization, with many advantages as reaching a higher percentage of clear margins in spite of smaller specimen size and scar length with less complications. SNOLL can be performed during the same procedure. Therefore, we recommend ROLL in nonpalpable breast lesion localization.

Key Words: Breast-conserving surgery, neoadjuvant chemotherapy, radio-guided occult lesion localization, sentinel lymph node and occult lesion localization.

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INTRODUCTION

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer-related deaths among women. Neoadjuvant chemotherapy (NAC) has become an essential part of modern breast cancer treatment, particularly for those with locally advanced stages of the disease [1]. The tumor burden can be decreased following NAC, enabling patients who initially needed mastectomy to be candidates for breast-conserving surgery (BCS). The aim of BCS is to entirely excise the breast tumor with clear margins while preserving the natural shape of the breast [2].

Surgical excision of the residual tumor or the tumor bed, if it has completely responded, is still required, and accurate intraoperative tumor localization is essential for this procedure. Various techniques have been developed for this purpose, with wire-guided localization (WGL) currently being the most commonly used method [3]. While WGL is effective in accurately localizing lesions, it has several drawbacks. Inserting the wire can be challenging in dense breast tissue, and during surgery the wire may be displaced. Moreover, to achieve clear margins during surgical excision, the surgeon must navigate through

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healthy tissue following the wire, which can result in the removal of a significant amount of healthy breast tissue. Additionally, wire displacement or fracture poses a small risk of pneumothorax [4]. Furthermore, the optimal entry point for the radiologist to accurately place the wire tip is often distant from the surgeon's preferred incision site. This discrepancy can result in extensive dissection or an inappropriate incision location. Additionally, the surgeon cannot accurately determine the position of the wire tip and thus the lesion, through the skin [5]. Therefore, the surgeon has to estimate the incision site and the tissue to be excised mainly based on postlocalization mammography. This approach often leads to high rates of carcinoma involvement at the excision margins, increasing the risk of unnecessary tissue removal or the need for reoperation [6].

As a result, radioguided localization techniques were developed, primarily including radioguided occult lesion localization (ROLL) and radioguided seed localization.

An additional modification, known as sentinel-node and occult-lesion localization (SNOLL), has also been proposed [7]. This method involves injecting a small amount of nuclear radiotracer directly into the tumor, guided by ultrasonography or stereotactic mammography. The radiotracer's radioactivity enables the lesion to be labeled, allowing for its surgical removal with the help of a handheld gamma probe detection device. SNOLL can be performed together for cancers diagnosed preoperatively through image-guided needle biopsy, intraoperative frozen section detection, or both [8]. The initial results of the ROLL technique, utilizing a portable gamma camera and probe, were published in 2008 by Paredes and colleagues [9]. They concluded that this method is effective for accurately localizing and excising nonpalpable breast cancers with sufficient margins while minimizing the removal of healthy tissue. Additionally, it eliminates the need for frozen section analysis, particularly in centers that do not offer this service.

Over the past decade, ROLL has become increasingly popular due to its numerous benefits, including reduced excision volume, more precise centering of the lesion within the surgical specimen, improved cosmetic outcomes, and a higher rate of tumor-free margins. Furthermore, recent studies assessing the feasibility of ROLL for lesion localization have demonstrated that it is a simple, quick, and accurate technique [10].

AIM OF THE WORK

To verify the efficiency of radioguided surgical management of breast cancer patients who present with nonpalpable residual breast lesions post-NAC and who are candidates for BCS or those with complete resolution and inserted metal clips, in addition to its value in the management of the axilla according to guidelines.

PATIENTS AND METHODS

This is a prospective cohort study that was held at the National Cancer Institute of Cairo university and included female breast cancer patients admitted to the Breast specialized surgery unit during the period between April 2021and 2023, with clinically nonpalpable breast lesions post-NAC and who fulfill the inclusion and exclusion criteria of this study. [Institutional Review Board (IRB) number 2017-310-034].

Inclusion criteria

Breast cancer patients post-NAC with nonpalpable residual breast lesion or those with complete resolution and an inserted metal clip.

Exclusion criteria

Patients with clinically palpable breast lesions or inflammatory breast cancer, patients with known hypersensitivity to the used Technetium Tc99, radio-isotope or to the nano-colloid in addition to pregnant or lactating patients.

Intervention

Patients were prepared for surgery. Full history taking and clinical examination were performed. Preoperative routine laboratory investigations in the form of complete blood count, urea, creatinine, ALT, AST, bilirubin, and coagulation profile were done. Routine metastatic workup was undertaken. The whole procedure was explained to the patient, who signed an informed consent.

Technique of localization

Ultrasound or mammographic guided preoperative intratumoral injection of Technetium Tc99-labelled colloid was carried out, under complete aseptic precautions and local anesthesia using an 18-gauge needle, at least 2 h before surgery on the morning of the procedure or the day before, with immediate skin marking of the injection site. Surgical incision was undertaken in accordance with oncoplastic rules,

Assessment of complete resection and margin status by frozen section, followed by sentinel lymph node biopsy (SLNB) also using the gamma probe, were undertaken with respect to the precautions and indications of sentinel node biopsy (SNOLL).

Data were collected from all available sources (admission sheets, operative, radiology, and pathology reports), and excel sheets were designed to include patients' age, size of breast lesion, axillary lymph node (LN) status, assessment of resection and margin status by

frozen section, further management of the tumor bed and/or the axilla (re-operation), duration of the whole procedure, encountered complications and achieved cosmetic results (length of scar and bilateral breast symmetry).

Primary outcome parameter

Radioguided surgical management of breast cancer patients who present with nonpalpable residual breast lesions post-NAC and who are candidates for BCS and those with complete resolution and inserted metal clips, in addition to management of the axilla according to guidelines.

Possible risks are hemorrhage, wound infection, deep venous thrombosis, and pulmonary embolism.

Statistical analysis

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, New York, USA). Data were summarized using mean, standard deviation, median, minimum, and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann–Whitney test [11]. For comparing categorical data, $\chi 2$ test was performed. Exact test was used instead when the expected frequency was less than 5 [12]. Correlations between quantitative variables were performed using the Spearman correlation coefficient[13]. *P values* less than 0.05 were considered statistically significant.

This study was prospective and posed no harm to patients, all data were kept anonymous to protect the privacy and confidentiality of patients' information, and all patients were consented for their approval of the procedures.

RESULTS

This study included 52 female patients with proven breast cancer who all received NAC. Their age ranged from 30 to 69 years, with a median of 49.5 years.

Forty-two patients were found to have IDC, with 20 patients being IDC grade III, 21 were grade II and one patient was grade I. In addition, 10 patients were found to have ILC with nine having ILC grade II and one having ILC grade III.

Eleven patients were Luminal A, eight were Luminal B, seven were HER2-enriched, while 26 patients were triple-negative. Regarding the Miller grade that classifies response to treatment, grade 5 was seen in 17 patients, grade 4 in eight, grade 3 in 23 and grade 2 in two patients.

The highest rate of pathological complete response (pCR) was seen with triple negative patients. It was found in 46.2% of these patients followed by 28.6% of HER-2 enriched patients, 25% of Luminal B patients and finally 9.1% of Luminal A patients. These findings are shown in (Table 1).

Thirty-three (63.5%) patients were submitted to SLNB and 19 (36.5%) patients underwent axillary lymph node dissection (ALND).

Comparison between the numbers of positive axillary nodes dissected by both methods was carried out and is illustrated in (Table 2). The maximum number of positive LNs for a patient who underwent SLNB was 2LNs, representing 33.33% of all excised LNs. While the maximum number of positive LNs for a patient who underwent ALND was 11 LNs, representing 66.67% of all excised LNs.

Correlation between scar length, radiological size of the tumor, and resected breast tissue was done as shown in Table (3). The median scar length was 4.5 cm, with a minimum of 2 cm and a maximum of 7 cm. The largest breast tissue excised was 8×6 cm, and the smallest was 3×2 cm with a median of 6×4 cm.

Correlation between the size of the tumor and the resected tissue was carried out and is illustrated in (Table 4).

Two patients were diagnosed with positive surgical margins. One of them underwent a simple mastectomy and SLNB while the other was submitted to Modified Radical Mastectomy.

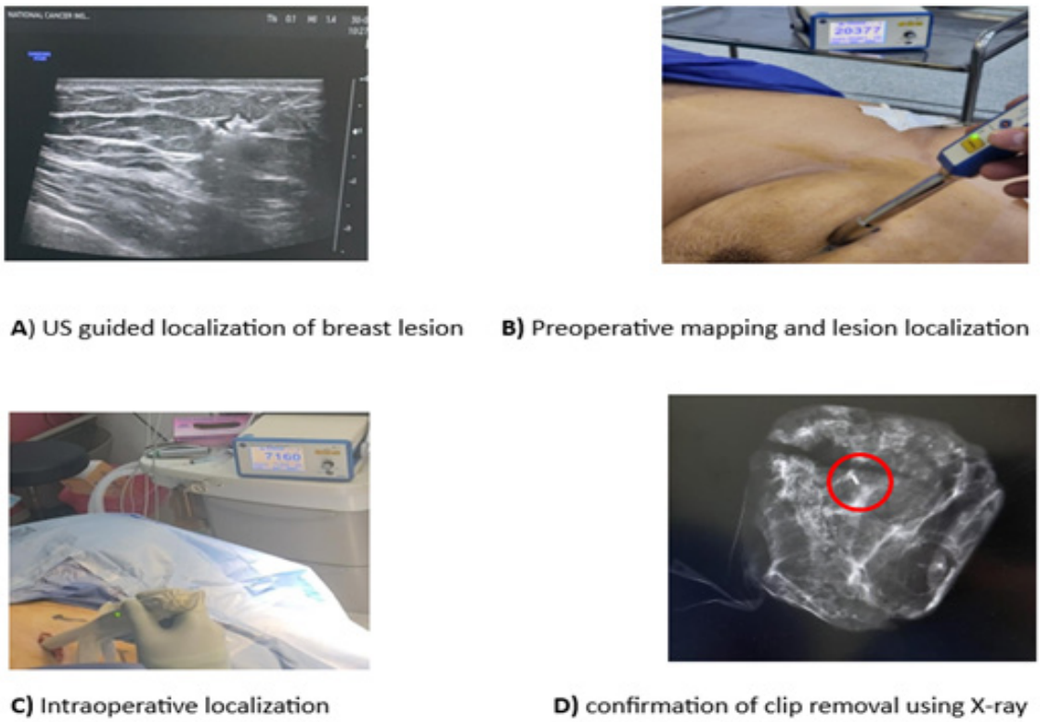

Fig. 1: Technique of localization. A) US-guided localization of breast lesion. B) Preoperative mapping and localization of tumor site by hand-held gamma probe. C) Intraoperative localization. D) Intraoperative confirmation of clip removal using radiography of the excised breast tissue. followed by resection of the tumor guided by and confirmed in-vivo and ex-vivo by the hand-held gamma probe (ROLL) (Figure-1).

Table 1: Pathological response in relation to the biological subtype.

	BIOLOGICAL SUBTYPE				
Pathological response (Miller grade)	**HER 2 enriched *N* (%)**	**LUMINAL A *n* (%)**	**LUMINAL B *n* (%)**	**TRIPLE-ve *n* (%)**	***P value***
Grade 2	0	2 (18.2)	1 (12.5)	1 (3.8)	0.324
Grade 3	3 (42.9)	7 (63.6%)	3 (37.5)	10 (38.5)	
Grade 4	2 (28.6)	1 (9.1)	2 (25.0)	3 (11.5)	
Grade 5	2 (28.6)	1 (9.1)	2 (25.0)	12 (46.2)	

Table 2: Sentinel lymph node biopsy versus axillary lymph node dissection.

	Axillary LN management										
	SLNB					ALND					***P value***
	Mean	**SD**	**Median**	**Min**	**Max**	**Mean**	**SD**	**Median**	**Min**	**Max**	
No of +ve LNs	0.30	0.59	0.00	0.00	2.00	6.16	2.81	7.00	1.00	11.00	<0.001
No of all LNs	6.06	1.87	6.00	3.00	9.00	16.47	4.31	16.00	10.0	25.00	<0.001
% of +ve LNs	5.86	11.30	0.00	0.00	33.33	37.16	15.30	40.00	5.88	66.67	<0.001

Table 3: Scar length compared with resected tissue.

	Mean	Standard Deviation	Median	Minimum	Maximum
Scar length cm	4.48	1.39	4.50	2.00	7.00
Mass length (cm)	1.89	0.87	2.00	0.20	3.00
Mass width (cm)	1.37	0.71	1.25	0.20	3.00
Radiologically length (cm)	3.26	0.96	3.25	1.00	5.00
Radiologically width (cm)	2.38	0.80	2.40	0.70	4.00
Resected tissue length (cm)	5.56	1.17	6.00	3.00	8.00
Resected tissue width (cm)	3.84	1.02	4.00	2.00	6.00

Table 4: Correlation between size of tumor and resected tissue.

Scar length cm			
Mass length (cm)	Correlation coefficient	0.062	
	P value	0.662	
	N		52
Mass width (cm)	Correlation coefficient	□0.153-	
	P value	0.279	
	N		52
Radiological length (cm)	Correlation coefficient	0.049	
	P value	0.732	
	N		52
Radiological width (cm)	Correlation coefficient	0.123	
	P value	0.383	
	N		52
Resected tissue length (cm)	Correlation coefficient	□0.081-	
	Sig. (2-tailed)	0.570	
	N		52
Resected tissue width (cm)	Correlation coefficient	□0.021-	
	Sig. (2-tailed)	0.883	
	N		52

DISCUSSION

Precise localization is vital for the accurate excision of lesions. De Cicco *et al.* [14] noted that ROLL enables surgeons to easily excise non-palpable lesions. Many studies comparing WGL and ROLL have indicated that ROLL is more precise than the WGL technique.

In Gennari *et al.'s* [15] study, 647 patients underwent the ROLL procedure, with lesions successfully detected in 99.1% of the cases. Control imaging verified the presence and central localization of the lesion in 99.5% of the cases.

Elzohery *et al.* [3] observed that the size of the removed breast specimens was smaller in the ROLL group (7.21±2.90 cm) compared with the WGL group (7.49±2.96 cm), with a *P value* of 0.37. The mean diameter of the excised lesions was larger in the WGL group than in the ROLL group (2.20±1.88 cm vs. 2.04±1.58 cm), showing a significant difference between the groups (*P*=0.07). Studies comparing lesion sizes found that the largest excised lesion diameter was 1.5 cm in ROLL patients and 2.5 cm in WGL patients; which was in concordance with our study, where the mean size of the excised specimens was 5.56 cm in length and 3.84 cm in width, with the mean diameter of the excised tumor being 1.89 cm.

Elzohery *et al.* [3] reported that ultra-sound (US) -guided localization was performed in 264 (82.5%) patients while stereotactic technique was used in 56 (17.5%) patients in the ROLL group, which is also concordant with our findings.

In our study US-guided ROLL was done for 43 (82.7%) patients and stereotactic guided ROLL was used for nine (17.3%) patients.

In the present study, we observed a positive margin rate of 3.8% in the ROLL group, which was lower than that found by other studies. Nadeem *et al.* [16], reported a 17% positive margin rate in the ROLL group, while Thind *et al.*[17] found a 16% positive margin rate, and Zgajnar *et al.*[18] reported a 30% rate of involved margins.

In a comprehensive study on ROLL by van Rijk *et al.*[19], involving 368 patients, only 11% of the patients had involved margins. This low rate of positive margins can be explained by better lesion centricity with ROLL, allowing the surgeon to excise the suspicious lesion with adequate margins guided by the intensity and frequency of the radioactivity. When the margin was involved, this meant that they tumor was away from the center of the specimen. The difference between the studies regarding positive margins could be attributed to different sample sizes and to the larger median excision size in our study.

Sajid *et al.* [20] conducted a meta-analysis of four studies comparing WGL and ROLL, finding a higher complication rate in the WGL group. However, no major complications or significant differences were observed between the two groups. In our study, we did not encounter any major complications.

Our study, in accordance with other research, demonstrated that the ROLL technique, when compared with other localization methods, yielded better cosmetic outcomes with reduced breast volume excision. Our study found that the scar length ranged between 2 and 7 cm with a mean length of 4.48 cm while Elzohery *et al.* [3] reported a scar length that ranged between 2.5–3 cm in the ROLL patients and 4–4.5 cm in the WGL patients. It was significantly smaller with ROLL.

The response to NAC is known to differ based on various breast cancer characteristics and molecular subtypes. Notably, achieving a pCR appears to be more closely linked with the most aggressive biological factors, such as HER-2-positive and triple-negative tumors [21].

In a meta-analysis including 30 studies that involved a total of 11 695 patients, the rate of pCR following NAC was assessed. The overall pooled pCR rate was found to be 19.2%. When compared with luminal-like breast cancer, the likelihood of achieving pCR was seven times higher for HER-2-positive disease and five times higher for triple-negative disease [20].

Our study showed that the highest rate of pCR was achieved with triple-negative patients representing 46.2% of these patients, followed by 28.6% of HER -2 enriched patient, 25% of Luminal B patients, and finally 9.1% of Luminal A patients.

In a recent retrospective analysis, Sasanpour *et al.* [21] demonstrated that achieving pCR in breast cancer patients treated with NAC was linked to both overall survival and disease-free survival. The presence of vascular invasion (OR=0.22, 95% CI=0.10–0.46, *P*=0.001) was still associated with a poorer response to NAC in multivariate analysis.

Pu *et al.* [22] created a nomogram incorporating various clinical and biological factors to predict response to NAC. Their findings indicated that vascular invasion was linked to lower response rates. Furthermore, they found that smaller histological tumor size continues to be a predictor of favorable prognostic outcomes following NAC.

In our study, 63.5% of patients were submitted to SLNB and 36.5% of patients underwent ALND and we found that the maximum number of positive LNs for patients who underwent SLNB was 2LNs, representing 33.33% of all excised LNs. The maximum number of positive LNs for patients who underwent ALND was 11 LNs, representing 66.67% of all excised LNs.

In this study, we used the single intratumoral injection of 99 mT Nano colloid to perform lesion localization with simultaneous SLNB (SNOLL). Our success rate for SLN detection was 100%. Other studies as Postma et al. [23] used the same method. However, in the large-scale studies by van Rijk et al. [24] and Postma et al. [23], which included 293 and 100 patients, respectively, the successful sentinel node (SN) detection rates was 98 and 100%, respectively, using the single intratumoral method.

Factors that can affect breast drainage include the size of the breast, any prior surgeries to the axilla or breast, and the tumor's location within the breast [25].

Most of the studies[25] that assessed various post-NAC SLNB techniques such as the targeted axillary dissection used a dual technique for SLNB. Some studies used only one technique for SLNB, but using dual techniques showed a better detection rate of SLN post-NAC, as the fibrosis and debris of the lymphatics with melting of the LNs after NAC leads to difficult detection of the SLNs with higher false negative rates.

In the ACOSOG Z1071 trial [26] the clipped node was found to be one of the SLNs in 78% of dual technique cases, compared with only 50% of cases where blue dye alone was used and 55% of cases where radiolabeled colloid alone was used.

CONCLUSION

This study concluded that ROLL is superior to WGL for nonpalpable breast lesion localization, with many advantages such as reaching a higher percentage of clear margin despite smaller specimen size and scar length with less complications than WGL. Moreover, SNOLL can be performed during the same procedur e (Fig. 1).

Therefore, we recommend ROLL as an easy, safe, and accurate procedure for excision of nonpalpable breast cancer, especially after NAC.

CONSENT FOR PUBLICATION

Ethical approval was obtained from National Cancer Institute Committee. IRB protocol number: 2017-310-034.

HUMAN ETHICS AND CONSENT TO PARTICIPATE DECLARATION

All patients provided signed written informed consent and informed consent for publication.

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Authors contributions: All the authors have proffered significant contribution to this manuscript, and have seen and approved the final manuscript. M.H.I. participated in Study concepts. M.F. participated in Study design and acquisition. Quality control of data and algorithms was performed by M.F.. Data analysis and interpretation was done by S.F.N. Manuscript preparation was done by M.H. Manuscript was reviewed by S.F.N.

CONFLICTS OF INTEREST

There is no competing interest.

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