

Wire Localization versus Intralesional Methylene Blue Marking for Surgical Excision of Impalpable Breast Lesions

Rabie Ramadan^{**}, MD, Tarek El-Fayoumy^{**}, MD, Rafik Mohamed Ibrahim^{***}, MD, Hany Saifeldin^{*}, MBBCh, Haytham Fayed^{**}, MD

^{*}Department of Surgery, Medical Research Institute, Alexandria University, Alexandria, Egypt

^{**}Department of Surgery, Faculty of Medicine, Alexandria University, Alexandria, Egypt

^{***}Department of Radiology, Faculty of Medicine, Alexandria University, Alexandria, Egypt

Please cite this article as: Ramadan R, El-Fayoumy T, Ibrahim RM, Saifeldin H, Fayed H. Wire localization versus intralesional methylene blue marking for surgical excision of impalpable breast lesions. Middle East J Cancer. 2023; 14(4):559-69. doi: 10.30476/mejc.2023.95919.1796.

Abstract

Background: Preoperative marking of impalpable breast lesions is crucial for limiting false negative results and reducing the size of the resected breast tissue, thus improving cosmesis. The aim of this study was to evaluate wire localization versus intralesional methylene blue marking for surgical excision of impalpable breast lesions regarding the success of localization, cost, and limitations of both techniques.

Method: This prospective cohort study included 50 patients with impalpable breast lesions or an area of suspicious microcalcification who were scheduled for surgical excision in the period between June 2020 and December 2021. Patients were randomly allocated into two groups: group I included 25 patients for surgical excision after preoperative ultrasound-guided methylene blue marking. Group II included 25 patients scheduled for surgical excision after preoperative guide wire localization under radiological guidance.

Results: Localization by methylene blue injection has been associated with significantly shorter time of operation with mean duration ($P = 0.018$) and much reduced cost in comparison with guide wire ($P < 0.001$). Postoperative pain, reactions, ecchymosis, accuracy of localization, margin status, and patient satisfaction did not vary significantly between both groups.

Conclusion: Localization by methylene blue injection is not only equally successful to guide wire in locating and identifying impalpable breast lesions for surgical excision, but also is significantly less costly and associated with a shorter duration of operation.

Keywords: Breast neoplasms, Methylene blue, Guide wire, Surgical margin

Corresponding Author:

Rabie Ramadan, MD
Department of Surgery, Medical Research Institute, Alexandria University, Alexandria, Egypt
Tel: (+203) 4285455
4282373
4288233
Fax : (+203) 4283719
Email: rr_mri.surg@yahoo.com

Introduction

The widespread use of advanced mammographic techniques has been associated with increased detection

of impalpable breast lesions. In the UK, one-third of all breast cancers diagnosed are non-palpable, and even higher rates approaching 50% are

observed in other developed countries, where breast-screening programs have been implemented, such as the Netherlands.^{1,2} Precise resection of impalpable breast lesions has been a challenge. Preoperative marking is crucial for limiting false-negative results and reducing the volume of breast tissue needed to be excised, thus improving cosmesis.^{3,4} Many techniques have been developed for marking impalpable breast lesions. Intraoperative ultrasound-guided resection has been previously used. Other methods include cryoprobe-assisted localization, clip location, near-infrared fluorescence optical imaging, carbon marking, and radioguided occult lesion localization (ROLL).⁵ ROLL was developed in 1998 at the European Institute of Oncology in Milan and has become increasingly popular. ROLL uses a radioisotope, mostly technetium-99m, which is injected intralesionally under radiological guidance preoperatively. The lesion is detected by a gamma probe.⁵ Among all localization techniques, guide wire and methylene blue injection have proven the most feasible and effective.⁶⁻⁸ One of the most commonly used techniques is preoperative guide wire localization (GWL) under ultrasound.⁶⁻⁸ Despite being effective, this technique has some drawbacks, such as pain during the procedure and wire displacement. The cost of the wire is another issue. Using a technique that is effective, low cost, and easy to learn has been a major concern. Taking the need to decrease the cost into consideration, preoperative intralesional methylene blue injection under ultrasound guidance may be an effective tool. Methylene blue is a readily available and inexpensive dye with a long history of use in humans and minimal side-effects.⁹ Another advantage is that it does not affect histologic or immunohistochemical assessment.¹⁰ The aim of this study was to compare ultrasound-guided intralesional methylene blue injection and GWL for surgical resection of impalpable breast lesions regarding: successful localization of the lesion, successful excision of the lesion, incidence of complications, cost, pain, and discomfort.

Patients and Method

Patient selection

This prospective study included 50 patients with radiologically and/or pathologically suspicious impalpable breast lesions or an area of suspicious microcalcification who were scheduled for surgical excision. They were admitted to the Department of Surgery, Medical Research Institute, University of Alexandria, and the Surgical Oncology Unit, Main University Hospital, Faculty of Medicine, University of Alexandria, Egypt. The studied patients were randomly allocated into two groups: group I included 25 patients scheduled for surgical excision of impalpable breast lesions after preoperative ultrasound-guided intralesional methylene blue marking. Group II included 25 patients scheduled for surgical excision of impalpable breast lesions after preoperative GWL under radiological guidance. Patients with pathologically proven malignant breast lesions, a history of allergy, previous breast surgery, and those with impaired renal functions were excluded from the current study.

Ethical considerations

The protocol was approved by the Alexandria University, Faculty of Medicine Ethics Committee before the study started (ethics code: 0106420/2020). The study was explained to prospective patients and written informed consent was obtained before study entry.

Study protocol

All patients included in the study were subjected to thorough history-taking, routine laboratory investigations, full clinical examination with detailed breast examination, ultrasound +/- mammography of both breasts, and ultrasound-guided fine needle aspiration cytology (FNAC) or core tissue biopsy for histopathological assessment. All patients were randomly assigned using a simple closed-envelope randomization technique to two groups at a 1:1 ratio: methylene blue and guide wire groups.

Intralesional methylene blue injection

The injection was performed by an expert radiologist under radiologic guidance of the mass during the immediate preoperative period. Lesions

Table 1. Clinico-demographic criteria of studied patients

	Group 1 (n=25)		Group 2 (n=25)		Total (n=50)	
Age (years)						
Min- Max	29.0-52.0		26.0-51.0		26.0-52.0	
Mean ± SD	40.32 ± 6.848		37.44 ± 6.634		38.88 ± 6.829	
Median ± IQR	40 ± 13		37 ± 9		38 ± 10	
<i>P</i>	*0.138					
Side						
Right	13	52%	15	60%	28	56%
Left	12	48%	10	40%	22	44%
<i>P</i>	##0.569					
Site						
Central	6	24%	4	16%	10	20%
UOQ	9	36%	8	32%	17	34%
UIQ	3	12%	6	24%	9	18%
LOQ	5	20%	5	20%	10	20%
LIQ	2	8%	2	8%	4	8%
<i>P</i>	###0.888					
Size						
Min- Max	10.0-22.0		8.6-22.0		8.6.0-22.0	
Mean ± SD	15.72 ± 3.518		17.834 ± 3.746		17.38 ± 3.747	
Median	15 ± 6		18		18 ± 7	
<i>P</i>	*0.112					
FNAC						
Fibroadenomatoid hyperplasia	5	20%	7	28%	12	24%
Ductal hyperplasia	4	16%	6	24%	10	20%
Duct papillomatosis	9	36%	6	24%	15	30%
Focal epithelial hyperplasia	7	28%	6	24%	13	26%
<i>P</i>	##0.703					
BIRADS						
3	8	32%	7	28%	15	30%
4a	11	44%	10	40%	21	42%
4b	6	24%	8	32%	14	28%
<i>P</i>	##0.819					

P: *P* value for comparing both groups, statistically significant at < 0.05; *Student t-test, ## chi-square test, ### Fisher exact test; IQR: Interquartile range; UOQ: Upper outer quadrant, UIQ: Upper inner quadrant, LOQ: Lower outer quadrant, LIQ: Lower inner quadrant; FNAC: Fine needle aspiration cytology; BIRADS: Breast imaging-reporting and data system

classified as nodules and complex cysts were marked during ultrasonography, while microcalcifications were labeled during mammography. A 1% methylene blue solution was used for all lesions, with a volume of 0.5 ml injected using an insulin syringe and a 26-gauge needle. An additional 0.2 ml was injected during withdrawal of the syringe to mark the tract between the mass and the skin, followed by marking the skin overlying the mass for the site of the incision. The success of the injection should be thoroughly assessed. A completely successful injection is encountered, if the operator can easily identify the mass with discoloration of the mass. A partially successful injection indicates that the surgeon has difficulty identifying the mass, mostly due to the dispersion of the dye in the surrounding

tissue. Pain during the procedure should be evaluated as well. Hypersensitivity reactions are reported by radiologists and surgeons.

GWL

GWL is done for all lesions detected by ultrasound. Adequate positioning of the patient is done. The patient takes the supine position, if the lesion is in the inner quadrants; and the supine oblique position, if the lesion is in the outer quadrants; with arms abducted in 90 degrees. The entrance point of the wire is chosen to have the shortest distance to the lesion. Local anesthesia is introduced by superficial injection of lidocaine followed by deeper injection into the tissues surrounding the lesion. The wire is introduced under a real-time guidance along the lateral margin of the transducer visualizing the whole wire during

insertion. The transducer is held in the non-dominant hand and the localization needle held by the other one. Ideally the tip of the wire is positioned 1 cm beyond the lesion. Once well-positioned, the wire is advanced and the needle is withdrawn carefully. For suspicious calcifications and architectural distortion, localization is done under mammographic guidance. Direct 90 degree mediolateral and craniocaudal mammograms are done to assess the position of the lesion. Local anesthesia is introduced. The patient is well positioned standing with her breast horizontally placed on the film cassette and compressed by compression paddles with the craniocaudal film taken. The needle wire is introduced through the hole opposite to the target lesion. Then, compression is applied by paddles in complete medio-lateral oblique view and films are taken. This allows better adjustment of the needle. After localization, two view mammograms are done with wire in position to ascertain good localization. The wire is firmly taped in position with full descriptive report of the localization process. Success of wire localization is assessed by confirmatory post localization 2 view mammogram. The ideal wire localization has to transfix the lesion, pass through its posterior aspect and extend beyond the lesion not more than 1 cm depth. Pain during the procedure should be evaluated as well. Hypersensitivity reactions are reported by radiologists and surgeons.

Surgical excision

All operations are performed under general anesthesia by breast surgeons. In all included patients from both groups, three ml of methylene blue is injected for possible sentinel lymph node biopsy (SLNB) if imprint cytology confirms the marked breast lesion as malignant. Dissection is carried out until the target lesion is reached. Accurate lesion identification is crucial for successful excision. Lesion discrimination relies on the discolored area in the first group (Figure 1) and the end of the wire in the second group (Figure 2). Imprint cytology is used to confirm or exclude malignancy and assess the margin status of proven malignant lesions. If margins are invaded, re-excision is performed to ensure oncological safety. Hemostasis is achieved, and the subcutaneous tissue is closed with absorbable sutures after inserting a drain. The skin is then closed with 3/0 Monocryl. A compression dressing is applied.

The analyzed criteria include:

1. Complete marking of the lesion.
2. Complete excision of the lesion.
3. In cases of malignant lesions proven by imprint cytology, the presence of free margins.
4. Allergic reactions.⁵
5. Difficult lesion identification, characterized by an operative time exceeding one hour from the skin incision.

Complete excision must be thoroughly

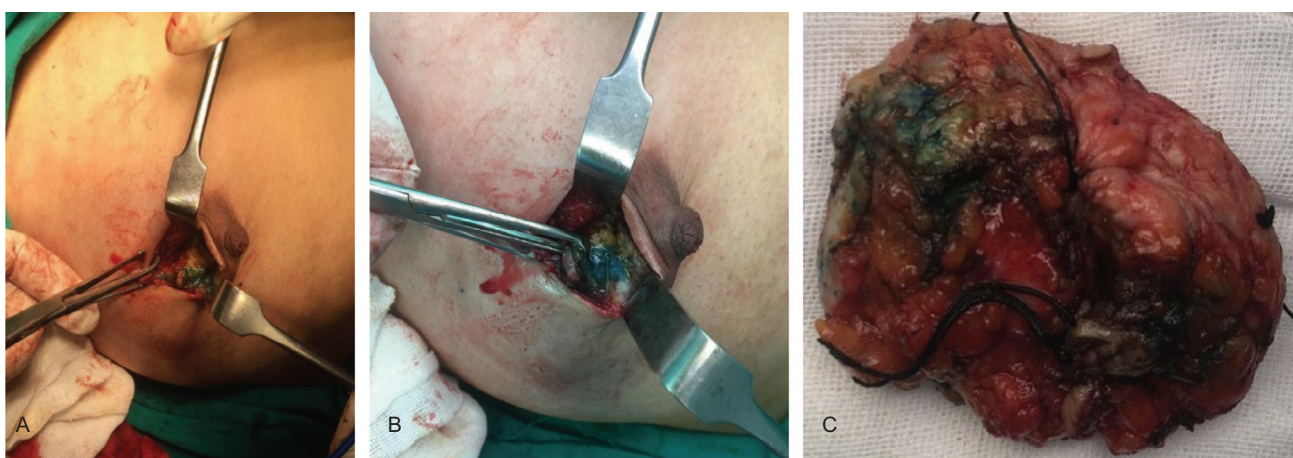


Figure 1. A 42-year-old female patient complaining of mastalgia, U/S mammography: 12 mm lesion (BIRADS 4b), U/S guided FNAC: Focal epithelial hyperplasia, U/S guided methylene blue marking for excision, frozen section: mammary carcinoma with negative margin, SLNB: negative.

BIRADS: Breast imaging-reporting and data system; SLNB: Sentinel lymph node biopsy; U/S: Ultrasound; FNAC: Fine needle aspiration cytology

Table 2. Distribution of the studied patients according to surgical procedure

	Group 1 (n=25)		Group 2 (n=25)		Total (n=50)	
Length of incision (mms)						
Min-Max	15.0-30.0		16.0-30.0		15.0-30.0	
Mean ± SD	21.68 ± 4.25		22.96 ± 4.269		22.29 ± 4.262	
Median ± IQR	20.0 ± 5.0		20.00 ± 5		20 ± 5	
<i>P</i>	#0.332					
Duration of operation in minutes						
Min- Max	55.0- 105.0		60.0- 120.0		55.0- 120.0	
Mean ± SD	77.29 ± 15.60		88.04 ± 16.00		82.78 ± 16.585	
Median ± IQR	72.5 ± 29		85 ± 60		80 ± 25	
<i>P</i>	*0.018					
Imprint cytology						
Benign	16	64%	13	52%	29	58%
Malignant	9	36%	12	48%	21	42%
<i>P</i>	##0.390					
Status of margins in malignant lesions						
Free	9	100%	9	75%	18	85.7%
1 margin invaded	0	0%	3	25%	3	14.3%
2 or more margins invaded	0	0%	0	0%	0	0%
<i>P</i>	###0.284					
SLNB in malignant lesions						
Positive	4	44.4%	4	33.3%	8	38%
Negative	5	55.6%	8	66.6%	13	62%
<i>P</i>	###0.5					
Pain score						
Min – Max	4-7		4-7		4-7	
Mean ± SD	5.32 ± 0.802		5.6 ± .816		5.46 ± .816	
Median ± IQR	5 ± 1		6 ± 1		5 ± 1	
<i>P</i>	#0.193					
Time between technique and operation						
Min – Max	30 -70		720.00 – 1350.00		30-1350	
Mean ± SD	45.60 ± 11.30		966.4 ± 165.65		506.00 ± 479.371	
Median ± IQR	45.00 ± 20		980.00 ± 255.00		395.00 ± 491.25	
<i>P</i>	*<0.001					

P: *P* value for comparing both groups, statistically significant at < 0.05; *Student t-test, # Mann-Whitney test, ## chi-square test, ### Fisher exact test; IQR: Interquartile range; SLNB: Sentinel lymph node biopsy

assessed. For lesions proven malignant by intraoperative imprint cytology, margin status is checked. Free margins indicate complete excision, while invaded margins necessitate enlarging the excised tissue. For lesions not determined as malignant by imprint cytology, complete excision primarily depends on the final histopathological review of the specimen. Slides from all patients are reviewed by an expert pathologist, and any adverse effects on the histopathologic examination should be reported. In cases of pathological discordance, an ultrasound is performed three months after surgery to exclude residual lesions and confirm complete excision.

Pain is assessed subjectively based on a numerical rating scale (NRS). Each patient is asked to provide two pain ratings: one at the time

of localization and another for the worst pain experienced during the first 48 postoperative hours. The average of the two ratings represents the patient's pain level. The numerical rating scale ranges from 0 to 10, with zero referring to no pain and 10 reflecting the worst experienced pain.¹¹

Statistical analysis of the data

Data were input into a computer and analyzed using the IBM SPSS software package version 22.0 (Armonk, NY: IBM Corp). Qualitative data were described using numbers and percentages. Quantitative data were described using range (minimum and maximum), mean, standard deviation, and median. The Shapiro-Wilk test was utilized to verify the normality of distribution. Significance of the obtained results was judged

at the 5% level.

The mean values of age, size of the lesion, duration of operation, and the time between localization and the start of the operation were calculated and compared across both groups using the independent sample T-test. Length of incision, pain scores, and overall cost of the localization procedure were calculated and compared across both groups using the Mann-Whitney U Test. Side of the lesion, site in relation to the breast, preoperative radiological and pathological findings, frozen section, and margin status were

compared across both groups using the chi-square test and Fisher's exact test.

Results

The current study included 50 female patients with radiologically and/or pathologically suspicious impalpable breast lesions or areas of suspicious microcalcifications who were scheduled for surgical excision. They were admitted to the Department of Surgery at the Medical Research Institute of the University of Alexandria, and the Surgical Oncology Unit at

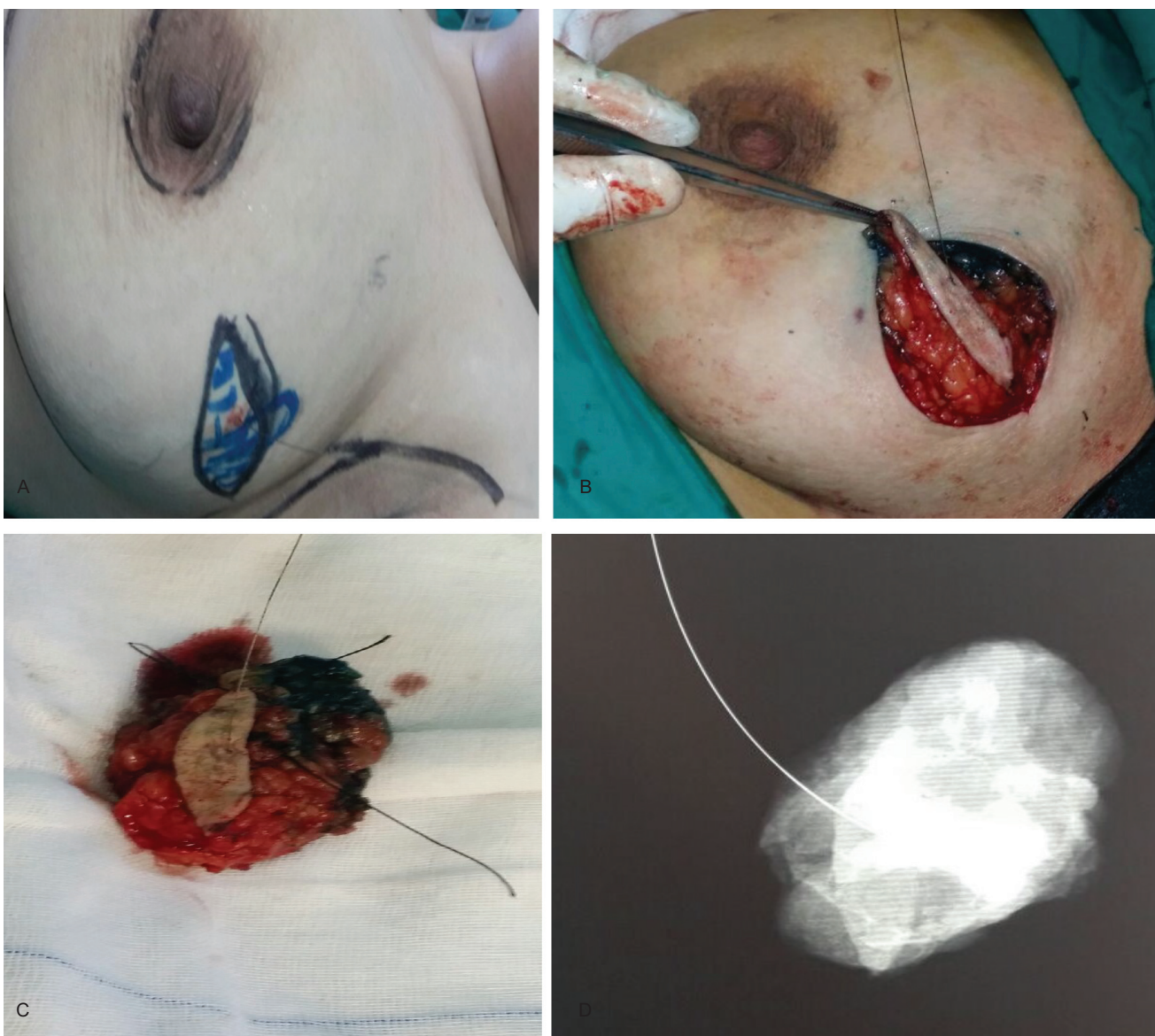


Figure 2. A 38-year-old female patient, U/S mammography: 9 mm lesion (BIRADS 4a), U/S guided FNAC: ductal hyperplasia, GWL for excision, specimen mammography: complete excision, frozen section: fibroadenomatoid hyperplasia.
 BIRADS: Breast imaging-reporting and data system; SLNB: Sentinel lymph node biopsy; U/S: Ultrasound; GWL: Guide wire localization; FNAC: Fine needle aspiration cytology

Table 3. Distribution of studied patients according to complications and outcome

Inaccurate localization dislodgement/ dispersion						
Occurred	2	8%	2	8%	4	8%
Not occurred	23	92%	23	92%	46	92%
P	###1.00					
Allergy						
Reaction	1	4%	0	0	1	2%
No reaction	24	96%	25	100%	49	98%
P	###1.00					
Ecchymosis						
Yes	1	4%	5	20%	6	12%
No	24	96%	20	80%	44	88%
P	###0.189					
Patient satisfaction						
Excellent	14	56%	8	32%	22	44%
Good	7	28%	10	40%	17	34%
Fair	3	12%	5	20%	8	16%
Insufficient	1	4%	2	8%	3	6%
P	###0.445					
Cost (Egyptian pounds)						
Min- Max	110-150		700-1020		110 – 1020	
Mean ± SD	126.40 ± 15.780		838.40 ± 96.725		482.40 ± 366.096	
Median ± IQR	120 ± 35		800 ± 185		425.00 ± 680	
P	#<0.001					

*P: P value for comparing both groups, statistically significant at < 0.05; # Mann-Whitney test, ### Fisher exact test; IQR: Interquartile range; IQR: Interquartile range

the Main University Hospital of the Faculty of Medicine, University of Alexandria, Egypt, in the period between June 2020 and December 2021. The studied patients were randomly allocated into two groups: group I (GI) included 25 patients scheduled for surgical excision of impalpable breast lesions after preoperative ultrasound-guided methylene blue marking, and group II (GII) included 25 patients scheduled for surgical excision of impalpable breast lesions after preoperative GWL under radiological guidance.

With regard to the distribution of the studied patients based on age, site, side, and size of the lesion, as well as pathological and radiological findings, no significant differences were observed between the two groups, as shown in table 1. Regarding the length of the incision needed for excision of the lesion, there was no significant difference between the two groups ($P = 0.332$). The duration of surgery was shorter in GI, with a significant difference between the two groups ($P = 0.018$), as shown in table 2.

Imprint cytology during surgery detected benign lesions in 16 cases (64%) and malignant

lesions in 9 cases (36%) in GI, while in GII, 13 cases were benign (52%) and 12 cases were malignant (48%), with no significant difference between the two groups ($P = 0.390$), as shown in table 2. Out of the 9 lesions proved malignant by imprint cytology in GI, all margins were found to be free in all 9 cases (100%). In GII; however, 3 (25%) out of 12 malignant lesions had one margin invaded and required re-excision of breast tissue related to the invaded margin. The re-excised margins were found to be free in those 3 cases, ensuring the adequacy of re-excision, as shown in table 2.

SLNB in cases proven malignant by imprint cytology was positive in 4 cases (44.4%) and negative in 5 cases (55.6%) in GI, while in GII, 4 cases (33.3%) were positive and 8 cases (66.6%) were negative. The positive cases in both groups were submitted to complete axillary lymph node dissection (ALND), as shown in table 2. Pain was assessed subjectively in patients of both groups.

Top of form

Data were collected on numerical rating scale (NRS) pain scores during the localization

procedure and at five days postoperative. Pain scores were slightly lower in group I, with no significant difference observed between the two groups ($P = 0.183$). As for the accuracy of localization, in group I, the lesion was found well-stained in 23 cases (92%), and dye dispersion occurred in 2 cases (8%), which hindered the accuracy of localization. This required the surgeon to excise more tissue, but no deformity occurred. In group II, wire dislodgement occurred in 2 cases (8%), affecting the margin status in one of them, while in the other 23 cases (92%), the wire was found well-positioned and fixed, as shown in table 3.

Hypersensitivity reactions were detected in 1 case (4%) in group I, while no reactions occurred in group II. No statistically significant difference was observed between the two groups ($P = 1.00$), as shown in table 3. Ecchymosis was observed after dye injection in 1 case (4%) in group I, while in group II, ecchymosis related to wire insertion occurred in 5 cases (20%), with no significant difference between the two groups ($P = 0.189$), as shown in table 3.

All patients were asked about their satisfaction with the technique used and the overall procedure about one month after the operation. Satisfaction was graded as excellent, good, fair, or insufficient. In group I, 14 patients (56%) evaluated the technique and the overall procedure as excellent, 7 patients (28%) reported the technique as good, 3 patients (12%) graded the technique as fair, and 1 patient (4%) was unsatisfied with the procedure. In group II, 8 patients (32%) found the procedure excellent and were completely satisfied with the overall outcome, 10 patients (40%) graded the technique as good, 5 patients (20%) were fairly satisfied, and 2 patients (8%) reported insufficient satisfaction. No statistically significant difference was found between the two groups ($P = 0.445$), as shown in table 3.

Regarding the cost needed for localization in both groups, it was significantly less costly in group I (110-150 L.E.) than in group II (700-1020 L.E.) ($P < 0.001$), as shown in table 3.

Discussion

In the current study regarding the overall cost of localization techniques, including the cost of dye/wire and fees for the performing radiologist, localization by methylene blue injection proved significantly less costly than guide wire insertion. Furthermore, localization by methylene blue injection reduced the total time of the surgical operation and provided fairly accurate localization. Accurate localization is judged by the intra-operative identification of the targeted lesion by the performing surgeon, leading to limited breast tissue resection and, subsequently, less breast deformity.² Accurate localization is also judged by margin status, if the excised lesion is proven malignant by imprint cytology.

Preoperative intralesional injection of methylene blue and guide wire insertion under radiological guidance are both effective techniques for localizing clinically impalpable suspicious breast lesions for surgical excision. It has always been a significant challenge for surgeons to decide between radical excision and limiting the amount of tissue resection.^{2,3} GWL has been the standard of care for a long time in the absence of a better alternative.² The use of a wire for preoperative lesion localization was first described by Dodd et al. in 1965.¹² The technique was later modified with the addition of a hooked tip to the wires to aid fixation in situ by Frank et al. in 1976.¹³ Despite being the current standard of care for impalpable suspicious breast lesions, GWL suffers from important drawbacks like wire dislodgement and migration, which can, on rare occasions, cause thoracic injuries, kinking, and wire fracture. Technical issues arising intraoperatively include diathermy burns and limitations in incision placement, adversely affecting cosmetic outcomes.¹⁴ Moreover, GWL necessitates the presence of an expert radiologist and takes longer to perform. This rationale mandates that GWL be performed at least several hours or the day before surgery.¹³⁻¹⁶ Furthermore, because GWL is advised to be performed on the same day as surgery to prevent migration, scheduling conflicts between the surgeon and the radiologist can occur,

resulting from the need to coordinate multiple procedures on the same day with different teams. Additionally, there is an inability to use wire location in the early morning without causing a significant delay in the operating room.^{3, 7, 10} For all these reasons and the increasing number of non-palpable breast lesions detected by ultrasound screening, the need for a rapid and precise alternative has become of great importance.

The blue dye marking offers the advantage of localizing the lesion through direct visualization of the blue area, providing a safe, simple, effective, and low-cost method for localizing non-palpable breast lesions, especially in areas with limited resources.¹⁷ Nasrinossadat et al. found that marking with methylene blue dye is a cost-effective method for localizing palpable breast lesions.³ Nasrinossadat et al.³ concluded that the cost of using metallic wire is four times greater than dye marking, which was confirmed by our results, which showed that the cost of GWL was nearly seven times higher than dye marking. Therefore, we recommend this method as potentially useful for developing countries.

In our study, localization with methylene blue dye has proven to be a cost-effective method for palpable breast lesions. Intralesional methylene blue injection offers an equally successful localization alternative to guide wires. Drawbacks of this method may include the possibility of excising a larger area than necessary, which may affect the aesthetic outcome, especially in small breasts. This may occur if a longer period passes between injection and excision due to dye dispersion. We attempted to avoid this by minimizing the interval between dye injection and the start of surgery, with a mean interval of 30-70 minutes. Dye dispersion occurred only in two cases (8%), which hindered the accuracy of localization, obligating the surgeon to excise more tissue, but no deformity occurred. This was similar to the results demonstrated by Filho et al.,¹⁶ who used patent blue dye, one of the best dyes for marking palpable lesions. Patent blue dye diffuses adequately, allowing for safe margins without leading to unnecessary dissection of adjacent tissues.¹⁶⁻¹⁸ However, methylene blue

is cheaper and more readily available, especially in developing countries, and its accuracy rate of identification and postoperative complications, including pain, persistent skin staining, and allergic reactions, are comparable to patent blue and charcoal.^{18, 19}

Methylene blue localization, in terms of localization accuracy, is comparable to GWL, yet much less costly. Another drawback of dye marking is the inability to perform specimen mammography after excision, which can be done using the GWL method to ensure complete removal of the mass. Athanasiou et al. reviewed 18 randomized controlled trials with 3,112 patients comparing different techniques for localizing palpable breast lesions²⁰ and concluded that all other techniques were equivalent to GWL in terms of successful excision, localization complications, operative time, and overall complications.¹⁹

Another drawback of using dye for localization is the incidence of allergic reactions, which have been reported to occur in 0.06 to 2.7% of cases, with an average value of 0.71%.¹⁷ In the current study, only one patient (4%) experienced a mild allergic reaction. One study suggested that the incidence of allergic events is mainly related to SLNB, which requires a larger volume of dye, usually 2 to 4 ml.²⁰ However, the volume of methylene blue used for marking non-palpable lesions is 0.2 mL,²¹ but this conclusion requires further investigation. In all included patients in both groups, 3 ml of methylene blue were injected for possible SLNB, if imprint cytology indicated that the marked breast lesion was malignant. Only one patient experienced an allergic reaction to the dye, but we still strongly recommend having hydrocortisone injections and epinephrine available at the radiology center where dye injections are performed in case of rare reactions. Methylene blue has an acceptable, relatively low rate of allergic reactions, which is significantly outweighed by its low cost and accurate localization rates.

The SAVI SCOUT[®] guidance system has been approved by the U.S. Food and Drug Administration since 2014.²² Briefly, a non-

radioactive infrared (IR)-activated electromagnetic wave reflector is placed into the breast under radiological guidance. The reflector is often placed under ultrasound or mammographic guidance, and an audible signal from the implanted reflector is then detected using the manufacturer's handpiece-and-console system.²³ Falcon et al. concluded that the SAVI SCOUT guidance system is comparable to guide wire localization and could achieve successful localization rates in up to 97% of cases,²⁴ similar to the 90 to 100% reported success rates for wire, RSL, or SCOUT.²⁵ The failed localizations were almost entirely due to technical defects. Compared with wire localization, a cited potential disadvantage of the reflector is the inability to move or retrieve it once deployed. The original SAVI SCOUT® console was approved to detect reflectors placed up to 5 cm in depth,²⁴ which is a drawback for deeply seated lesions. A major advantage is that the SAVI SCOUT® reflector was approved for up to 30 days of implantation.

Our prospective cohort study compared intralesional methylene blue injection for localizing breast lesions to one of the most successful techniques, GWL. It demonstrated a statistically significant preference for dye injection over guide wire in terms of cost and operation time. Moreover, it provided equally successful localization, raising the possibility of using dye injection as an alternative. Although we can conclude that localization by methylene blue injection is as successful as GWL for impalpable breast lesions requiring surgical excision and is significantly less costly and associated with shorter operation durations, this study has one important limitation: it could not be applied to non-ultrasound-detected impalpable lesions. We cannot conclude the feasibility of intralesional dye marking under mammographic guidance, which requires a more skilled surgeon. Therefore, we recommend further studies to confirm our findings with a larger volume of cases.

Conclusion

Preoperative marking of impalpable breast

lesions is crucial for limiting false negative results and reducing the size of the resected breast tissue, thereby improving cosmesis. Localization by methylene blue injection is not only equally successful as the guide wire in locating and identifying impalpable breast lesions for surgical excision, but it is also significantly less costly and associated with a shorter duration of operation.

Conflict of Interest

None declared.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424. doi: 10.3322/caac.21492. Erratum in: *CA Cancer J Clin*. 2020;70(4):313.
2. Ahmed M, Rubio IT, Klaase JM, Douek M. Surgical treatment of nonpalpable primary invasive and in situ breast cancer. *Nat Rev Clin Oncol*. 2015;12(11):645-63. doi: 10.1038/nrclinonc.2015.161.
3. Nasrinossadat A, Ladan F, Fereshte E, Asieh O, Reza C, Akramossadat S, et al. Marking non-palpable breast masses with injected methylene blue dye, an easy, safe and low cost method for developing countries and resource-limited areas. *Asian Pac J Cancer Prev*. 2011;12(5):1189-92.
4. Tang J, Wang X, Wu YP, Wang X, Lian ZQ, Fu JH, et al. Significance of methylene blue dye for localization biopsy of nonpalpable breast lesions. *Ai Zheng*. 2009;28(1):79-81.
5. Tromberg BJ, Pogue BW, Paulsen KD, Yodh AG, Boas DA, Cerussi AE. Assessing the future of diffuse optical imaging technologies for breast cancer management. *Med Phys*. 2008;35(6):2443-51. doi: 10.1118/1.2919078.
6. Cheang E, Ha R, Thornton CM, Mango VL. Innovations in image-guided preoperative breast lesion localization. *Br J Radiol*. 2018;91(1085):20170740. doi: 10.1259/bjr.20170740.
7. Masannat YA, Shaaban AM, Speirs V, Coast G, Jackson P, Horgan K, et al. Adverse effects of dyes used in sentinel node biopsy on immunocytochemical determination of hormone receptors in breast cancer cells. *J Clin Pathol*. 2007;60(6):730-2. doi: 10.1136/jcp.2006.044974.
8. Fusco R, Petrillo A, Catalano O, Sansone M, Granata V, Filice S, et al. Procedures for location of non-palpable breast lesions: a systematic review for the radiologist. *Breast Cancer*. 2014;21(5):522-31. doi: 10.1007/s12282-012-0427-1.

9. Surry KJ, Mills GR, Bevan K, Downey DB, Fenster A. Stereotactic mammography imaging combined with 3D US imaging for image guided breast biopsy. *Med Phys.* 2007;34(11):4348-58. doi: 10.1118/1.2794175.
10. Alikhassi A, Saeed F, Abbasi M, Omranipour R, Mahmoodzadeh H, Najafi M, et al. Applicability of radioguided occult lesion localization for nonpalpable benign breast lesions, comparison with wire localization, a clinical trial. *Asian Pac J Cancer Prev.* 2016;17(7):3185-90.
11. Coca KP, Amir LH, Alves M, Barbieri M, Marcacine KO, de Vilhena Abrão ACF. Measurement tools and intensity of nipple pain among women with or without damaged nipples: A quantitative systematic review. *J Adv Nurs.* 2019;75(6):1162-72. doi: 10.1111/jan.13908.
12. Joe BN, Sickles EA. The evolution of breast imaging: past to present. *Radiology.* 2014;273(2S):S23-S44. doi: 10.1148/radiol.14141233.
13. Postma EL, Koffijberg H, Verkooijen HM, Witkamp AJ, van den Bosch MA, van Hillegersberg R. Cost-effectiveness of radioguided occult lesion localization (ROLL) versus wire-guided localization (WGL) in breast conserving surgery for nonpalpable breast cancer: results from a randomized controlled multicenter trial. *Ann Surg Oncol.* 2013;20(7):2219-26. doi: 10.1245/s10434-013-2888-7.
14. Siegmann-Luz KC, Bahrs SD, Preibsch H, Hattermann V, Claussen CD. Management of breast lesions detectable only on MRI. *Rofo.* 2014;186(01):30-6. doi: 10.1055/s-0033-1335972.
15. Gerrard AD, Shrotri A. Surgeon-led intraoperative ultrasound localization for nonpalpable breast cancers: results of 5 years of practice. *Clin Breast Cancer.* 2019;19(6):e748-e52. doi: 10.1016/j.clbc.2019.05.008.
16. Ahmed M, Douek M. Intra-operative ultrasound versus wire-guided localization in the surgical management of non-palpable breast cancers: systematic review and meta-analysis. *Breast Cancer Res Treat.* 2013;140(3):435-46. doi: 10.1007/s10549-013-2639-2.
17. Filho WMNE, de Medeiros Neto AM, de Melo Rodrigues RM, Alves ACBR, Vieira SC. Use of the patent blue and air in the preoperative marking of impalpable breast lesions. *Eur J Breast Health.* 2018;15(1):7-12. doi: 10.5152/ejbh.2018.4321.
18. Ko K, Han BK, Jang KM, Choe YH, Shin JH, Yang JH, et al. The value of ultrasound-guided tattooing localization of nonpalpable breast lesions. *Korean J Radiol.* 2007;8(4):295-301. doi: 10.3348/kjr.2007.8.4.295.
19. Zhou Y, Liang Y, Zhang J, Feng Y, Li X, Kong X, et al. Evaluation of carbon nanoparticle suspension and methylene blue localization for preoperative localization of nonpalpable breast lesions: a comparative study. *Front Surg.* 2021;8:757694. doi: 10.3389/fsurg.2021.757694.
20. Athanasiou C, Mallidis E, Tuffaha H. Comparative effectiveness of different localization techniques for non-palpable breast cancer. A systematic review and network meta-analysis. *Eur J Surg Oncol.* 2022;48(1):53-9. doi: 10.1016/j.ejso.2021.10.001.
21. Tong M, Guo W. Indocyanine green fluorescence-guided lumpectomy of nonpalpable breast cancer versus wire-guided excision: A randomized clinical trial. *Breast J.* 2019;25(2):278-81. doi: 10.1111/tbj.13207.
22. Cox CE, Russell S, Prowler V, Carter E, Beard A, Mehindru A, et al. A prospective, single arm, multi-site, clinical evaluation of a nonradioactive surgical guidance technology for the location of nonpalpable breast lesions during excision. *Ann Surg Oncol.* 2016;23(10):3168-74. doi: 10.1245/s10434-016-5405-y.
23. Mango VL, Wynn RT, Feldman S, Friedlander L, Desperito E, Patel SN, et al. Beyond wires and seeds: reflector-guided breast lesion localization and excision. *Radiology.* 2017;284(2):365-71. doi: 10.1148/radiol.2017161661.
24. Falcon S, Weinfurter RJ, Mooney B, Niell BL. SAVI SCOUT® localization of breast lesions as a practical alternative to wires: Outcomes and suggestions for trouble-shooting. *Clin Imaging.* 2018;52:280-6. doi: 10.1016/j.clinimag.2018.07.008.
25. Pouw B, de Wit-van der Veen LJ, Stokkel MP, Loo CE, Vrancken Peeters MJ, Valdés Olmos RA. Heading toward radioactive seed localization in non-palpable breast cancer surgery? A meta-analysis. *J Surg Oncol.* 2015;111(2):185-91. doi: 10.1002/jso.23785.