Preoperative localization of nonpalpable breast cancer using clip insertion and skin marking: a prospective controlled study

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Background
Many cases of breast cancer are detected at early stages mainly due to the adoption of screening programs and the increase of public awareness about breast cancer. This requires preoperative localization of the mass for adequate excision and precise planning for breast-conservative surgery. The aim of this study was to demonstrate noninferiority of preoperative ultrasound-guided clipping with skin marking of nonpalpable breast lesions for obtaining negative surgical margins.
Patients and methods
Fifty patients diagnosed with nonpalpable breast cancer, were recruited for the study and were compared with the last 50 correlated patients in the database, who underwent wide local excision of their lesions under wire-guiding as regards the surgical margins assessed by intraoperative frozen section technique.
Results
Free surgical margin was achieved in 47/50 patients when 'sonographic' skin marking and clip application was applied. Level-I oncoplasty was done to all the 50 patients in the study group as well as those retrieved from the database.
Conclusion
Omitting the application of wire for nonpalpable breast lesions and replacing it with skin marking is feasible and cost-effective.

Keywords:
early breast cancer, preoperative skin marking, wire guidance

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Introduction

Breast cancer is the fifth cause of cancer-related deaths worldwide with an estimated annual incidence of 2.3 million new cases according to the GLOBOCAN 2020 data [1]. Breast cancer originates in the duct epithelium (85%) or lobule acini (15%). Initially, it is '*in situ*' causing no symptoms and has minimal potential for distant metastasis [2]. The widespread adoption of breast-screening programs has increased the numbers of patients diagnosed at early stages, that is, 'clinically occult nonpalpable stage' [3]. Wide local excision, followed by radiotherapy, is the standard of care for such lesions [3]. A successful breast-conservation treatment is a balance between margin negativity and breast cosmesis [4]. Such procedure poses a challenge for surgeons, having to rely on their radiologist colleagues to provide preoperative guidance on the proper area to excise [3]. An ideal procedure for precise localization of nonpalpable breast lesions should facilitate performing a complete single surgical session excision [5]. Adequate surgical margin is defined by the absence of any malignant cells on ink margin [4]. Many preoperative tumor localization techniques have been described [wire-guided excision, carbon marking localization, ultrasound (US) skin marking, etc.], but no single technique proved to be superior [6,7]. Wire-guided localization is the most commonly used method in the modern era: being easy to apply with no specific prerequisites, except for radiological team collaboration [5]. With time, drawbacks of this technique became obvious. The aim of our study was to demonstrate the proposed technique of omitting wire application preoperatively, depending solely upon the preoperative inserted metallic clips with US skin marking for excision of nonpalpable breast cancer lesions.

Patients and methods

After achieving the acceptance of the Ethical Committee Board upon the research protocol, 50 patients with 'pathologically proven' breast cancer having their breast lesions not detected clinically, were recruited and consented about the whole study protocol. All the patients were presented to the outpatient breast clinic at our hospital. Trucut biopsy was taken as a part of the triple assessment of the patients followed by clip insertion within the lesion under sonographic guidance. According to the adopted strategy for patients with

early breast cancer, that is, T1/2, N0, M0, and after competing their triple assessment (trucut biopsy and sonomammogram), patients with T1N0 lesions were taken for upfront surgical excision after preoperative localization of nonpalpable lesions, that is, those less than 1 cm in size (T1a, b lesions). Cases with T1c lesions with small breast size, T2 and T3 lesions were sent for neoadjuvant treatment (with the metallic clips left *in situ*). They were restaged after completing the course of their treatment and those with yT1a, b were taken for conservative breast surgery after preoperative localization. Patients with nonpalpable breast lesions were our study population, that is, those with T1a, b lesions with and without neoadjuvant treatment. For technical accuracy, it was decided to include only patients with their suspected mass not more than 4-cm deep to the skin. Instead of wire guidance over the in-situ clips, two concentric circles with skin marker were drawn by the radiology team: an inner circle (actually a thick dot) representing the skin projection of the mass and the clip, and an outer circle one cm wider as a safety margin. At the operative theater, patients were draped, and wide local excision was done for all patients guided by the skin markings previously drawn at the radiology department (instead of the wire localization in the control group) via direct incision removing the mass and the inserted clips with the overlying marked skin. The specimens were imaged using intraoperative C-arm device to assure the excision of the mass with the metallic clips before being sent for frozen section examination. The volume of the specimen was recorded. 'Pathologically' negative resection margin was defined as no tumor in ink for invasive carcinoma and 2 mm for ductal carcinoma in situ (DCIS). Patients with negative surgical margins completed their predetermined operation, while those with positive margins had another wider margin excised and resent for frozen section examination as the residual breast tissue allows. Otherwise, total mastectomy was done. The results of our study group were compared with those of the last 50 correlated patients in our data registry where the technique of 'immediate preoperative' wire localization was adopted, as regards the surgical margin adequacy, volume of the excised specimen, and complications related to the process of the lesion localization.

Statistical analysis

Data were collected, revised, coded, and entered into the Statistical Package for the Social Sciences (IBM SPSS, Armonk, NY: IBM Corp) version 23. The quantitative data were presented as mean, SDs, and ranges when parametric and median, interquartile range when data were found nonparametric. Also, qualitative variables were presented as numbers and percentages. The comparison between groups regarding qualitative data was done by using χ^2 test and/or Fisher's exact test when the expected count in any cell found was less than 5. The quantitative data and parametric distribution were done by using independent *t*-test. The comparison between more than two groups regarding quantitative data and parametric distribution was done by using one-way analysis of variance test. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the *P* value was considered significant at the level of less than 0.05.

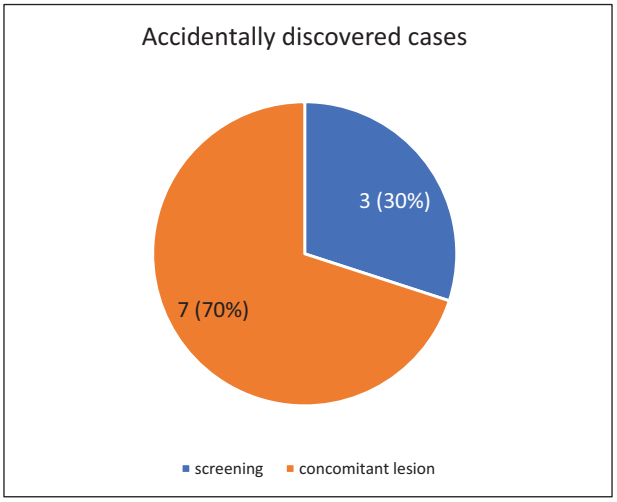
Results

Starting from June 2020 to January 2022, fifty patients with 'clinically non detected' breast cancer, with their lesion found within 4-cm depth from the skin, were included in our study, whether the mass was accidentally discovered (10 cases) or became nonpalpable after neoadjuvant treatment (40 cases) (Table 1). As for the accidentally discovered cases, three cases were discovered during routine screening for positive family history and seven cases were discovered during metastatic workup for other malignancies (four cases for contralateral previously controlled breast cancer, two cases for ovarian cancer, and one for colorectal cancer) (Fig. 1). Those seven cases were diagnosed as suspicious foci in PET scan and the lesion was

Table 1 Basic data of the patients

	Study group (*n*=50)	Control group (*n*=50)
Age	32–65 (~52.8)	35–66 (~52.6)
Mode of discovery	Accidentally discovered=10, postneoadjuvant=40	
Percent of menopausal patients	15/50	17/50

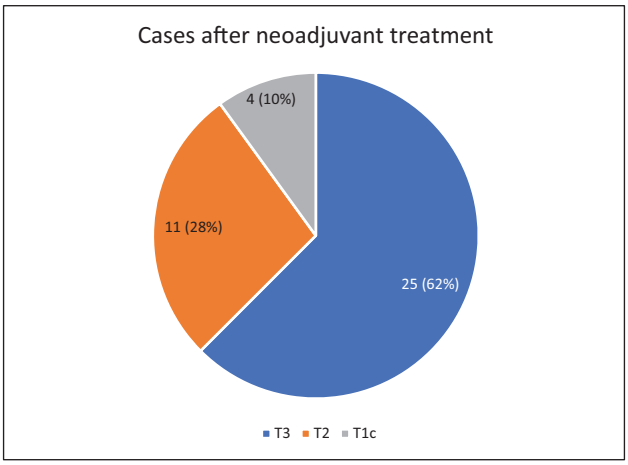
Figure 1



Accidentally discovered nonpalpable cases.

confirmed by sonomammogram with MRI breast (if still suspicious after sonomammogram). Cases recruited after neoadjuvant treatment had their pretreatment diagnosis as follows: 25 cases with T3, 11 cases with T2, and four cases with T1c lesions (Fig. 2). The breast size of the recruited patients and the control group patients with their mammographic density is shown in Table 2 and Figures 3 and 4. The site of the lesions as detected by preoperative radiology is shown in Figure 5. Having the lesions excised completely as shown by the C-arm images of the specimens with adequate safety margins around the intralesional metallic clips, frozen section results were as shown in Table 3 and Figures 6 and 7. Deeper analysis of the results of the frozen section examination of each of the study and control group in correlation to the breast cup size is shown in Tables 4 and 5 and Figures 8–11. For cases with positive margins (three in the study group and two in the control group), extended specimens were sent and were negative before including their data within the statistical analysis. Investigating whether there was a correlation to other factors, cases with initially positive margins were re-analyzed (Table 6). All the five patients (three in the study group and two in the control group) were postmenopausal, on hormonal replacement therapy before diagnosis, and had received

Figure 2



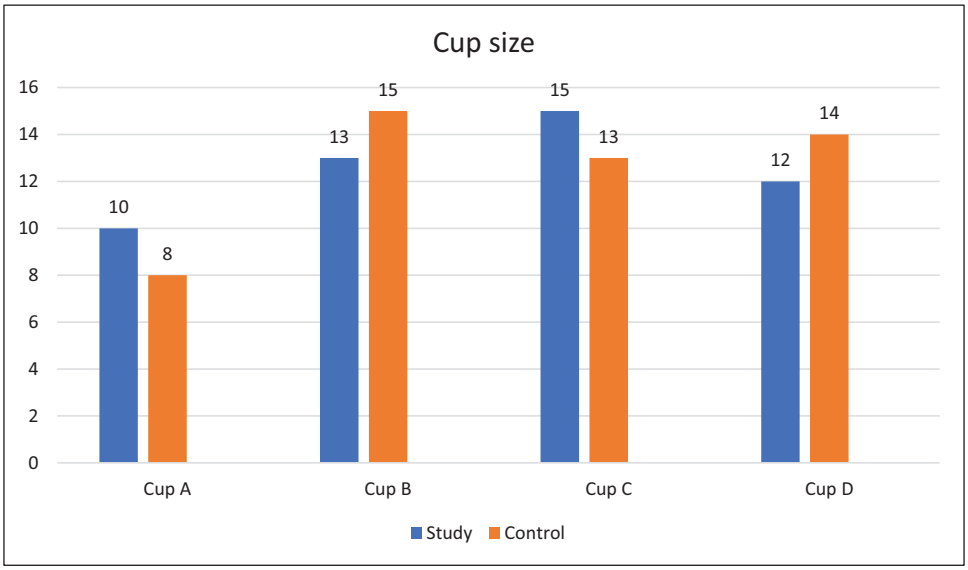
Cases recruited postneoadjuvant treatment.

Table 2 Breast size and density

	Study group (*N*=50) [*n* (%)]	Control group (*N*=50) [*n* (%)]	Test value*	*P* value	Significance
Breast cup size					
A	10 (20.0)	8 (16.0)			
B	13 (26.0)	15 (30.0)	0.662	0.882	NS
C	15 (30.0)	13 (26.0)			
D	12 (24.0)	14 (28.0)			
Breast density					
A	12 (24.0)	11 (22.0)			
B	19 (38.0)	23 (46.0)	0.784	0.853	NS
C	14 (28.0)	11 (22.0)			
D	5 (10.0)	5 (10.0)			

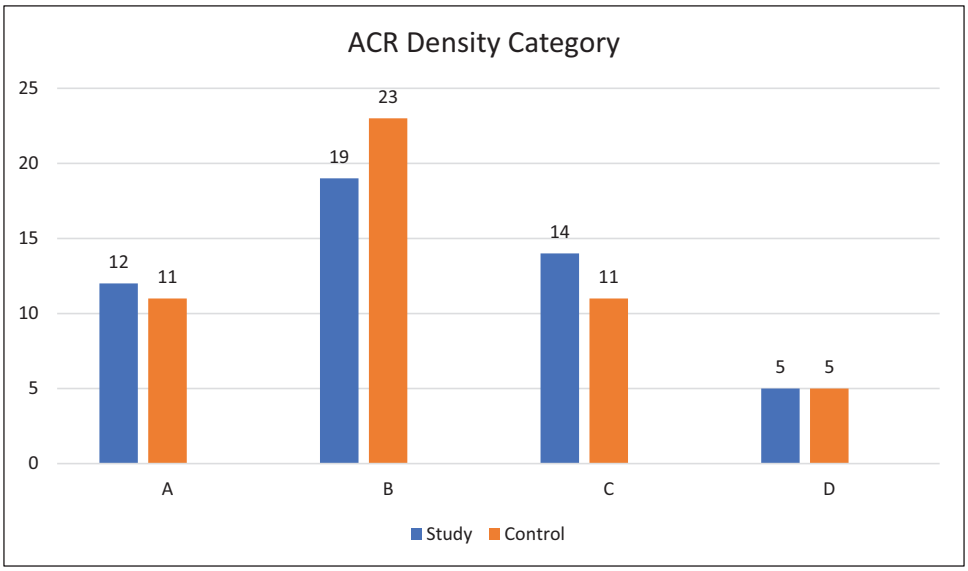
*χ^2-test. *P*>0.05, nonsignificant. *P*<0.05, significant. *P*<0.01, highly significant.

Figure 3



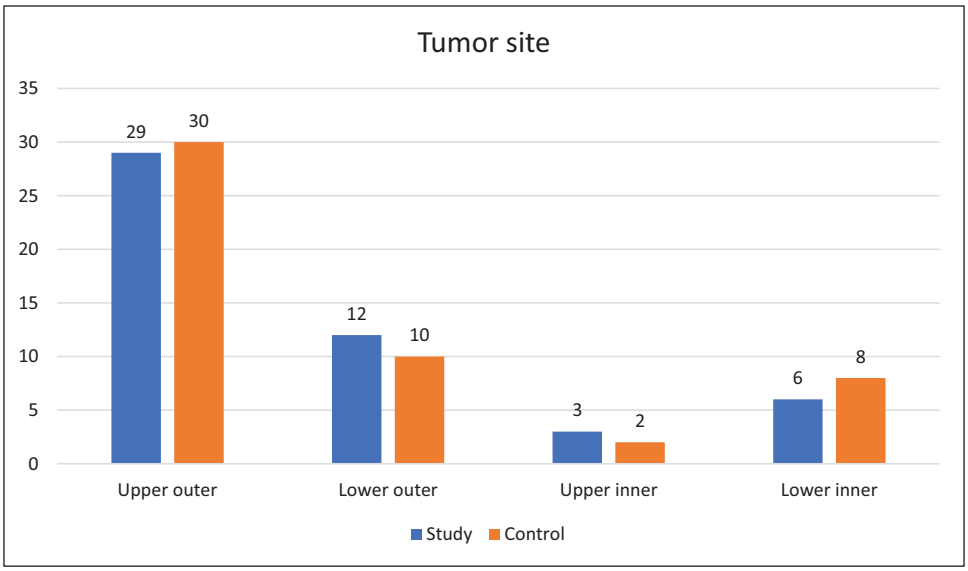
Breast size.

Figure 4



Breast density by mammogram.

Figure 5



Tumor site immediately preoperative.

neoadjuvant therapy. They had radiologically dense breasts (American college of radiology (ACR) grades C and D). It is worth mentioning that two of the cases with wire localization had their wire slept before the operation. One of those cases was resent to the radiology department for wire relocation. That option was not possible for the second case as the wire slept during induction of anesthesia, so, intraoperative US was used to insert a spinal needle at the lesion.

Discussion

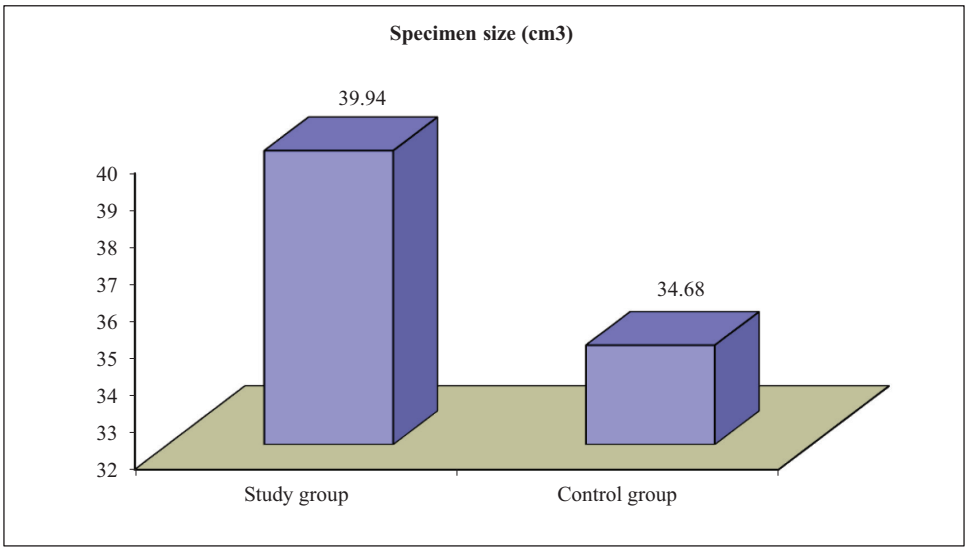
Surgical excision of the 'clinically nonpalpable' breast cancer lesions is a challenging procedure for breast surgeons, having to preoperatively 'localize' the tumor within the context of the predetermined breast-reconstruction procedure [8]. Such a challenge is obvious in having myriad techniques and nearly all of them are in collaboration with the radiology team [3]. The wire-guided localization technique is preferred by most surgeons [5]: being easy, rapid, performed under local anesthesia under radiological guidance, and cost-effective [3]. By time, drawbacks of such a technique became apparent. Logistic problems for scheduling the operation in coordination among three different departments (surgery, radiology, and clinical pathology) are the first issue as the wire should be inserted at the day of the operation to avoid its displacement [9]. That

Table 3 Results of frozen section

	Study group (*N*=50)	Control group (*N*=50)	Test value•	*P* value	Significance
Specimen size (cm^3)					
Mean±SD	39.94±5.16	34.68±5.76	4.807	0.000	HS
Range	30–48	24–44			
Nearest safety margin (cm)					
Mean±SD	0.90±0.25	0.63±0.18	6.227	0.000	HS
Range	0.5–1.3	0.4–1			

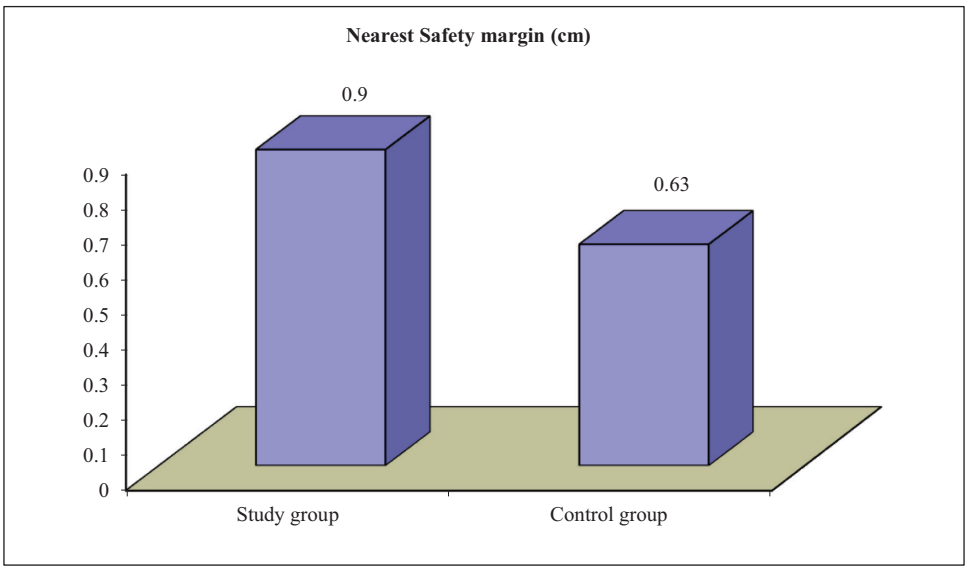
HS, highly significance. •Independent *t*-test. *P*>0.05, nonsignificant. *P*<0.05, significant. *P*<0.01, highly significant.

Figure 6



Specimen size.

Figure 7



Nearest margin.

complication was encountered in our research in two cases within the control group. Although we could manage the case, such an issue resulted in significant delay within the operation schedule as well as doubling the costs, having the initially applied wire discarded. Having the lesion mapped on the skin of the patient in the study group offers flexibility for timing of the operation as it can be done on days other than the day

Table 4 Frozen section of the study group

	Breast cup size				Test value*	*P* value	Significance
	A *N*=10	B *N*=13	C *N*=15	D *N*=12			
Specimen size (cm^3)							
Mean±SD	34.20±3.71	37.62±3.25	41.13±3.85	45.75±1.42	26.355	0.000	HS
Range	30–43	32–42	34–46	43–48			
Nearest safety margin (cm)							
Mean±SD	0.65±0.13	0.74±0.12	1.01±0.19	1.16±0.15	27.121	0.000	HS
Range	0.5–0.9	0.5–0.9	0.7–1.2	0.8–1.3			

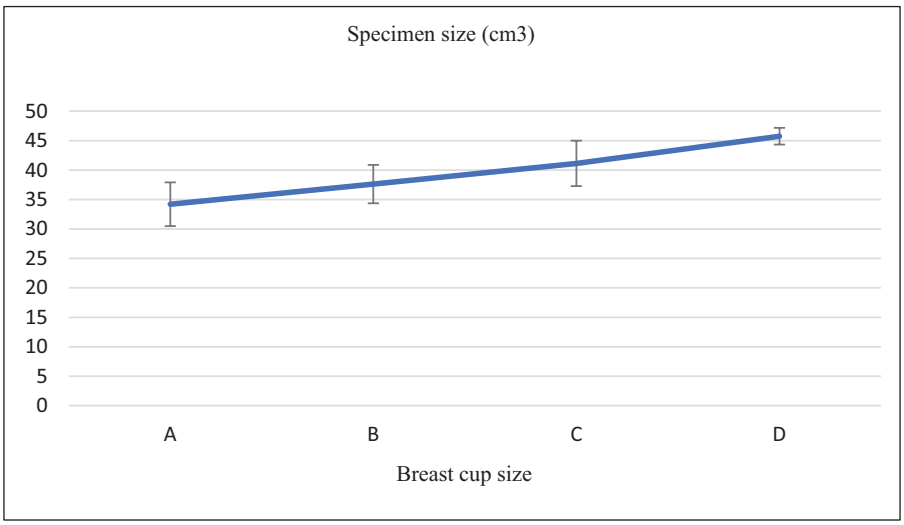
HS, highly significance. *One-way analysis of variance test. *P*>0.05, nonsignificant. *P*<0.05, significant. *P*<0.01, highly significant.

Table 5 Frozen section results of the control group

	Breast cup size				Test value*	*P* value	Significance
	A *N*=8	B *N*=15	C *N*=13	D *N*=14			
Specimen size (cm^3)							
Mean±SD	28.25±3.41	31.47±3.94	36.00±4.81	40.57±2.06	24.096	0.000	HS
Range	24–35	24–37	28–41	36–44			
Nearest safety margin (cm)							
Mean±SD	0.44±0.07	0.58±0.16	0.70±0.16	0.73±0.18	7.363	0.000	HS
Range	0.4–0.6	0.4–0.9	0.5–1	0.4–1			

HS, highly significance. *One-way analysis of variance test *P*>0.05, nonsignificant. *P*<0.05, significant. *P*<0.01, highly significant.

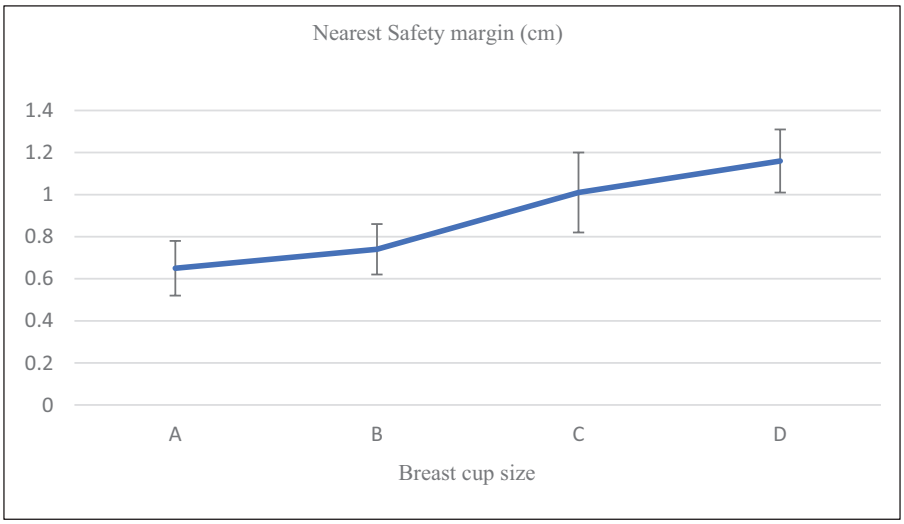
Figure 8



Specimen size to cup size in study group.

of the operation. Displacement of the marking after application is not an option in that technique. Both techniques were shown to be nearly equally effective to guide surgical excision of nonpalpable breast lesions, having only 3/50 and 2/50 cases with positive margins in the study and control group, respectively. On assessing the excised specimens, some observations were found. The volume of the excised specimens tends to be more in the study group, and it is positively correlated to the volume of the breast within each group. The same observation applies to the length of surgical safety margin as measured in the excised specimens. This can be explained by the surgeons' attitude to feel safe excising more breast tissue around the tumor without compromising the later procedure for reconstruction in cases with large breast size. The same principle applies for the excised surgical margin feeling safe to excise more tissue around the tumor as the breast size permits to assure free surgical margin, especially when the surgeon had to excise the lesion, depending only on projection of preoperative skin marking in the study group. The last point (i.e. having

Figure 9



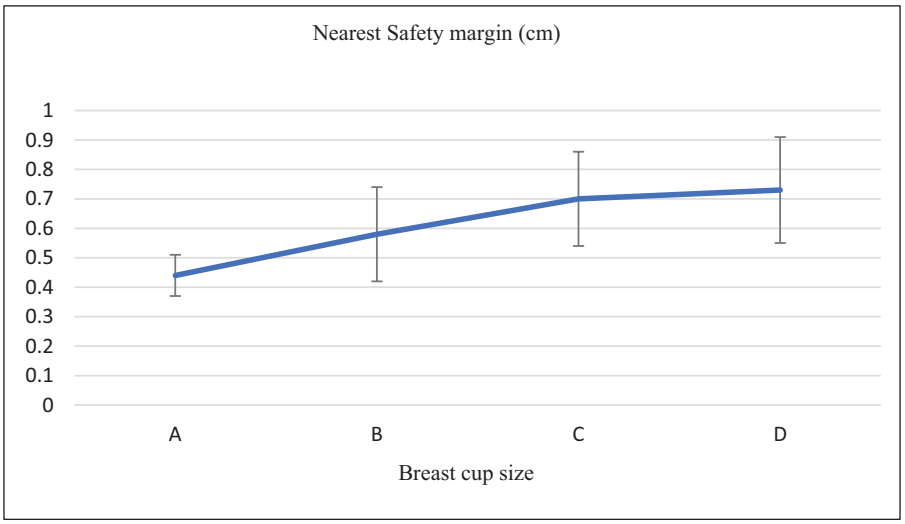
Nearest margin to cup size in study group.

Figure 10

Specimen size to cup size in control group.

to depend only on skin marking) explains the reason why we excluded patients with lesions more than 4-cm deep within the breast parenchyma. Deeper lesions would be easily lost and not excised properly without a visual, in-situ marking, even though a metallic clip was inserted for radiological detection of the mass within the excised specimen. Further analysis of cases with positive margins assured certain points. Having the five cases (three in the study group and two in the control group) with dense breasts according to the ACR classification explains the reason for having positive margins, despite preliminary assurance of the margins with the intraoperative C-arm imaging. Returning to the literature, such a point was reached by many authors [10,11] stating that X-ray may be deceiving in cases of dense breast. All cases were found to have received neoadjuvant treatment. This point may raise a concern about the effect of neoadjuvant treatment on tumor cells and radiological findings after the course of treatment in the era of biological classification of breast cancer and the consideration of isolated tumor cells and micrometastasis in modern staging systems. This could be an idea for further research in the future. The idea of depending solely on skin marking was proposed to be noninferior to wire localization by many authors [3,4,6,12]. Ahmed *et al.* [3] in their review, stated insufficient data in the literature to adopt such a technique. In their work, Mokhtar *et al.* [6] confirmed superiority of US-guided skin marking to palpation-guided tumor excision and that the same fact applies for nonpalpable lesions when being excised under wire guidance. However, they raised the concern about

Figure 11



Nearest margin to cup size in control group.

Table 6 Reassessment of cases with positive margins

	Study group (*n*=3)	Control group (*n*=2)
Form of margin involvement	DCIS=2, IDC (focal)=1	DCIS=1, IDC (focal)=1
Breast cup size	A=1, C=2	B=1, C=1
ACR grade on mammogram	D=3	C=1, D=1
Neoadjuvant treatment	3/3 (100%)	2/2 (100%)

DCIS: ductal carcinoma in situ, IDC: invasive duct carcinoma.

tumor-size underestimation due to the subjectivity of US examination. Our results go in concordance with those of Jaiswal *et al.* [4] and Franceschini *et al.* [12], confirming that preoperative skin marking is sufficient when being confronted with impalpable breast lesions. In our study population, only patients with their lesion within 4 cm from the skin were included based on personal experience of our team caring that deeper masses would be lost intraoperatively without a wire or tattoo localization, especially in patients with large breast size, that is, cups C and D. This point should be investigated separately in dedicated research.

Conclusion

Within certain depth from the skin, application of wire for localizing nonpalpable breast lesions can be omitted and superficial skin marking is sufficient.

Limitation

The relationship among the depth of the lesion, breast size, and accuracy of lesion projection on the skin has to be investigated in separate research. Despite being convenient, easy to perform, and generally an accurate means of breast lesion localization, ultrasonography is investigator-dependent. The accuracy of ultrasonography for detecting deep nonpalpable breast lesions, especially with breasts of large cup size, should be compared with other objective modalities, for example, MRI paying attention to the cost-effectiveness. The effect of neoadjuvant treatment on residual tumor cells and their radiological appearance in the era of isolated tumor cells and microsatellites is still to be investigated.

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Nil.

Conflicts of interest

There is no conflicts of interest.

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