The Analysis of Preoperative Wire Localization in Breast Conserving Surgery and Predictors of Surgical Margin Status

Cholatip Wiratkapun MD¹, Pawida Wattanatada MD¹

¹ Department of Diagnostic and Therapeutic Radiology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Background: At present, the breast conserving therapy (BCT) is considered a treatment of choice for early-stage breast cancer. BCT aims to achieve complete tumor resection with adequate margin and offers better cosmetic outcome.

Objective: To describe the experience with preoperative wire localization technique for early breast cancer and analysis of factors affecting positive margin status.

Materials and Methods: The authors retrospectively reviewed 190 patients with 206 malignant breast lesions treated by breast conserving surgery (BCS) after mammographic- or ultrasound- guided wire localization. Patient age, lesion type such as mass, mass with calcifications, calcifications alone, and architectural distortion, BI-RADS assessment categories, size, location, modalities of imaging guidance, number of wires used, radiological and surgical margin status, pathological diagnosis, and tumor focality were recorded.

Results: A 14.56% of positive surgical margin rate was observed. Mixed-effects logistic regression analysis showed larger lesion size was a significant predictor for positive surgical margin status at larger than 1.5 cm versus 1.0 cm or smaller (p=0.033).

Conclusion: The present study data suggested that larger tumor size is the only significant predictor for positive surgical margin status. To deal with non-palpable large tumor, surgeon and radiologist should pay particular attention to achieve adequate surgical margin.

Keywords: Wire localization; Breast conserving surgery; Surgical margin status; Specimen radiography

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Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among female^(1,2). Globally, about 2.1 million cases of female breast cancer were newly diagnosed in 2018⁽¹⁾. Early detection with screening mammography significantly reduces breast cancer deaths by 20% to 40%^(3,4). The aim of the screening is to detect cancer in early stage⁽³⁾.

There are many surgical options for breast cancer. Breast conserving surgery (BCS) is a part of the breast-conserving therapy (BCT), which is referred to as a conservative surgery for removal of the tumor and is usually accompanied by radiation

Correspondence to:

Wiratkapun C.

Department of Diagnostic and Therapeutic Radiology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, 270 Rama VI Road, Ratchathewi, Bangkok 10400, Thailand.

Phone: +66-2-2012465, Fax: +66-2-2011297

Email: cholatipp@gmail.com, cholatip.wir@mahidol.ac.th

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therapy⁽⁵⁾. Accurate localization for non-palpable lesions is an important step for successful BCS. At present, image-guided wire localization is the standard preoperative localization technique. Wire or needle localization of non-palpable breast lesions is a safe, effective, and uncomplicated procedure⁽⁶⁾. Indications for pre-surgical localization include a biopsy proven malignancy or high-risk lesions, patients with imaging pathological discordant result at core needle biopsy (CNB), and patients who are unsuitable for CNB or fail to give a definitive diagnosis by CNB⁽⁶⁾. Preoperative needle localization can be performed under imaging guidance including mammography, ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI)⁽⁷⁾. However, failure rate of localized mammographic abnormality has been reported up to $17\%^{(8)}$.

Wide excision with areas of normal tissue surrounding the tumor is necessary to obtain sufficient margin to minimize the risk of local recurrence⁽⁹⁻¹²⁾. Prior studies reported positive margins in 20% to 40% of the patients that underwent BCS⁽¹³⁾. Several studies reported on predictive factors for surgical margin status in BCS and yielded varying results⁽¹⁴⁻¹⁷⁾.



Figure 1. A 37-year-old woman with ductal carcinoma in situ (DCIS). (a) Left craniocaudal mammogram reveals several groups of fine pleomorphic and coarse heterogeneous calcifications in segmental distribution spanning 5.8 cm. (b) Left lateromedial mammogram obtained during wire localization procedure using compression paddle with an alphanumeric grid shows 2 needles placed to outline lesion boundaries. (c) Left craniocaudal mammogram after wire deployment demonstrates position of 3 localized wires. (d) Specimen radiography after wide excision confirms presence of the suspicious calcifications and wires. The calcifications are seen close to the margin of the specimen (arrows). The pathology revealed multifocal DCIS with tumor close to medial, lateral, and posterior resected margins (1 mm).

The aim of the current study was to describe the authors' experience with preoperative wire localization technique for BCS at Ramathibodi Hospital between January 2015 to December 2019, as well as analysis of radiological and pathological factors affecting positive surgical margin status.

Materials and Methods

The present study was a retrospective study approved by the Institutional Review Board of Ramathibodi Hospital, Mahidol University (COA. MURA2019/1186). The necessity for informed consent was waived owing to the retrospective nature of the study.

Patient selection

The authors retrospectively reviewed the database of the patients that underwent preoperative mammography- and ultrasound-guided wire localization breast excision at Ramathibodi Hospital, which is a large tertiary care academic hospital, between January 2015 and December 2019. All patients with pathological-proven malignancy underwent BCS were included in further analyses. Cases with benign histopathology, non-breast lesion such as chest wall lesion after mastectomy and axillary lesion, procedural shifting to mastectomy, no specimen radiography, and no residual tumor after surgery were excluded.

Procedures

Preoperative imaging was obtained by mammogram with ultrasound or ultrasound alone. The present study was performed using imaging equipment by Hologic Selenia Dimensions (Hologic, Bedford, MA, USA) for mammography, Philips iU22 ultrasound system (Phillips Medical Systems, Bothell, WA, USA) with a L12-5 linear transducer (5 to 12 MHz frequency range) and Samsung RS85 ultrasound machines (Samsung Medison, Seoul, South Korea) with a LM4-15B linear probe (4 to 15 MHz frequency range).

Wire localizations were done in the radiology unit by seven breast imaging radiologists with 5 to 20 years' experience. Mammography guided wire localizations were performed in sitting position. Ultrasound guided wire localizations were performed in supine or decubitus position with ipsilateral arm raise above head. The procedures were done using standard aseptic technique and local anesthesia. Wire localization was performed on all lesions using standard technique parallel to the chest wall approach under either mammographic or ultrasound guidance. Single-hook system of in-house wires and commercial wires (20G×10cm, Hawkins III FlexStrand BLN/ Argon Medical Devices, Athens, TX, USA) were used in the present study. After the procedures, the wires were taped in place to prevent retraction of the wire into the breast and radiopaque markers were pasted at the skin entry site. To confirm the position of the wire, post-wire-insertion mammograms were obtained in craniocaudal and true lateral view with either mediolateral or lateromedial views (Figure 1).

Wide excisions were performed under general anesthesia on the same day as wire localizations by eight surgeons with 8 to 25 years' experience. Postsurgical specimen radiographs were obtained to determine whether the lesion and the wire had been removed. Specimen radiographs were obtained in



Figure 2. Specimen radiography (a) and ultrasound (b) show mass and inserted wire with adequate resection margin. The pathology showed invasive ductal carcinoma with DCIS and free all resection margins.

single compression-magnification view (Figure 1, 2). For non-calcified lesions or lesions that were not visualized in radiography, postsurgical specimen ultrasound was also done (Figure 2). The surgeon was notified immediately if the suspicious lesion was not presented in the specimen and additional excision was done. Subsequently, the specimens were sent to the pathological department.

Data collection and definitions

Demographic data including patient age, clinical presentation, and personal history of breast cancer were reviewed from the hospital electronic medical record (EMR).

The lesions were classified as non-calcified mass, mass with associated calcifications, calcifications alone, or architectural distortion. Lesion type, BI-RADS assessment categories, lesion size based on imaging, and location were reviewed from the picture archiving and communication system (PACS)⁽¹⁸⁾.

Position of the hook related to the lesion were reviewed in post-wire localization mammogram. The number of wires used in each procedure were also recorded.

The specimen radiography or specimen ultrasound were used to assess distance of lesions from excised margin, which was further classified as positive, close, or negative. The authors recorded the distance in four dimensions (Figure 3). The shortest distance was used to determine the margin status. Positive radiological margin status was defined as presence of the lesion on the resection surface. The radiological margin status was considered as being close when the value was less than 10 mm. Negative radiological margins are defined as the value of greater than or equal to 10 mm⁽¹⁹⁻²²⁾.



Figure 3. Example of radiological margin measurement of specimen radiography. The surgeon has marked the specimen for orientation with silks at each surface of the specimen. The specimen radiography suggests sufficient margin width in all directions and confirms presence of the inserted wire. The pathology showed invasive cribriform carcinoma with negative surgical margins.

Preoperative imaging and specimen radiography were reviewed independently by the authors, blinded to the pathological results.

The pathological reports were obtained from the hospital EMR. The pathological diagnosis, pathological size, tumor focality, and surgical margin status were recorded. The pathological findings were compared with the imaging findings.

The pathological margin distance was recorded in six dimensions as superior, inferior, anterior, posterior, medial, and lateral margins. The closest margin was used to define the margin status and was classified as positive, close, or negative. Positive surgical margin status was defined as presence of tumor cells on the resection surface. Close margins were defined as less than 2 mm tumor-free margin. Negative margins were defined as tumor-free margin of greater than or equal to 2 mm⁽²³⁻²⁵⁾.

Factors affecting positive margin status including lesion characteristics as lesion type and imaging size, modalities of the imaging guidance as mammogram or ultrasound, number of wires used, radiological margin status, pathological diagnosis, and number of tumor foci were analyzed.

Statistical analysis

Statistical analysis was carried out by two statisticians using Stata Statistical Software, version 16.0 (StataCorp LLC, College Station, TX, USA). The quantitative parameters were presented as mean and range. The categorical variables were presented as counts and percentages. Mixed-effects logistic regression was used to analyze categorical outcome. A p-value of less than 0.05 was considered statistically significant.

Results

Between January 2015 and December 2019, 570 patients were preoperatively wire-marked. All cases with pathologically-proven malignant breast lesions were included for further analysis and included 190 patients with 206 lesions. The present study excluded 380 cases with benign histopathology, non-breast lesion such as chest wall lesion after mastectomy and axillary lesion, procedural shifting to mastectomy, no specimen radiography, and no residual tumor after surgery (Figure 4).

The age of the patients ranged from 31 to 86 years, with a mean age of 56.55 years. All were female. Indications for mammogram and ultrasound were screening in 119 patients (62.63%), palpable breast lump in 35 patients (18.42%), follow-up study in 23 patients (12.11%) and others in 13 patients (6.84%). Most of patients had negative personal history of breast cancer (162 patients, 85.26%), three patients (1.58%) had previous ipsilateral breast cancer, and 25 patients (13.16%) had previous contralateral breast cancers.

The mean lesion size based on imaging was 1.49 cm with a range of 0.2 to 10.0 cm. Lesion type, BI-RADS assessment categories, imaging size, and location are summarized in Table 1.

Of 206 lesions, wire localizations were performed under mammographic guidance in 77 lesions (37.38%) and under ultrasound guidance in 129





Table 1. Lesion characteristics and location

Lesion characteristics	Number of lesions; n (%)	
Lesion type		
Non calcified mass	94 (45.63)	
Mass with associated calcifications	23 (11.16)	
Calcifications alone	84 (40.78)	
Architectural distortion	5 (2.43)	
BI-RADS categories		
3	1 (0.49)	
4A	34 (16.50)	
4B	101 (49.03)	
4C	34 (16.50)	
5	36 (17.48)	
Tumor size		
≤1.0 cm	108 (52.43)	
>1.0 cm to ≤1.5 cm	46 (22.33)	
>1.5 cm	52 (25.24)	
Depth		
Anterior third	23 (11.17)	
Middle third	139 (67.48)	
Posterior third	34 (16.50)	
More than 1/3	10 (4.85)	

lesions (62.62%). In all patients, wires were placed within the lesion or not more than 1 cm in distance from the target lesion. Single wire was used in 193 lesions (93.69%). Two wires were used in 11 lesions (5.34%), and three wires were used in two lesions (0.97%).

Table 2. Radiological and surgical margin status

Margin status	Number of lesions; n (%)		
Radiological margin status			
Negative	82 (39.81)		
Close (not including positive)	99 (48.06)		
Positive	25 (12.13)		
Surgical margin status			
Negative	114 (55.34)		
Close (not including positive)	62 (30.10)		
Positive	30 (14.56)		

Table 3. Pathology of breast lesions

Pathology	Number of lesions; n (%)	
IDC	32 (15.53)	
IDC with associated DCIS	51 (24.76)	
DCIS	104 (50.48)	
Invasive mammary carcinoma	5 (2.43)	
Invasive mammary carcinoma with CIS	3 (1.46)	
Papillary carcinoma	4 (1.94)	
ILC	2 (0.97)	
Others*	5 (2.43)	

IDC=invasive ductal carcinoma; DCIS=ductal carcinoma in situ;

ILC=invasive lobular carcinoma

* Other cancer types are adenosquamous carcinoma, metastatic carcinoma in lymph node, invasive mucinous carcinoma, invasive cribiform carcinoma and mixed invasive ductal and lobular carcinoma.

Radiological and surgical margin status are summarized in Table 2. The present study found that positive surgical margin rate was 14.56%. The average lesion size based on pathological report was 1.46 cm with a range of 0.1 to 10.0 cm. The distribution of pathological diagnoses is shown in Table 3. Multifocal diseases were present in 40 lesions (19.42%).

A series of mixed-effects logistic regression analyses were used to estimate factors that may affect surgical margin status (Table 4). The present study analyses showed that larger lesion size was the significant predictor for positive surgical margin status at greater than 1.5 cm versus 1.0 cm or smaller (p=0.033). Other factors including lesion type of calcifications, localization method of mammographic guidance, localization with more than single wire used, positive radiological margin status, presence of ductal carcinoma in situ (DCIS), and multifocal disease showed increased odds ratio but did not reach statistical significance. **Table 4.** Mixed effects logistic regression analysis to assess factors with increased odds ratio of positive margin

Factors	OR for positive margin	95% CI	p-value
Imaging factors			
Lesion type: calcifications	1.489	0.522 to 4.248	0.457
Tumor size			
• >1.5 cm vs. ≤1 cm	3.139	1.1 to 8.959	0.033
• >1.0 cm to \leq 1.5 cm vs. \leq 1 cm	1.342	0.435 to 4.144	0.435
Mammographic guidance	1.835	0.585 to 5.76	0.298
Number of wires used			
2 vs. 1	2.83	0.471 to 16.997	0.255
3 vs. 1	9.369	0.212 to 407.815	0.245
Positive radiological margin status	79.91	0.844 to 7568.068	0.059
Presence of DCIS	2.445	0.618 to 9.709	0.203
Multifocal disease	1.88	0.583 to 6.06	0.291

DCIS=ductal carcinoma in situ; OR=odds ratio; CI=confidence interval

Discussion

BCS is a safe and effective procedure for early breast cancer treatment^(26,27). There are many options for preoperative localization for non-palpable breast cancer. Wire-guided, carbon marking, biopsy clips, radio-guided occult lesion localization (ROLL), ultrasound-guided, radioactive seed localization (RSL), and cavity shave are commonly used^(10,28). Preoperative image-guided wire localization is a costeffective standard technique to assist surgical excision for non-palpable breast cancer. Wire migration or dislodgement, retention of wire fragments, vasovagal episodes, bleeding, hematoma, infection, pain, and pneumothorax are the potential complications of the procedure^(10,28). Standard aseptic technique and local anesthesia were done to decrease pain and incidence of infection. The standard used in parallel to the chest wall approach under imaging guidance helps to avoid pneumothorax. Corsi et al published a review on preoperative localization and surgical margins in BCS and reported rate of clear margins after wire-guided excision to be 70.8% to 87.4%⁽¹⁰⁾. In the current study, the authors found negative surgical margins in 114 lesions (55.34%) and close margins in 62 lesions (30.10%).

Positive surgical margin status has a significant impact on both local and distance recurrences^(9-12,24,29). In 2000, Park et al explored the correlation between pathologic margin status and results at eight years after BCT in 533 patients with clinical stage I or II breast cancer underwent BCS and radiation therapy. Their study revealed that patients with negative and

close margins had a local recurrence rate (LRR) of 7%, patients with focally positive margins had a LRR of 14%, while patients with extensively positive margins had a LRR of $27\%^{(9)}$. The present study also found 14.56% of lesions had positive surgical margins.

Previous studies had analyzed the variables related with surgical margin status and yielded varying results. According to the study of Kurniawan et al (n=1,648), the presence of microcalcifications on mammograms, absence of a mammographic mass, presence of DCIS, high tumor grade, large histological size of 3 cm or greater, multifocal disease and lobular histology were associated with involved margins⁽¹⁴⁾. Reedijk et al performed a prospective study of 305 patients with non-palpable invasive breast cancer or DCIS and found that localization under stereotactic guidance, presence of in situ disease, high tumor grade, larger tumor size of 2 cm or greater versus 1 cm or smaller, multifocal tumor, and presence of mammographic microcalcifications were the predictive factors of positive margin⁽¹⁵⁾. In a large cohort study of van Deurzen (n=25,315), the variables with the greatest association with involved margins (OR >2) were multifocality, lobular subtype, large tumor size of more than 2 cm, and the presence of DCIS⁽¹⁶⁾. Dryden et al conducted a retrospective study to identify factors that influence surgical margins after preoperative RSL (n=127) and wire localization (n=533) in 2016. Their results showed that the presence of calcifications and increasing radiological tumor size increased odds ratio of close and positive margins in both RSL and wire localization groups(17). Hong et al found that factors associated with positive or close margins after BCS were wire-guided localization using mammography and ultrasound versus none, mammographic microcalcifications, large-sized in situ carcinomas, the presence of an in-situ component accompanied by invasive breast carcinoma, and lumpectomy versus quadrantectomy⁽³⁰⁾.

The present study findings support the studies above, which suggested that larger lesion size was a significant predictor for positive surgical margin status at greater than 1.5 cm versus 1.0 cm or smaller (p=0.033). This is probably because that large nonpalpable lesions are mostly microcalcifications, making it difficult for the surgeon to accurately outline the lesions despite the increased number of wires used. Some other studies, however, showed no significant relationship between tumor size and margin status^(20,31). In assessing other factors influencing margin status, the present study results suggest that positive margin status tends to be associated with a lesion type of calcifications, localization method of mammographic guidance, and presence of DCIS and multifocal disease, though these correlations were not statistically significant.

Specimen imaging is widely used as a tool assisting the surgeon to ensure that the lesion has been excised. The study of Graham et al confirmed the value of specimen radiography when the tumor extends to the edge of the specimen radiography, which is associated with involved surgical margin with positive predictive value (PPV) of 98%(32). Mazouni et al analyzed the association between specimen radiography and surgical margin status (n=164) and reported that a close radiological margin of less than 5 mm and multifocal disease were the predictors for close histological margins⁽²²⁾. The study of Naz et al supported the usefulness of specimen radiography to predict complete tumor excision after BCS with PPV of 83.3%, sensitivity of 80.7%, and specificity of 81%⁽²⁰⁾. Recently, Funk and colleagues analyzed the efficacy of specimen radiograph in evaluation of surgical margin status and their results showed a sensitivity of 36.8%, a specificity of 86.8%, a PPV of 25.6%, and a negative predictive value (NPV) of 91.8%⁽³³⁾. Their study concluded that specimen radiograph is an applicable tool to predict margin status and to decrease rate of secondary surgeries by suggesting targeted margin re-excisions⁽³³⁾. According to Britton et al, a radiological margin of 9.5 mm correlates most strongly with a histological margin of 2 to 3 mm⁽²¹⁾. Apart from specimen radiography, the role of specimen ultrasound was also examined⁽³⁴⁻³⁶⁾. The study of Moschetta et al reported the efficacy of the specimen ultrasound in histological margin prediction with sensitivity, specificity, accuracy, PPV, and NPV of 44%, 94%, 80%, 73%, and $82\%^{(34)}$. The research of Tan et al indicated that specimen ultrasound is a useful tool in predicting histologically free margins during BCS⁽³⁵⁾. Although many previous studies supported the usefulness of specimen radiography and ultrasound, some studies showed the contrary results. The study of Rua et al reported that the sensitivity of the specimen radiographs was only 33.3% for non-palpable in situ and 50% for invasive ductal carcinoma (IDC)⁽¹⁹⁾. They concluded that radiographic imaging of the surgical specimens is not sufficient for evaluation of histological margin. Maloney et al reviewed several methods for intraoperative margin assessment during BCS including specimen radiography and ultrasound and found that no current method is sufficient for

positive margin detection⁽³⁶⁾. Their study revealed that specimen radiography decreased the number of re-excisions but produced many false positives that led to unnecessary tissue excision⁽³⁶⁾. The authors found positive radiological margin status tends to be associated with positive histological margin status, but this factor did not reach statistical significance in the present study (p=0.059).

Occasionally, preoperative wire localization may need more than one wire placement. Silverstein et al suggested placement of multiple wires to 'bracket' large area of microcalcifications⁽³⁷⁾. There are prior studies that reported outcome of multiple-wire localization. Burkholder et al reported that number of wires placed was not related to surgical margin status or re-excision and additionally multiple-wire localization can be used to significantly decrease the volume of breast tissue removed in malignant cases⁽³⁸⁾. Cordiner et al performed a retrospective study of 101 cases with malignant calcifications⁽³⁹⁾. They found that cases with larger areas of microcalcifications that had been bracketed by more than single wire did not appear to have greater need for re-excision⁽³⁹⁾. Hernanz et al analyzed factors related to margin status including number of wires used⁽⁴⁰⁾. They found that only multifocality was strongly associated with involved margins while number of wires was not correlated with margin status⁽⁴⁰⁾. Dryden et al also studied the association of number of wires in wire localization or seeds (in RSL) used and surgical margin status⁽¹⁷⁾. They reported the presence of mammographic calcifications including calcifications alone and masses with associated calcifications significantly needed more than single wire. However, the uses of more than single wire or seed did not appear to reduce the chance of a close or positive margin⁽¹⁷⁾. In the current study, the authors found that multiple-wire localization tends to be associated with involved margin status, but this factor was not statistically significant.

There were a few limitations in the present study. First, it was a single institutional-based study over a limited study period, resulting in limited power of the data. The authors would suggest having largescale multi-institutional study for better prediction of factors associated with positive surgical margin status. Radiologists performing localization and surgeons performing surgery may be factors influencing the margin status. The population was small, and some radiologists and surgeons contributed only a few cases to the present study. Therefore, the authors cannot analyze these factors. Second, because of the retrospective design of the present study, some important information was not available. The authors could not identify the accurate sides of the specimen radiograph in some cases as some silks were not clearly seen on the specimen radiography and some pathological report did not mention about the silks. Hence, the authors cannot directly compare radiological margin with surgical margin in each side. In the authors' institution, specimen radiograph was obtained only in a single view. Consequently, radiological margin distance can be measured in only four dimensions while the information about the other two remaining margins is lacking. This may affect the accuracy of specimen radiography. In addition, type of wires such as in-house or commercial wires, used in each procedure was not recorded in procedural report. This may be another factor influencing surgical margin status.

Conclusion

The BCS is a treatment of choice for patients with early breast cancer. Accurate localization for non-palpable lesions is an important step for successful BCS. Image-guided wire localization is the standard preoperative localization technique, which is uncomplicated, safe, and effective. The current study examined factors associated with involved surgical margin following BCS. The present study findings suggest that larger tumor size is the only significant predictor for positive surgical margin status. To deal with larger size tumors, surgeon and radiologist should pay particular attention to achieve sufficient surgical margin.

What is already known on this topic?

At present, BCT is considered a treatment of choice for early-stage breast cancer. The aim of BCS is to achieve complete tumor resection with adequate margin. Several prior studies conducted outside Thailand reported on predictive factors for surgical margin status in BCS and yielded varying results.

What this study adds?

The authors studied radiological and pathological factors affecting positive surgical margin status in Thai patients underwent BCS at Ramathibodi Hospital. The study results reveal that larger tumor size is the only significant predictor for positive surgical margin status.

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Conflicts of interest

The authors declare no conflict of interest.

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