Clinical efficacy of intraoperative ultrasound for margin assessment in breast conserving surgery

Jeeyeon Lee
Kyungpook National University School of Medicine
Ho Yong Park
Kyungpook National University School of Medicine
Wan Wook Kim
Kyungpook National University School of Medicine
Chan Sub Park
Kyungpook National University School of Medicine
Yungeun Ji
Kyungpook National University School of Medicine
Hye Jung Kim
Kyungpook National University School of Medicine
Won Hwa Kim
Kyungpook National University School of Medicine
Ji-Young Park
Kyungpook National University School of Medicine
Jee-Young Park
Kyungpook National University School of Medicine
Yee Soo Chae
Kyungpook National University School of Medicine
Soo Jung Lee
Kyungpook National University School of Medicine
Jin Hyang Jung (jjh01@knu.ac.kr)
Kyungpook National University School of Medicine

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Abstract

Background: Surgical margin negativity is highly related to local recurrence of breast cancer. The authors performed this study to evaluate if specimen mammography or ultrasonography can replace the frozen section procedure for surgical margins.

Methods: One-hundred fifty five patients with breast cancer were included in this study. After the surgery, the frozen biopsies were assessed in more than three different directions, and all specimens were analyzed with mammography and ultrasonography. The clinicopathologic characteristics of the patients were assessed, and closest tumor margin–resection margin distance (TM–RM distance) to the tumor was compared among specimen mammography, ultrasonography, and pathology.

Results: On comparing initial cases of positive and negative margins, the mean closest TM–RM distance in specimen ultrasonography and final pathologic reports was statistically different between both groups (DCIS: $p < 0.001$, $p = 0.006$; IDC: $p = 0.042$, $p = 0.022$).

Conclusion: When the closest TM–RM distance is less than 1.8 mm in specimen ultrasonography, the frozen section cannot be waived because of high risk of margin positivity. However, if the closest TM–RM distance is >4 mm in specimen ultrasonography, the frozen section can be omitted carefully because of the very low risk of margin positivity.

Background

Negative surgical margins are essential to reduce the local recurrence rate after breast conserving surgery for breast cancer [1, 2]. Many breast surgeons use frozen sections for intra-operative margin assessment; this helps avoid re-operation by complete re-excision during the ongoing surgery [3–5]. However, viewing frozen sections can be a burden to pathologists and may prolong the surgery. In addition, several local clinics do not hire their own pathologists. To overcome these disadvantages, many physicians recommend using intraoperative mammogram or ultrasound instead of frozen sections [6–9].

Since Schwartz et al. suggested ultrasound as an accurate and effective diagnostic tool for localization of a non-palpable breast mass [4], the intraoperative ultrasound (IOUS) has been applied to identify the location, shape, and number of breast masses during and immediately after resection in the surgery room [6, 10–12]. Using IOUS, the surgeon can assess whether the breast cancer is well removed with sufficient surgical margins, whether the daughter nodule is removed together, and what is the closest tumor margin–resection margin (TM–RM) distance. Specimen mammography is also a useful diagnostic tool to detect non-palpable breast mass with microcalcification or complete removal of localized wire after resection [13, 14].

Although there are many advantages of IOUS and specimen mammography in breast cancer surgery, it is still difficult to completely replace frozen sections in margin assessment because the ultrasound generally shows subjective results depending on the operator[15–17]. Therefore, the authors evaluated the incidence of negative or positive surgical margin with a closest TM–RM distance in specimen mammography, specimen ultrasonography and final pathologic reports.

Methods

From 2008 to 2014, 1040 patients with operable breast cancers underwent surgical management at the Kyungpook National University Hospital. Among them, 557 (53.56%) patients who underwent breast conserving surgery with intraoperative margin evaluation were reviewed for this study, and single mass-forming ductal carcinoma in situ (DCIS) and invasive ductal carcinoma (IDC) cases were included in this study. In addition, nine patients who had mixed type of invasive cancer were excluded. Finally, 155 eligible patients with breast cancer who underwent breast conserving surgery and intra-operative margin evaluation with frozen sections as well as specimen mammogram and ultrasound were included for this study.

All breast cancers were diagnosed by needle biopsy, and the size, location, number of tumors were evaluated with mammography, ultrasonography, and breast magnetic resonance imaging (MRI) before surgery. The treatment strategy of each patient was determined by a multidisciplinary team discussion which comprised breast and plastic surgeons, oncologists, radiologists, pathologists, and radiation oncologists. Based on the tumor stage and characteristics, adjuvant chemotherapy, radiotherapy, or endocrine treatment therapy was additionally applied. The clinicopathologic characteristics were assessed, including patient's age, history of contralateral breast cancer, clinical and pathologic tumor size, nodal status, stage and tumor characteristic including estrogen receptor (ER), progesterone receptor (PR), HER2 gene status.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Review Board of the Kyungpook National University Chilgok Hospital (KNUCH 2015-05-205).

Surgical management and margin evaluation with pathologic finding

The breast cancers were identified with preoperative ultrasonography, and the wire localization with skin marking was performed when the tumor was non-palpable or a daughter nodule existed. The breast cancer was removed with at least a 2-mm safety margin by palpation or blue-dye stained gel marking technique. Either sentinel lymph node biopsy or axillary lymph node dissection was performed according to the axillary lymph node status. For margin assessment, the parenchymal tissues were obtained from more than three different directions of the surgical cavity. The positive result of surgical margin was defined as atypical ductal hyperplasia, ductal carcinoma in situ, or invasive ductal carcinoma. Additional excision and secondary margin evaluation were performed when margin positivity was diagnosed in the intraoperative frozen section until negative surgical margins were secured.

The pathologists assessed the diameters between tumor edge and superior, inferior, lateral, and medial margins and described the same in their final pathologic findings. The closest TM–RM distance was also described in pathologic reports.

Margin evaluation in specimen mammography and ultrasonography

After the breast cancer was removed, the specimen was marked with a black silk tie 3 – 0 for identification of directions. A short tie with one metal clip was fixed in the superior direction and a long tie with two metal clips was fixed in the lateral direction. The specimen was then delivered to the mammography room for specimen mammography, which was performed using a dedicated mammography unit (Lorad Selenia, Hologic) with a single anteroposterior 1.8 × magnification. The specimen was compressed using a standard rigid plastic compression plate during mammography. Then, it was delivered to the radiology unit to be subjected to ultrasonography. For the acoustic wave transmission, water was used instead of ultrasonic gel; water has similar acoustic impedance as that of the ultrasonic gel. The sample was immersed in water, and the radiologists obtained ultrasonographic images of the specimen with various directions of margin (Fig. 1).

After mammographic and ultrasonographic images of specimen were linked to Picture Archiving and Communication System (PACS), the surgeon measured the closest TM–RM distance in the surgery room and determined where the frozen tissue should be evaluated further.

Statistical analysis

Statistical analyses were performed using SPSS ver. 25.0 (SPSS, Chicago, IL, USA). Categorical variables were analyzed using the χ^2 and Fisher's exact tests, and oncologic outcomes were assessed using Kaplan–Meier analysis to identify factors affecting locoregional recurrence or distant metastasis. The p-value < 0.05 was regarded as statistically significant.

Results

There were 86 cases of DCIS and 69 cases of IDC. There was no significant difference in patient age, history of contralateral breast cancer, and type of breast surgery between the two groups. Axillary lymph node dissection and adjuvant chemotherapy were only performed in the IDC group.

Although most pathologic findings, including pathologic tumor size, did not show statistical difference between two groups, the HER2 gene was significantly highly expressed in the DCIS group. Positive results in the initial frozen section were identified in eight cases of DCIS and five cases of IDC ($p = 0.645$). There were three cases of atypical ductal hyperplasia and five cases of DCIS in the DCIS group, and five cases of DCIS in the IDC group. The incidence of locoregional recurrence and distant metastasis occurred only in the IDC group ($p = 0.024$, < 0.001) (Table 1).

Table 1

Clinicopathologic factors of patients with breast cancer who received breast conserving surgery

Variables	Ductal carcinoma in situ (n = 86)	Invasive ductal carcinoma (n = 69)	p-value
Age (mean ± SD, years)	51.52 ± 11.00	50.52 ± 10.01	0.387
History of contralateral breast cancer (n, %)	5 (5.8)	3 (4.4)	0.484
Clinical tumor size (mean ± SD, cm)	1.68 ± 1.52	1.61 ± 0.59	0.778
Pathologic tumor size (mean ± SD, cm)	1.69 ± 1.52	1.51 ± 0.53	0.340
Metastasis of axillary lymph node (n, %)	0	15 (21.7)	< 0.001
Type of breast surgery (n, %)			
Breast conserving surgery	67 (77.9)	55 (79.7)	0.103
Partial mastectomy with reconstruction	19 (22.1)	14 (20.3)	0.096
Type of axillary surgery (n, %)			
Sentinel lymph node biopsy	72 (83.7)	51 (73.9)	0.237
Axillary lymph nodes dissection	-	18 (26.1)	< 0.001
Number of frozen tissues (mean ± SD)	3.18 ± 1.36	3.19 ± 0.65	0.187
Positive results in initial frozen section (n, %)	8 (9.3)	5 (7.3)	0.645
Atypical ductal hyperplasia	3 (3.5)	0	
Ductal carcinoma in situ	5 (5.8)	5 (7.3)	
Positivity of estrogen receptor (n, %)	59 (68.6±)	55 (79.7)	0.326
Positivity of progesterone receptor (n, %)	51 (59.3)	47 (68.1)	0.511
Positivity of HER2/neu gene (n, %)	25 (29.1)	11 (16.0)	0.027
Triple negative breast cancer	10 (11.6)	11 (16.0)	0.116
Adjuvant chemotherapy (n. %)	-	42 (60.9)	< 0.001
Adjuvant radiotherapy (n, %)	79 (91.9)	64 (92.8)	0.094
Adjuvant hormone treatment (n, %)	51 (59.3)	51 (73.9)	0.768

Variables	Ductal carcinoma in situ (n = 86)	Invasive ductal carcinoma (n = 69)	p-value
Follow-up period (mean ± SD, months)	96.15 ± 25.05	87.37 ± 7.15	0.691
Breast cancer-specific events (n, %)			
Locoregional recurrence	-	4 (5.8)	0.024
Distant metastasis	-	3 (4.4)	< 0.001

In both groups, the closest TM–RM distance was lesser in specimen mammography than in specimen ultrasonography and final pathology. The closest TM–RM distance in specimen mammography was larger in the DCIS group than in the IDC group. On comparing the mean closest TM–RM distance between specimen images and pathologic findings according to the tumor types, including DCIS and IDC, there was no significant difference between the two groups in specimen mammography (1.87 ± 1.35 vs. 1.13 ± 0.45), ultrasonography (3.74 ± 0.83 vs. 3.30 ± 0.54), and pathologic findings (4.37 ± 2.81 vs. 3.82 ± 0.53) (Fig. 2, Table 2).

Table 2
Comparison of closest margin between specimen images and pathologic margin status between ductal carcinoma in situ and invasive ductal carcinoma

	Total (n = 155)	Tumor types		
		Ductal carcinoma in situ (n = 86)	Invasive ductal carcinoma (n = 69)	p-value
Closest distance of tumor margin in specimen mammography (mean ± SD, mm)	1.72 ± 0.71	1.87 ± 1.35	1.13 ± 0.45	0.103
Closest distance of tumor margin in specimen ultrasonography (mean ± SD, mm)	3.58 ± 0.71	3.74 ± 0.83	3.30 ± 0.54	0.851
Closest distance of tumor margin in final pathologic reports (mean ± SD, mm)	2.97 ± 2.39	4.37 ± 2.81	2.82 ± 0.53	0.077

When each group was identified and divided according to the initial margin (positive or negative) status in frozen sections, the mean closest TM–RM distance in specimen mammography were similar in positive and negative groups of both DCIS and IDC. However, the group with positive initial margins in frozen sections showed shorter distance of the mean closest TM–RM distance in specimen ultrasonography in DCIS (1.78 ± 1.14 vs. 3.97 ± 2.86, p = 0.001) and IDC (1.02 ± 0.64 vs. 3.82 ± 0.53, p = 0.042). In addition, the positive group of initial margin status in frozen sections showed shorter distance of mean closest margin in final pathologic findings in DCIS (2.06 ± 1.86 vs. 4.61 ± 3.18, p = 0.006) and IDC (0.70 ± 0.52 vs. 2.86 ± 0.52, p = 0.022), and the mean closest distance of tumor margin in specimen ultrasonography and pathologic findings were very similar patterns in both groups (Table 3).

Table 3
Comparison of closest distance of tumor margin between specimen images and pathologic margin status according to the initial margin status

	Ductal carcinoma in situ (n = 86)			**Invasive ductal carcinoma (n = 69)**		
	Positive (n = 8)	Negative (n = 78)	p-value	Positive (n = 5)	Negative (n = 64)	p-value
Closest distance of tumor margin in specimen mammography (mean ± SD, mm)	1.09 ± 1.00	1.88 ± 0.82	0.814	1.40 ± 0.37	1.54 ± 0.46	0.461
Closest distance of tumor margin in specimen ultrasonography (mean ± SD, mm)	1.78 ± 1.14	3.97 ± 2.86	0.001	1.02 ± 0.64	3.82 ± 0.53	0.042
Closest distance of tumor margin in final pathologic reports (mean ± SD, mm)	2.06 ± 1.86	4.61 ± 3.18	0.006	0.70 ± 0.52	2.86 ± 0.52	0.022

Discussion

Negative surgical margins in breast conserving surgery are critical to reduce local recurrence of breast cancer [18–20], and the local control of breast cancer is an essential factor in oncologic outcome because it may prevent distant metastasis. Although the surgical margin can be confirmed on the final pathologic reports, a re-operation would be needed when if positive surgical margins are identified. If the surgical margin can be confirmed during surgery, only re-excision under general anesthesia is needed to secure negative results.

Many breast surgeons use the intra-operative frozen sections to evaluate surgical margin [1, 2, 7]. However, the frozen section for margin assessment requires time and effort on the part of the pathologist which prolongs the operation. Therefore, researchers have tried to predict the margin status using imaging modalities, including specimen mammography, tomosynthesis, and IOUS, to overcome these shortcomings [9, 12, 21–23]. However, most of these are 2D imaging modalities, and their results for the closest distance between tumor and surgical margin would be different compared to the true margin; this is particularly true for specimen mammography because of compression technique, but there are some differences depending on clinics. In addition, because the sonographic images cannot detect an existence of microscopic tumor, a pathologic margin assessment cannot be completely omitted. The authors assumed that a certain distance can be a standard point which has a high probability of positive or negative potential in margin assessment. Then, the number of frozen sections can be reduced, which may lead to reduced surgery duration and reduced burden to the pathologists.

In a recent study, the closest distance was shorter in specimen mammography than in specimen ultrasound and final pathologic reports in both DCIS and IDC groups. Clingan et al. reported that the TM–RM distance of specimen mammography could be distorted by compression of specimen [24]. Conversely, the closest margins of specimen ultrasound showed a similar pattern as those of the final pathologic report. In addition, although the possibility of margin positivity was higher when the closest margin was less than 1.8 mm (1.78 mm in DCIS, 1.02 mm in IDC), the possibility of margin negativity was significantly higher when the closest TM–RM distance was larger than 4 mm (3.97 mm in DCIS, 3.82 mm in IDC). Therefore, the surgeons can carefully skip the frozen sections in which direction the TM–RM distance is more than 4 mm of safety margin.

The authors suggest that the frozen section for margin assessment should be obtained from the cavity in the surgical field by the surgeons themselves. It would be difficult for other physicians, except the surgeon, to have an accurate orientation about the directions of the specimen.

Although the current study provides information on when the frozen sections are needed for margin assessment during surgery, there are several limitations. If a frozen section can be omitted, the operation time and pathologist's burden can be reduced. However, the frozen section cannot be completely omitted in breast conserving surgery to evaluate the status of surgical margins. Several studies reported the results of fluorescence-guided margin assessment in breast conserving surgery to compensate for this disadvantage [25–28]. However, a specific device and agent are necessary to conduct such studies. Another limitation of this study is that the closest TM–RM distance of each technique could not be exactly matched in comparison, which is a common limitation in retrospective studies. More accurate data could have been produced if the tissue could be sampled or measured only in the same direction by staining or placing a clip. However, it is possible to assume that a similar position would have been measured without necessarily indicating the position.

Conclusion

For margin assessment in breast conserving surgery, it would be considerable to omit the frozen section directions wherein the closest TM–RM distance in specimen ultrasound is longer than 4 mm; however, frozen sections should be used in the directions that show the closest TM–RM distance in specimen ultrasound to be shorter than 1.8 mm.

According to our results, the burden on the operators and pathologists who perform frozen sections could be reduced in breast conserving surgery, and the IOUS could be considered a more essential diagnostic tool for breast conserving surgery.

Abbreviations

IOUS: Intraoperative ultrasound; TM-RM: Tumor margin–Resection margin; DCIS: Ductal carcinoma in situ: IDC: Invasive ductal carcinoma; MRI: Magnetic resonance imaging; ER: Estrogen receptor; PR: Progesterone receptor

Declarations

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Not Applicable

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The funder had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Availability of data and material

The datasets generated and/or analyzed during the current study are not publicly available due to the data includes personal information of patients. But are available from the corresponding author on reasonable request.

Author contributions

Guarantor of the integrity of the study: JL; Study concepts: JHJ, JL; Study design: JHJ, WWK; Definition of intellectual content: JL, CSP; Literature research: YJ; Clinical studies: JL< HYP, CSP, HJK, WHK, J(i)-YP, J(e)-YP; Data acquisition: WWK, YSC, SJL; Data analysis: JL; Manuscript preparation: JL, JHJ; Manuscript editing: JHJ; Manuscript review: JHJ, HYP, WWK

And all authors have read and approved the manuscript.

Ethics approval and consent to participate

This study was approved by the institutional review board (IRB) of Kyungpook National University Chilgok Hospital, Daegu, Republic of Korea ((KNUCH 2015-05-205). And the specific inclusion and exclusion criteria were defined in the approved IRB protocol. The informed consents were obtained by written documents from all patients.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

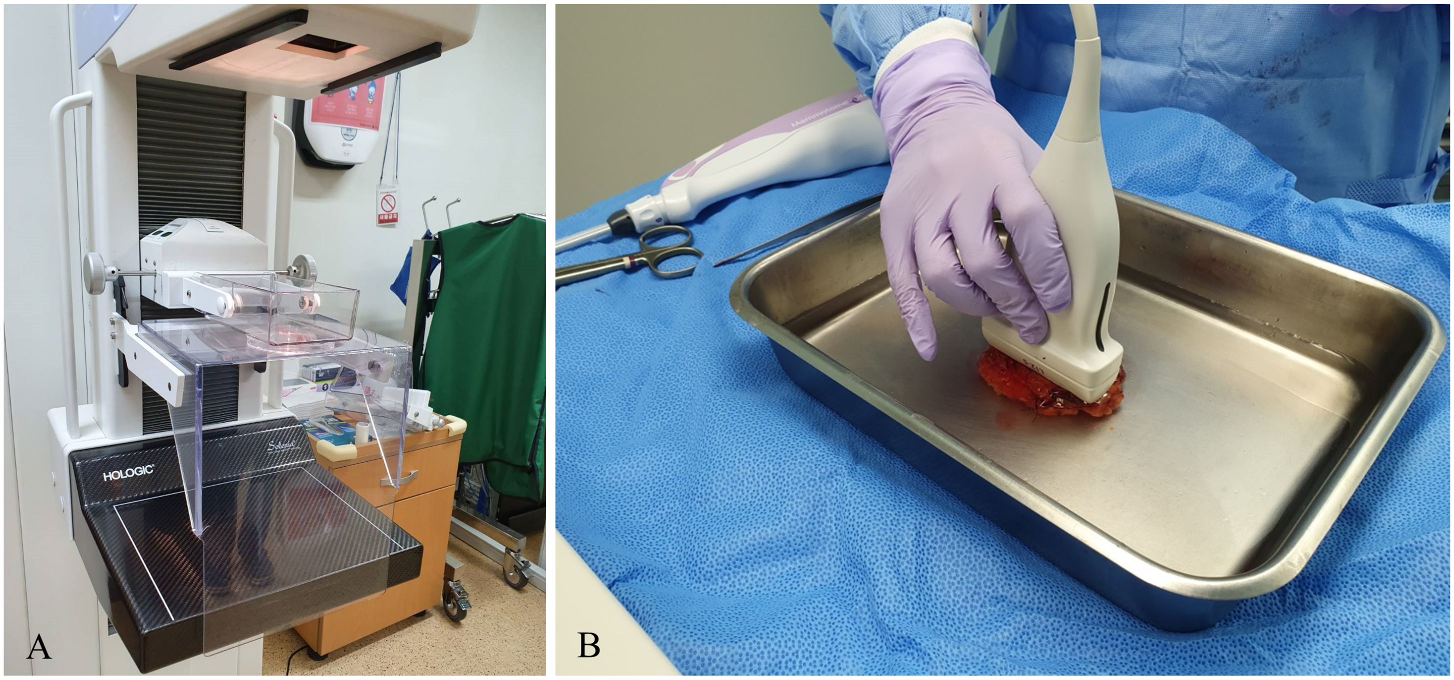

Figure 1

Techniques of specimen mammogram and ultrasound. (A) The specimen was mildly compressed with a standard rigid plastic compression plate for specimen mammography. (B) The surgeon or radiologist performed a specimen ultrasound with water-immersed specimens.

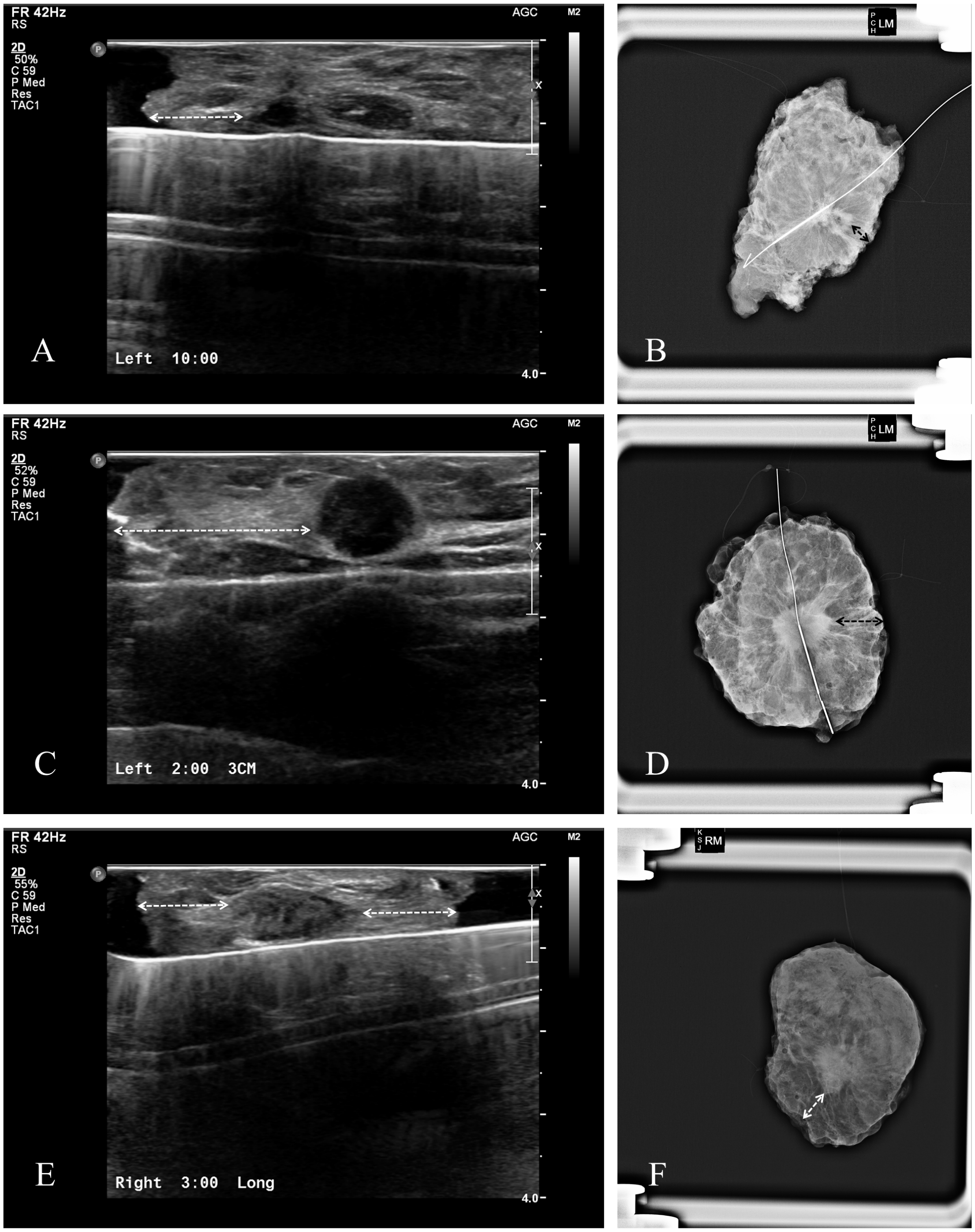

Figure 2

Images of specimen ultrasonography (A,C,E) and mammography (B,D,F). The closest distance between tumor and surgical margin was measured by surgeons themselves when the images were transmitted to Picture Archiving and Communication System (PACS).