

Comparative Evaluation of Ultrasound and Mammography for Assessing Resection Margins in Breast-Conserving Therapy for Breast Cancer

Rares Georgescu¹, Orsolya Bauer¹, Sabin Turdean², Flavian Tutuianu³, Eugeniu Darii⁴, Paula Moraru⁵, Anca Toganel⁶, Cristina Tutuianu Radoi^{1*}

¹Department of Surgery, G.E. Palade University of Medicine, Pharmacy, Science and Tehnology, Târgu Mureș, Romania

²Department of Pathology, G.E. Palade University of Medicine, Pharmacy, Science and Tehnology, Targu Mureș, Romania

³Department of Gynecology, G.E. Palade University of Medicine, Pharmacy, Science and Tehnology, Targu Mureș, Romania

⁴Department of General Surgery, Oncocard Brașov, Romania

⁵Department of Radiology, G.E. Palade University of Medicine, Pharmacy, Science and Tehnology, Targu Mureș, Romania

⁶Department of Oncology, G.E. Palade University of Medicine, Pharmacy, Science and Tehnology, Targu Mureș, Romania

***Corresponding author:**

Cristina Tutuianu Radoi, MD
Gheorghe Marinescu no 1
Targu Mures, Romania
E-mail: Cristina.radoi13@gmail.com

Rezumat

Evaluarea comparativă a ecografiei și mamografiei pentru aprecierea marginilor de rezecție în chirurgia conservatoare a sânului în cancerul mamar

Introducere: Au fost explorate diverse tehnici de măsurare intraoperatorie a marginilor de rezecție pentru a preveni marginile pozitive în chirurgia conservatoare a sânului. Deși există mai multe metode, niciuna nu este perfectă, iar majoritatea sunt costisitoare și dificil de accesat.

Materiale și Metode: Acest studiu prospectiv a fost realizat în Clinica de Chirurgie a Spitalului Clinic Județean Mureș, utilizând date de la paciente cu cancer mamar care au suferit tratament conservator între 2014 și 2019. Marginile de rezecție au fost măsurate prin ecografie și mamografie, iar aceste valori au fost comparate cu rapoartele histopatologice.

Rezultate: Au fost înscrși 166 de pacienți, dintre care 10 pacienți (6,02%) au avut margini de rezecție pozitive. Pentru ecografie, la o limită de 2 mm, sensibilitatea a fost de 63,86%, iar specificitatea a fost de 93,98%; la o limită de 5 mm, sensibilitatea a crescut la 95,78%, cu aceeași specificitate de 93,98%. Pentru mamografie, la o limită de 2 mm, sensibilitatea a fost de 6,627%, iar specificitatea de 93,98%; la o limită de 5 mm, sensibilitatea a fost de 37,35%, specificitatea rămânând la 93,98%.

Concluzii: Ecografia la o limită de 5 mm a demonstrat o sensibilitate mai mare comparativ cu o limită de 2 mm, în timp ce mamografia a demonstrat o sensibilitate scăzută la ambele limite. Aceste rezultate indică faptul că, deși ambele metode au o specificitate ridicată, acuratețea și sensibilitatea lor variază, necesitând o interpretare prudentă pentru utilizarea clinică.

Cuvinte cheie: cancer de sân, chirurgie conservatoare a sânului, ecografie intraoperatorie, mamografie

Simple Summary

This research investigates methods to improve the accuracy of intraoperative measurements of resection margins during breast-conserving surgery, aiming to reduce the likelihood of leaving behind cancerous tissue. Conducted at Mures County Clinical Hospital between 2014 and 2019, the study compares the effectiveness of ultrasound and mammography in measuring these margins against histopathological reports. The findings show that while ultrasound and mammography have varying levels of sensitivity and specificity depending on the margin cut-off used, neither method is perfect. Understanding the strengths and limitations of these techniques can help surgeons make more informed decisions during surgery, potentially improving patient outcomes in breast cancer treatment.

Abstract

Introduction: Various techniques for intraoperative measurement of resection margins have been explored to prevent positive margins in breast-conserving surgery. Although multiple methods exist, none is perfect, and most are costly and not easily accessible.

Material and Methods: This prospective study was conducted at the Surgical Clinic of Mures County Clinical Hospital, utilizing data from breast cancer patients who underwent conservative treatment between 2014 and 2019. Resection margins were measured using ultrasound and mammography, and these values were compared with histopathological reports.

Results: A total of 166 patients were enrolled, with 10 patients (6.02%) having positive resection margins. For ultrasound, at a 2 mm cut-off, sensitivity was 63.86% and specificity was 93.98%; at a 5 mm cut-off, sensitivity increased to 95.78% with the same specificity of 93.98%. For mammography, at a 2 mm cut-off, sensitivity was 6.627% and specificity was 93.98%; at a 5 mm cut-off, sensitivity was 37.35% with the specificity remaining at 93.98%.

Conclusions: Ultrasound at a 5 mm cut-off showed higher sensitivity compared to a 2 mm cut-off, while mammography showed low sensitivity at both cut-offs. These results indicate that, while both methods have high specificity, their accuracy and sensitivity vary, necessitating cautious interpretation for clinical use.

Keywords: breast cancer, breast conserving surgery, intraoperative ultrasound, mammography

Introduction

Breast cancer remains the most frequent malignancy among women and is also one of the main causes of mortality in both Europe and the United States (1).

Initially, surgical management of early breast cancer was not breast-preserving. In 1894 William Halsted revolutionized his time with the radical mastectomy. Half a century later, in 1948 Patey and Madden refined the procedure, introducing the modified radical mastectomy (2-4). Medicine evolved and paradigms shifted, making breast conservation therapy the desired technique after the 1991 National Institute of Health Consensus on breast cancer, determined by the Veronesi and Fisher studies, a few years earlier (5-7).

For individuals diagnosed with early-stage breast cancer, the primary objective is to achieve tumor-free margins at the definitive histopathological evaluation (8,9). Some of the earliest studies addressing this issue were conducted by the

Gustave Roussy Institute (1988), Stanford University Medical Center (1972–1992), and the START trial (1992–2002) (10-12).

The introduction of mammographic screening has facilitated the detection of smaller, frequently impalpable tumors suitable for conservative approaches instead of mastectomy, that are amenable to breast-conserving surgical approaches as opposed to mastectomy (13).

According to two large randomized controlled trials, ESMO and NCCN guidelines, breast conserving therapy consists of lumpectomy and postoperative radiotherapy represents the gold standard treatment for early-stage breast cancer (14,15).

The most important factor in the management of breast conserving surgery is the status of resection margins. Positive resection margins require re-excision. Currently, the resection margins are considered negative from the histopathological point of view if they respect the principle “no ink on tumor” for invasive breast

cancer (16). Even if re-excision does not affect the overall survival, it can increase the perioperative anxiety, it has poor cosmetic results and delay in adjuvant chemotherapy and radiotherapy (17).

The incidence of local recurrence in the case of positive or close resection margins is well documented: 27% and 15% for positive or close resection margins, respectively, versus 7% for negative margins. Reported re-excision rates due to positive margins vary widely among different centers, ranging from 4.2% to 60% (18,19).

Having positive margins approximately doubles the likelihood of developing a local recurrence (20).

Theoretical, a mass is clearly identifiable and the distance to various resection margins measurable, but in reality, the mass is irregular. This confirms the fact that the macroscopic and palpatory examination of the operative specimen is not enough for the evaluation of the resection margins (21).

The current intraoperative approach often combines diagnostic and therapeutic methods, giving rise to the so-called 'theranostic' concept, where ultrasound plays a key role in evaluating margin status and distinguishing normal tissue from benign or malignant lesions (22-24). As early as 1988, Schwartz introduced ultrasound as an alternative tool for identifying non-palpable breast tumors (25,26).

Subsequently, multiple studies have validated its practicality and safety in both palpable and non-palpable breast tumor cases (27-31).

Over the years, several techniques of intraoperative measurement of resection margins have been tried in order to avoid positive margins.

Specimen mammography is widely used to assess margin status intraoperatively. However, its diagnostic accuracy remains controversial. Some studies have shown that specimen mammography was reliable in identifying clear margins and reduced the rate of reintervention, while others have indicated it to be not accurate enough.

The performance of these techniques has been reviewed in a recent meta-analysis (32,33). At present, there is no method that combines high accuracy with minimal disruption of the surgical workflow.

High-resolution FDG-PET/CT can facilitate intra-operative margin assessment during BCS. (34).

The ROLL method has demonstrated comparable reliability and effectiveness to wire-guided localization (WGL) for identifying non-palpable breast lesions. Moreover, ROLL seems to outperform WGL by reducing localization time

and surgical duration, while achieving a greater proportion of tumor-free margins, even though the excised specimen weight is generally lower (35).

Innovative intraoperative modalities, including positron emission tomography, radioguided occult lesion localization, and near-infrared fluorescence imaging, are being explored for their potential to enhance surgical results and minimize the necessity of re-excision in breast-conserving therapy (10).

Even though numerous intraoperative techniques have been developed to measure margins during conservative breast surgery, all present limitations, being either imperfect, costly, or not widely accessible.

The aim of the study was to evaluate which one of the two methods (ultrasound and mammography of the operating specimen) is more accurate in assessing the surgical resection margins in breast conserving surgery for breast cancer.

Material and Method

This is a prospective study performed in the Surgical Clinic of Mures County Clinical Hospital. We used patient data, all female, diagnosed with breast cancer, who benefited from conservative breast treatment between 2014 and 2019. All 166 patients included in the study were operated on by the same surgeon, the same one who measured the resection part by ultrasound. The mammography of the operative specimen was performed and interpreted by the same radiologist, and the histopathological report was issued by the same pathologist. We used the database of the clinic to collect general information about the patients, the surgical notes to collect the information related to the type of surgery, re-mammography report and ultrasound report for the measurement of the surgical margins and the histopathological reports for the status of resection margins.

For initial diagnosis, all patients with a lesion suspicious of breast carcinoma underwent core biopsy with subsequent histological tissue analysis; therefore, the diagnosis of breast carcinoma of all patients enrolled in this study was histopathologically assessed (light microscopy), including a determination of the intrinsic subtypes viz. "Luminal A", "Luminal B", "HER2", "Triple negative", by means of additional immunohistochemical analyses. All tumors that benefited from neoadjuvant chemotherapy were marked (clipped) immediately after biopsy, a standard

procedure marking the initial area of first tumor occurrence pre-therapeutically which allows for safe tumor area identification and removal in case of proven pCR. All patients included in the study were pre-staged according to national guidelines; the cancer staging of all patients enrolled was M0 according to the TNM Classification of Malignant Tumors (UICC/AJCC staging system).

For the histopathological report, there is a series of mandatory required information: date of the surgical intervention, date of arrival in the pathology department; patient's contact and identification data, clinical diagnostic, location of the lesion (specimen laterality right/left, bilateral, quadrant), type of surgical intervention (tru-cut biopsy, sectorectomy, mastectomy, axillary excision, sentinel lymphnode biopsy, previous oncological treatment, previous investigations (mammography, ultrasonography, MRI, previous histopathological diagnosis, including immunohistochemistry).

The specimen route includes: fixation in buffer formalin (10%) for at least 24 hours before submission, sampling and re-mammography if necessary, especially for cases which received previous oncological treatment, histopathological processing for hematoxylin and eosin stained slides (washing, dehydration, clarification, paraffin imbedding, sectioning, deparaffination, rehydration, staining, mounting, and labeling).

For the local excision of a palpable tumoral mass, the specimen processing includes the following procedures: orientation of the specimen (localization wires), size of the specimen (three dimensions in millimeters), measure and describe

the attached skin if present, re-mammography is performed if necessary. After that, the specimen is dried and inked and the excess ink is removed. We slice the entire specimen into about 1 cm thick slices and describe the cut section appearance (presence of fibrosis, cystic structures: size, number, content, calcifications, tumoral lesions: number, if multiple -distance between lesions, size -three dimensions in millimeters, color, border, consistency, presence of necrosis, distance from each resection margin -anterior, posterior, inferior, superior, medial, lateral).

In our study, 10 patients out of 166 had at least one positive resection margins according to the final histopathological report.

After the excision of surgical specimen, the surgeon measured the surgical margins by ultrasound. In the case of patients who had a complete imaging response, the measurement of the margins was made from the marker clip.

Ultrasound measurement of resection margins is illustrated in *Fig. 1*.

The next step was intraoperative ultrasound assessment of the specimen, using ultrasound machine with the frequency linear transducer set at 12 MHz. The procedure was performed into the operating room directly on the specimen after resection, without prior immersion of the surgical piece in saline solution.

If one or more margins were very close (less than 2 mm), he performed a re-excision of the margin in order to obtain the adequate oncological margins and avoid re-excision. At the end of the surgery, every surgical specimen was mammographed in order to measure the resection margins.

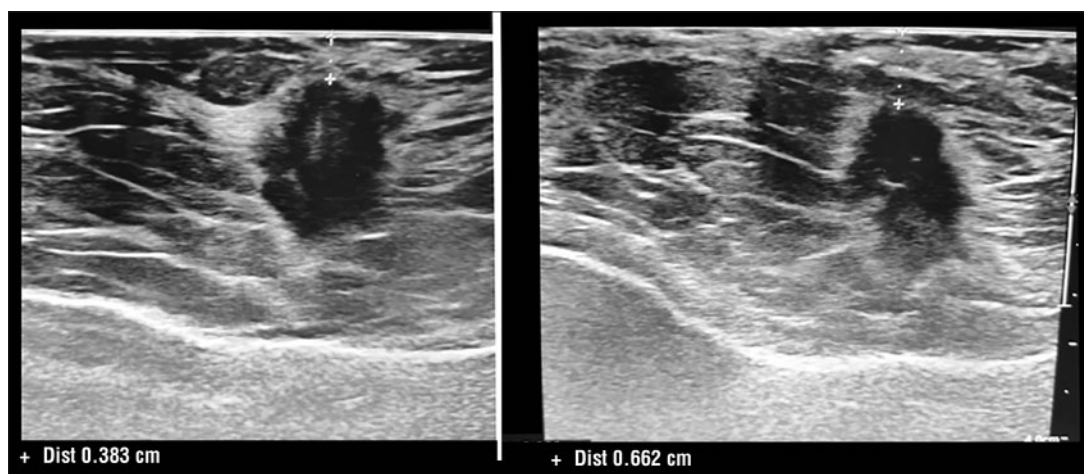


Figure 1. Ultrasound measurement of resection margins

Specimen ultrasonography (USG) was carried out after the surgical piece was oriented by team members experienced in breast ultrasound. Orientation was achieved by the surgeon using sutures, following the standard convention of '12 o'clock,' '9 o'clock,' and 'short/long wire.' The tumor-to-margin distances were then measured sonographically and documented for superior, inferior, lateral, medial, anterior (often including skin), and posterior (frequently involving the fascia of the pectoralis major muscle). For every case, it was noted whether margins were tumor-free, if additional excision was performed, whether these corresponded to the closest histological margins, and if reoperation became necessary.

The ultrasonographic measurements were subsequently compared with the final pathology report provided by the pathologist. Therefore, each resection margin was measured by ultrasound and mammography and we compared these values with the histopathological reports.

Statistical Analysis

Statistical data analysis was performed using GraphPad Prism 9, using Fisher's exact test, and ROC curves, and we analyzed the sensibility and sensitivity of each technique, establishing two cut-off values (2-5 mm).

Results

A total number of 166 patients were included in the study. The youngest patient included in the study was 33 years old and the oldest was 89 years old with a mean age of 58 years old. All patients

underwent conservative surgery, and all the surgical procedures were performed by the same surgeon. After surgery, the resections margins were measured by the same surgeon using ultrasound.

Of the 166 patients, 57 patients benefited from re-excision during the surgery after ultrasound evaluation of the resection margins representing 34.33%. Also, 33 patients underwent 2 or more re-excised margins.

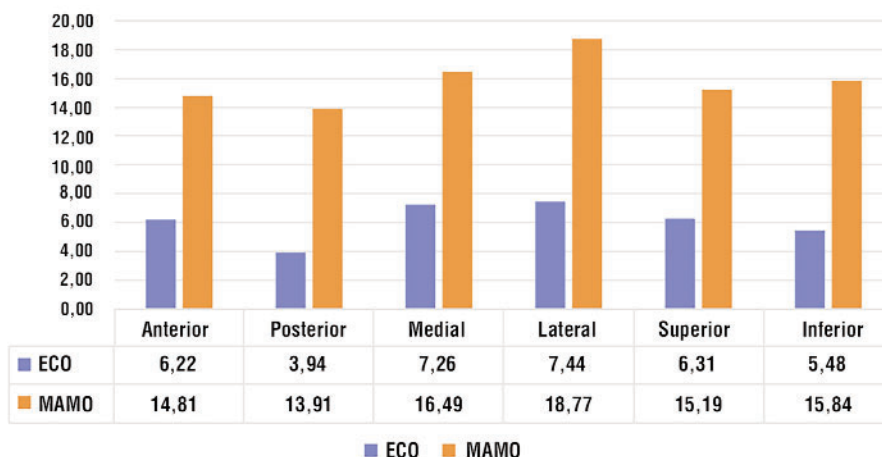
We calculated the average distances of surgical resection margins measured by ultrasound and mammography and we obtained the following results which are summarized on *Fig. 2*. The average of the anterior resection margins was 6.22 mm measured by ultrasound and 14.81 mm by mammography. Posteriorly, it was 3.94 mm measured by ultrasound and 13.91 mm mammographically. On the medial edge, it was 7.26 mm on ultrasound and 16.49 mm on mammography. The average of the lateral resection margins measured by ultrasound was 7.44 mm and 18.77 mm measured mammographically. The average of the superior resection margins measured by ultrasound was 6.31 mm and 15.19 mm measured mammographically. The average of the inferior resection margins measured by ultrasound was 5.48 mm and 15.84 mm mammographically.

After excision of the surgical specimen and its ultrasound measurement, the surgical specimen was marked with positioning wires and metal clips, re-mammographed and later sent for histopathological examination.

The mammographic measurement of the resection margins was made by the same radiologist.

After the histopathological examination, 10

Figure 2. Average resection margins



patients from the total of 166 patients included in our study were identified with positive resection margins representing a percentage of 6.02%. In one of the 10 patients, the histopathologically identified positive resection margin was the anterior one representing the skin, which is why she did not benefit from surgical re-intervention. The fascia of the pectoralis major muscle was excised in all patients included in our study, however, in 2 patients the positive resection margin was the posterior one representing the pectoral major muscle. The medial resection margin was positive in 1 case, and the lateral resection margin was involved in 1 patient. In 2 patients, the superior resection margin was positive. In 3 patients, the positive resection margin was the inferior one.

In one of the 10 patients with histopathologically positive resection margins, the involved resection margin was re-excised intraoperatively because it measured 1 mm on ultrasound. The re-excised resection margin was negative, which is why the 2nd

operation was not necessary for this patient.

We chose a cut-off of 2 mm, respectively 5 mm and analyzed the data using ROC curves.

In terms of ultrasound, at a cut-off of 2 mm, we obtained a sensitivity of 63.86% and a specificity of 93.98%, while for a cut-off of 5 mm, the sensitivity is 95.78 %, and 93.98% specificity (*Fig. 3 A,B*).

In terms of mammography for the same cut-off of 2mm we obtained a sensitivity of 6.627% and specificity of 93.98%. For the cut-off of 5mm the sensitivity was 37.35% and 93.98% specificity (*Fig. 4 A,B*).

Using the actual values from *Table 1* and the statistic formula of accuracy from *Fig. 5*, we estimated the accuracy for each measurement from our study, and we obtained the results shown in *Table 2*.

Discussions

There is no unanimously accepted theory for positive resection margins in breast conserving

Figure 3. (A) ROC curve: eco < 2 mm;
(B) ROC curve: eco < 5 mm;

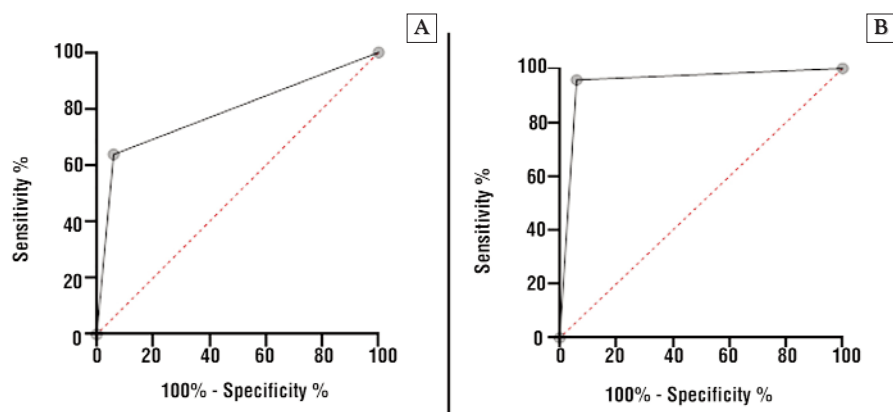


Figure 4. (A) ROC curve: mammo < 2 mm;
(B) ROC curve: mammo < 5 mm;

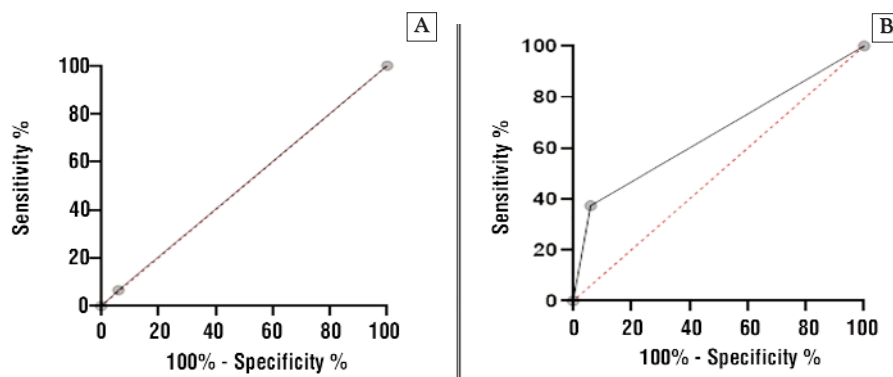


Table 1. Actual values

	Eco<2 mm	Eco<5 mm	Mamo<2 mm	Mamo<5 mm
TP	6	9	4	6
FN	100	150	8	56
TN	56	6	149	100
FP	4	1	6	4
TOTAL	166	166	166	166

TP=true positive; FN=false negative; TN=true negative; FP=false positive

surgery for invasive breast cancer, but currently the “no ink on tumor” principle is accepted (36). It is known that positive resection margins are associated with an increased risk of local recurrence, which is why the reduction of positive resection margins in breast conserving surgery for breast cancer is a major concern (37).

According to the guidelines, all patients underwent postoperative radiotherapy after breast conservative surgery, and for patients with positive margins, re-intervention was performed in order to re-excite the involved margin.

Nowadays, considering the fact that all patients follow postoperative radiotherapy, in some cases of positive margins the surgical re-excision can be omitted.

According to a study published in 2014 which represents a meta-analysis of 33 studies, the percentage of positive resection margins after conservative breast surgery is between 20-40% (37). In our study, the percentage of positive resection margins is 6.02%. We consider that the lower percentage of positive resection margins in our study is due to the use of intraoperative ultrasound for each patient.

In a meta-analysis published in 2022, the authors indicated that the mammography specimen was an accurate intraoperative imaging technique for margin assessment in BCS (38) which correlates with the results obtained in our study.

A 2010 study aimed to measure intraoperative ultrasound margins and to evaluate their correlation with tumor size, multifocality, palpability, histological type, and intraductal component. The authors concluded that intraoperative ultrasound can contribute to maintaining a low reoperation rate following breast-conserving surgery. Margins smaller than 0.5 cm detected by ultrasound should be re-excised during the initial procedure. However, its accuracy in predicting the closest pathological margins was reduced in patients with multifocal disease (39). These findings are consistent with the observations made in our own study

Table 2.

	Eco>2 mm	Eco>5 mm	Mamo>2 mm	Mamo>5 mm
Accuracy	63%	91%	8%	37%

$$\text{Accuracy} = \frac{(TP + TN)}{(TP + FP + TN + FN)}$$

Figure 5.

Romanucci et al. investigated the accuracy of digital breast tomosynthesis compared to full-field digital mammography for evaluating tumor-free resection margins in the intraoperative specimen during breast-conserving surgery and they found that digital breast tomosynthesis is more accurate in the assessment of margin status than digital mammography; it could be a more accurate technique than full-field digital mammography for the intraoperative delineating of tumor resection margins (40).

Several factors may influence the diagnostic precision of specimen mammography. Goldfeder reported that agreement between radiographic and histopathological findings was greater when a single-view image was used compared with two-view imaging. Specimen mammography proved more accurate in assessing margins of lesions with microcalcifications than in other breast tumor types. In certain subtypes, such as medullary carcinoma, positive margin signs on radiography may not indicate true tumor presence but rather a non-neoplastic lymphocytic infiltrate.

Additional significant drawbacks of intraoperative specimen mammography include: (1) its two-dimensional nature, which limits the representation of a three-dimensional specimen, and (2) its reduced soft-tissue contrast, which makes margin evaluation increasingly difficult in dense breasts (41). Another possible explanation for the discrepancy between US and histo-pathologic results can be the “pancake phenomenon” that may contribute to the inaccuracy of margin assessment. Breast specimen presents a substantial change in shape and size at imaging and histo-pathological analysis: in fact the specimen compression during sonography (or radiography) cause a flattening of the specimen that may have significant implications for margin assessment, resulting in false margin positivity and in unnecessary surgery (re-excisions for margins incorrectly classified as positive at imaging). In Dooley’s series, 29 the false-

positive lumpectomy margins related to specimen handling accounted for 63% of un-necessary re-excision lumpectomies (42).

In order to minimize the risk of having positive resection margins, we try to obtain a minimum of 5 mm ultrasound measured for each resection margin whenever possible. But, in certain situations, when the tumor is very close to the areola, or in the case of the posterior resection margin (fascia of the pectoralis major muscle) or the anterior resection margin (skin), the resection margin is smaller (2 mm from the tumor to the margin of operating piece).

Conclusions

1. In terms of ultrasound, at a cut-off of 2 mm, we obtained a sensitivity of 63.86% and a specificity of 93.98%, while for a cut-off of 5 mm, the sensitivity is higher (95.78 %) and the specificity is the same. Concerning the cut-off that we should consider in ultrasonography, our study proves the 2 mm cut-off is more appropriate considering that we are discussing a surgical technique that attempts to preserve the breast.
2. In terms of mammography for the cut-off of 2 mm we obtained a sensitivity of 6.627% and specificity of 93.98%. For the cut-off of 5 mm the sensitivity was much higher (37.35%) and the same specificity.
3. According to our study, the accuracy of ultrasound, at a cut-off of 2 mm for negative resection margin, is of 63%, while for a cut-off of 5 mm for negative resection margin, the accuracy is 91%. For the mammography, the accuracy was 8% at a cut-off of 2 mm for negative resection margin and 37% at a cut-off of 5 mm.

In conclusion, both mammography of the surgical specimen and ultrasound of the surgical specimen are useful tools in assessing resection margins and should be used whenever available, especially in the absence of other more expensive techniques.

Conflicts of Interest

We also confirm that the authors of this article have no conflicts of interest.

Financial Disclosure

We also confirm that the authors of this article have not received any funds for this study.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin*. 2012;62(1):10.
2. Brunnicardi CF, Andersen DK, Billiar TR, Dunn DL, Hunter JG, et al. Schwartz's principles of surgery tenth edition. Ed. McGraw-Hill Education. 2015, p. 17, 497-499, 537-548.
3. De Moulin D. A short history of breast cancer. Ed. Kluwer Academic Publishers. 1989, p. 1-9, 17-30.
4. Halsted WS. I. The Results of Operations for the Cure of Cancer of the Breast Performed at the Johns Hopkins Hospital from June, 1889, to January, 1894. *Ann Surg*. 1894;20(5):497-555.
5. Mohsin SK. Frozen section library: breast. Ed. Springer. 2012; p. 2:33-34.
6. Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. *N Engl J Med*. 2002;347(8):567-575.
7. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med*. 2002;347(16):1227-1232.
8. Houssami N, Macaskill P, Marinovich ML, Dixon JM, Irwig L, Brennan ME, et al. Meta-analysis of the impact of surgical margins on local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy. *Eur J Cancer*. 2010;46:3219-3232.
9. Smitt MC, Nowels K, Carlson RW, Jeffrey SS. Predictors of reexcision findings and recurrence after breast conservation. *Int J Radiat Oncol Biol Phys*. 2003;57:979-985.
10. Sarrazin D, Arriagada R, Contesso G, Fontaine F, Spielmann M, et al. Ten-year results of a randomized trial comparing a conservative treatment to mastectomy in early breast cancer. *Radiother Oncol*. 1989;14(3):177-84.
11. Smitt MC, Nowels KW, Zdeblick MJ, Jeffrey S, Carlson RW, Stockdale FE, et al. The importance of the lumpectomy surgical margin status in long-term results of breast conservation. *Cancer*. 1995;76(2):259-267.
12. START Trialists' Group, Bentzen SM, Agrawal RK, Aird EG, Barrett JM, Barrett-Lee PJ et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet Oncol*. 2008;9:331-341.
13. Morrow M, White J, Moughan J, et al. Factors predicting the use of breast-conserving therapy in stage I and II breast carcinoma. *J Clin Oncol*. 2001;19(8):2254.
14. <https://www.esmo.org/guidelines>
15. <https://www.nccn.org/guidelines/nccn-guidelines>
16. Coates AS, Winer EP, Goldhirsch A, Gelber RD, Gnant M, Piccart-Gebhart M, et al. Tailoring therapies--improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. *Ann Oncol*. 2015;26(8):1533-46.
17. Vos EL, Jager A, Verhoef C, Voogd AC, Koppert LB. Overall survival in patients with a re-excision following breast conserving surgery compared to those without in a large population-based cohort. *Eur J Cancer*. 2015;51(3):282-91.
18. Schiller DE, Le LW, Cho BCJ, Youngson BJ, McCready DR. Factors associated with negative margins of lumpectomy specimen: potential use in selecting patients for intraoperative radiotherapy. *Ann Surg Oncol*. 2008;15(3):833-42.
19. Aziz D, Rawlinson E, Narod SA, Sun P, Lickley HLA, McCready DR, et al. The role of reexcision for positive margins in optimizing local disease control after breast-conserving surgery for cancer. *Breast J*. 2006;12(4):331-7.
20. Houssami N, Macaskill P, Marinovich ML, Dixon JM, Irwig L, Brennan ME, et al. Meta-analysis of the impact of surgical margins on local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy. *Eur J Cancer*. 2010;46(18):3219-32.
21. Emmadi R, Wiley EL. Evaluation of resection margins in breast conservation therapy: the pathology perspective--past, present, and future. *Int J Surg Oncol*. 2012;2012:180259.
22. Pleijhuis RG, Graafland M, de Vries J, Bart J, de Jong JS, van Dam GM. Obtaining adequate surgical margins in breast-conserving therapy for patients with early-stage breast cancer: current modalities and future directions. *Ann Surg Oncol*. 2009;16(10):2717-30.
23. Mamou J, Oelze ML, O'Brien WD Jr, Zachary JF. Extended three-dimensional impedance map methods for identifying ultrasonic scattering sites. *J Acoust Soc Am*. 2008;123(2):1195-1208.
24. Li C, Duric N, Huang L. Breast imaging using transmission ultrasound: recon-

- structing tissue parameters of sound speed and attenuation in 2008 International Conference on BioMedical Engineering and Informatics: 27-30 May 2008, Sanya, China. Peng Y, Zhang. 2008;708-712.
25. Schwartz GF, Goldberg BB, Rifkin MD, D'Orazio SE. Ultrasonography: an alternative to x-ray-guided needle localization of nonpalpable breast masses. *Surgery*. 1988;104(5):870-3.
 26. Rahusen FD, Bremers AJ, Fabry HF, Taets van Amerongen AH, Boom RP, Meijer S. Ultrasound-guided lumpectomy of nonpalpable breast cancer versus wire-guided resection: a randomized clinical trial. *Ann Surg Oncol*. 2002;9(10):994-8.
 27. Davis KM, Hsu CH, Bouton ME, Wilhelmson KL, Komenaka IK. Intraoperative ultrasound can decrease the re-excision lumpectomy rate in patients with palpable breast cancers. *Am Surg*. 2011;77(6):720-5.
 28. Fisher CS, Mushawah FA, Cyr AE, Gao F, Margenthaler JA. Ultrasound-guided lumpectomy for palpable breast cancers. *Ann Surg Oncol*. 2011;18(11):3198-203.
 29. Olsha O, Shemesh D, Carmon M, Sibirsky O, Abu Dalo R, Rivkin L, et al. Resection margins in ultrasound-guided breast-conserving surgery. *Ann Surg Oncol*. 2011;18(2):447-52.
 30. Scaranelo AM, Moshonov H, Escallon J. A prospective pilot study of analysis of surgical margins of breast cancers using high-resolution sonography. *Springerplus*. 2016;5:251.
 31. Devolli-Disha E, Manxhuka-Kërliu S, Ymeri H, Kutlllovci A. Comparative accuracy of mammography and ultrasound in women with breast symptoms according to age and breast density. *Bosn J Basic Med Sci*. 2009;9(2):131-6.
 32. St John ER, Al-Khudairi R, Ashrafian H, Athanasiou T, Takats Z, Hadjiminas DJ, et al. Diagnostic accuracy of intraoperative techniques for margin assessment in breast cancer surgery: a metaanalysis. *Ann Surg*. 2017;265(2):300-310.
 33. Dowling GP, Hehir CM, Daly GR, Hembrecht S, Keelan S, Giblin K, et al. Diagnostic accuracy of intraoperative methods for margin assessment in breast cancer surgery: A systematic review & meta-analysis. *Breast*. 2024;76:103749.
 34. Göker M, Marcinkowski R, Van Bockstal M, Keereman V, Van Holen R, Van Dorpe J, et al. 18F-FDG micro-PET/CT for intra-operative margin assessment during breast-conserving surgery. *Acta Chir Belg*. 2020;120(5):366-374.
 35. Ocal K, Dag A, Turkmenoglu O, Gunay EC, Yucel E, Duce MN. Radioguided occult lesion localization versus wire-guided localization for non-palpable breast lesions: randomized controlled trial. *Clinics (Sao Paulo)*. 2011;66(6):1003-7.
 36. Houssami N, Macaskill P, Marinovich ML, Dixon JM, Irwig L, Brennan ME, et al. Meta-analysis of the impact of surgical margins on local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy. *Eur J Cancer*. 2010;46(18):3219-32.
 37. Houssami N, Macaskill P, Marinovich ML, Morrow M. The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. *Ann Surg Oncol*. 2014;21(3):717-30.
 38. C Lin, Wang KY, Chen HL, Xu YH, Pan T, Chen YD. Specimen mammography for intraoperative margin assessment in breast conserving surgery: a meta-analysis. *Sci Rep*. 2022;12(1):18440. A
 39. Oded Olsha MB, BS, David Shemesh MD, Moshe Carmon MD et al. Resection margins in ultrasound-guided breast-conserving surgery. *Ann Surg Oncol*. 2011; 18(2):447-52.
 40. Romanucci G, Mercogliano S, Carucci E, Cina A, Zantedeschi E, Caneva A, et al. Diagnostic accuracy of resection margin in specimen radiography: digital breast tomosynthesis versus full-field digital mammography. *Radiol Med*. 2021; 126(6):768-773.
 41. Lin C, Wang Ky, Chen HL, Xu YH, Pan T, Chen YD. Specimen mammography for intraoperative margin assessment in breast conserving surgery: a meta-analysis. *Sci Rep*. 2022;12(1):18440.
 42. Londero V, Zuiani C, Panozzo M, Linda A, Girometti R, Bazzocchi M. Surgical specimen ultrasound: Is it able to predict the status of resection margins after breast-conserving surgery? *Breast*. 2010;19(6):532-7.