Ultrasound-Assisted Tumor Surgery in Breast Cancer – A Prospective, Randomized, Single-Center Study (MAC 001)

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Ultraschall-assistierte Tumorchirurgie beim Mammakarzinom – eine prospektive, randomisierte, monozentrische Studie (MAC 001)

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ABSTRACT

Purpose Breast-conserving therapy is associated with a risk of tumor-involved margins. For intraoperative orientation, non- palpable or indistinctly palpable lesions are wire-marked prior to surgery. Ultrasound-guided surgery has the potential to reduce the number of tumor-involved margins. In the MAC 001 trial we evaluated ultrasound-guided breast-conserving surgery compared to wire-guided surgery with regard to free tumor margins, duration of surgery and resection volume.

Materials and Methods In this randomized, prospective, single-center controlled trial, patients with ductal invasive breast cancer were recruited for either ultrasound-guided or wire localization surgery. Primary outcomes were tumor-free resection margins, the reoperation rate and the resection volume in each group. The results were analyzed by intention to treat. The trial was registered under ClinicalTrials.gov NCT02222675.

Results 56 patients were assessed, and 47 patients were evaluated in the trial. 93 % (25/27) of the patients in the ultrasound arm had an R0 reoperation compared to 65 % (13/20) in the wire localization control arm. This result was statistically significant ($p = 0.026$). No statistical difference was found for the resection volume or the duration of surgery between the two arms. No major complication was seen in either arm.

Conclusion Ultrasound-assisted breast surgery significantly increases the possibility of tumor-free margins and therefore reduces the risk of reoperations. Breast surgeons should be trained in ultrasound and ultrasound should be available in every breast surgery operating room.

ZUSAMMENFASSUNG

Ziel Die brusterhaltende Therapie des Mammakarzinoms unterliegt dem Risiko der R1-Resektion. Zur intraoperativen Orientierung werden nicht oder unsicher palpable Tumoren vor der Operation mittels Draht markiert. Mittels der ultraschall-assistierten Tumorchirurgie kann die Rate an R1 Resektionen reduziert werden. Die MAC 001 Studie verglich die ultraschall-assistierte Tumorchirurgie mit der konventionellen drahtmarkierten Chirurgie und untersuchte dabei die R0-Resektionsrate, Operationszeit und das Resektionsvolumen.

Material und Methode Patientinnen mit einem invasiv duktalen Mammakarzinom wurden in die prospektiv, randomisierte, unizentrische Studie eingeschlossen und entweder in den ultraschall-assistierten oder Draht markierten Arm randomisiert und ausgewertet. Die Studie war unter ClinicalTrial.gov NCT02222675 registriert worden.

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Ergebnisse 56 Patientinnen erfüllten die Einschlusskriterien von dehnen 47 ausgewertet werden konnten. 93 % (25/27) der Patientinnen im ultraschall-assistierten Arm hatten im Vergleich zu 65 % (13/20) im Draht markierten Kontrollarm eine R0 Resektion. Das Ergebnis war statistisch signifikant (p = 0.026). In Bezug auf das entnommene Resektionsvolumen und die Operationsdauer wurde kein signifikanter Unterschied beobachtet. Revisionspflichtige Komplikationen traten nicht auf.

Schlussfolgerung Die ultraschall-assistierte Tumorchirurgie kann im Vergleich zur konventionellen Draht markierten Tumorchirurgie die R0-Rate bei brusterhaltender Operation signifikant erhöhen. Aus unserer Sicht sollten Brustchirurgen im Ultraschall ausgebildet sein. Ein Ultraschallgerät sollte Bestandteil jedes Brustoperationssaales sein.

Introduction

Breast-conserving treatment of breast cancer has undergone enormous advances since its introduction, with both safety as well as the cosmetic and functional results undergoing steady improvement. Major milestones were the optimization of preoperative local staging through imaging techniques as well as the introduction and development of breast reconstruction surgery [1 – 7]. An important criterion for deciding whether to perform breast-conserving surgery is the breast-to-tumor size ratio.

A key objective of surgical treatment for breast cancer is complete tumor excision with free margins. However, removal of the optimal target volume is only partially predictable for palpable tumors and non-palpable tumors (following wire localization). Although the surgeon knows the location and the tumor size from prior imaging, the operation is basically performed blind and palpation is not valid due to swelling of the tumor following core needle biopsy. Furthermore, surgical margins with tumor infiltration are associated with a significantly increased rate of local recurrence [3 – 9]. In these cases, repeat surgery to achieve clear margins is necessary. However, reoperation places both a physical and mental burden on the patient, resulting in health and economic impairment which are both potentially avoidable.

To avoid “blind tumor surgery”, intraoperative ultrasound can be integrated in the operating room to allow the surgeon to visualize rather than just palpate breast tissue. However, ultrasound-assisted surgery requires qualified ultrasound training for breast surgeons.

The aim of this study was to investigate the value of ultrasound-assisted tumor surgery with respect to the R0 resection rate. Secondary objectives included evaluation of the resection volume, the duration of surgery for each study arm as well as the incidence of complications.

Patients and methods

Study participants

The MAC 001 trial was a prospective, randomized, two-arm, single-center, controlled study. Patients with a unifocal breast lesion (BIRADS 4 or 5 on ultrasound) and core needle biopsy-confirmed invasive ductal breast carcinoma undergoing primary breast-conserving surgery were included. The diagnosis of breast cancer was performed according to guidelines. In addition to clinical examination, mammography, ultrasound and magnetic resonance imaging (MRI) were used for specific indications. All ultrasound examiners were qualified equivalent according to DEGUM II standards for breast ultrasound. The maximum permitted tumor size was 3 cm. The tumor had to be clearly visible on ultrasound.

The exclusion criteria were unclear lesions on ultrasound, invasive lobular breast carcinoma, suspicion of an extensive ductal carcinoma in-situ (DCIS) component upon imaging (defined as microcalcifications overlapping the solid tumor border on the mammogram), multifocal or multicentric breast cancer, primary systemic therapy, or a previous history of ipsilateral breast surgery.

All cases were presented in a multidisciplinary staff meeting, where the different images were discussed and evaluated for breast conserving surgery.

All patients provided written informed consent to participate in the study. The study was approved by the local ethics committee (101/2009BO1).

Randomization

Patients who met the inclusion criteria were randomized into one of two parallel study arms. Randomization was performed centrally using a randomization list and following stratification of patients according to tumor size, nodal status and grading.

Value of intraoperative palpation

Intraoperative palpation following core needle biopsy was not considered to be reliable due to swelling and hematoma. Therefore, all included tumors were defined as inaccurate palpable tumors. Therefore, the location of the target volume was determined using either intraoperative ultrasound or a wire marker, which was placed inside the tumor prior to surgery, depending on the study arm.

Operation

All participating surgeons were qualified according to the German cancer society as “senior breast surgeons” and perform at least 100 surgical breast cancer procedures per year.

Ultrasound-assisted arm (ultrasound-assisted tumor surgery)

Wire localization of the lesion was not performed in this arm. Instead, all patients were preoperatively examined with ultrasound by the surgeon to reliably reproduce the location during the operation. An ultrasound device with a 12 MHz linear transducer, 5 cm width, was used (HD 11, Phillips Healthcare, Hamburg).

The ultrasound examination during the surgical procedure was performed by the surgeon. All surgeons were trained in breast ultrasound and were qualified at least equivalent to DEGUM II standard. The transducer was encased in a sterile protective cover with ultrasound gel. Either sterile ultrasound gel or H_2O was used when applying the transducer to the skin. The tumors were examined using B-mode ultrasound with compound imaging and then resected by the surgeon under repetitive ultrasound visualization. All resected specimens were suture marked in three dimensions for pathological orientation. A specimen ultrasound was then performed intraoperatively by the surgeon. If the tumor margins were not sonographically tumor-free, then further re-excision of the corresponding margins was performed during the same procedure. For specimen ultrasound purposes, a minimal distance in millimeters for sonographically tumor-free margins was not defined in the study protocol. If indicated, additional mammography of the specimen and macroscopic pathological evaluation were performed. If tumor margins were not found to be macroscopically tumor-free following these assessments, re-excision of the corresponding edges was performed during the same procedure.

Control arm (conventional tumor surgery)

In the control arm, the tumors were wire marked using ultrasound the same day prior to surgery by either a gynecologist or radiologist who participated at the multidisciplinary staff meeting. The wire was used as guidance for tumor resection. All specimens were suture marked in three dimensions for pathological workup. Ultrasound and, if necessary, mammography of the specimen were performed to ensure complete removal of the tumor. Macroscopic pathological assessment of the resection margin was subsequently conducted. Further resection was performed if tumor margins were not macroscopically tumor-free.

Frozen sections were not performed in either study arm.

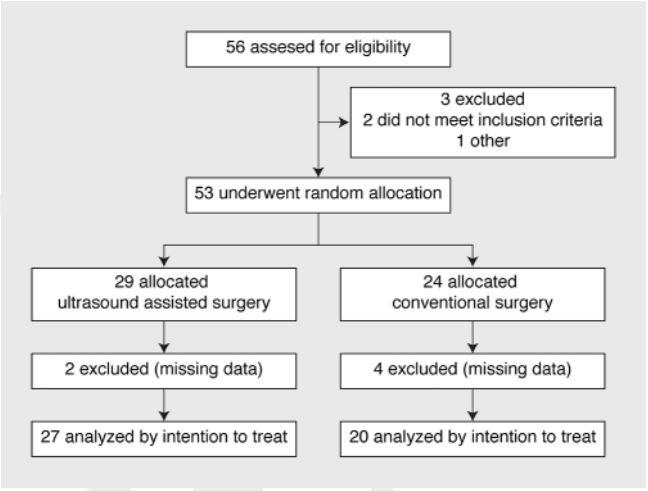
R0 was achieved if there was no ink on the tumor during pathological workup. If tumor-free margins measured less than 1 mm, a reoperation in which the margin was excised was recommended according to the German S3-guidelines. The reoperation was planned within 14 days after the initial surgery.

The weight of the fresh specimen was determined postoperatively. Specimen volume was calculated from the size specifications given by the pathologist. In the same session, patients underwent staging of the axillary lymph nodes according to the guidelines. Further postoperative care was carried out in accordance with guidelines issued at the interdisciplinary tumor conference at the University of Tuebingen Breast Center, Germany.

The recommendations regarding possible reoperation, adjuvant systemic therapy and adjuvant radiotherapy as well as tumor aftercare were followed.

Statistical analysis

We expressed values as mean, SD and range and gave proportions when appropriate. We generally used an independent samples t-test, $\chi 2$ test, or an exact test for nominal data to compare the two intervention groups. We presented our results with corresponding p-values which were considered significant at values of <0.05. All analyses were performed with JMP version 2.0 (SAS Institute).



▶ **Fig. 1** Trial profile.

Study sponsorship

This study was designed as a single-center investigator-initiated trial.

Results

In this study, 56 patients were assessed, 53 were included and 47 patients were evaluated between 02/2010 and 08/2011. 27 patients were included in the ultrasound-assisted arm (ultrasound-assisted tumor surgery) and 20 in the control arm (conventional breast surgery) (▶ **Fig. 1**). Patient and tumor characteristics were comparable between the groups (▶ **Table 1**). The mean patient age was 52.4 and 51.8 years in the study and control arms, respectively.

Duration of operation

The mean duration of surgery from skin incision to skin suture was 80 minutes in the ultrasound-assisted arm and 85 minutes in the control arm. The difference was not significant. It should be noted that for the study arm, the extra time required for setting up the ultrasound transducer, including the sterile covering, was included (▶ **Table 2**).

Resection weight and resection volume

The tumor resection specimen was on average 18 g heavier in the control arm compared with the ultrasound-assisted arm. Accordingly, the tumor resection volume was on average 28.6 cm^3 greater in the control arm compared with the ultrasound-assisted arm. However, these differences were not significant ($p>0.05$) (▶ **Table 3**).

▶ **Table 1** Overview of patient age, height, weight, surgery status and tumor classification.

	ultrasound-assisted arm (n = 27)	control arm (n = 20)	p-value
age (years ± SD)	52.4 ± 9.2	51.8 ± 2.2	0.77
height (cm)	164.4 ± 6.5	165.9 ± 5.1	0.41
weight (kg)	65.9 ± 11.4	74.6 ± 12.5	0.02
previous breast surgery	none	none	
nodal status (N) ▪ N- ▪ N+	 ▪ 22 (81.5 %) ▪ 5 (18.5 %) (from 1mic)	 ▪ 18 (90.0 %) ▪ 2 (10.0 %)	0.82
grading ▪ G1 ▪ G2 ▪ G3	 ▪ 6 (22 %) ▪ 14 (52 %) ▪ 7 (26 %)	 ▪ 7 (35 %) ▪ 10 (50 %) ▪ 3 (15 %)	0.51
T status ▪ T1a ▪ T1b ▪ T1c ▪ T2	 ▪ 0 ▪ 6 (22 %) ▪ 14 (52 %) ▪ 7 (26 %)	 ▪ 1 (5 %) ▪ 2 (10 %) ▪ 8 (40 %) ▪ 4 (25 %)	0.99
DCIS extent (mm) (median/CIs)	12.0 (5.0/20.0)	10.5 (0.0/26.5)	0.91
initial sonographic tumor size (length × height × width in cm^3) (median/CIs)	1.18 (0.50/2.91)	1.29 (0.43/3.31)	0.97

DCIS = ductal carcinoma in-situ.

▶ **Table 2** Duration of surgery and complications.

	ultrasound-assisted arm (n = 27)	control arm (n = 20)	p-value
duration (min; median/CIs)	80.0 (60/92)	85.0 (69/91)	0.69
hematoma not requiring treatment (% patients)	3 (11 %)	2 (10 %)	1.00

▶ **Table 3** Resection volume, weight and status.

	ultrasound-assisted arm (n = 27)	control arm (n = 20)	p-value
specimen volume (cm^3) (median/CIs)	61.4 (7.8/108.6)	90.0 (30.0/200.4)	0.34
specimen weight (g) (median/CIs)	38.0 (26.5/63.0)	56.0 (33.5/85.5)	0.19
R0 resection (yes/no)	25 (92.6 %)/2 (7.4 %)	13 (65 %)/7 (35 %)[1]	0.026

[1] Fisher's exact test

Tumor-free margins (R0 resection)

The R0 resection rate was significantly higher in the ultrasound-assisted arm than in the control arm (93 % [25/27] vs. 65 % [13/20] of patients; p = 0.026), even though the resection volume was smaller in the ultrasound-assisted arm. Consequently, fewer patients in the ultrasound-assisted arm underwent reoperation compared with the control arm (7 % vs. 35 % of patients) (▶ **Table 3**).

The extent of peritumoral ductal carcinoma in situ (DCIS) in the ultrasound-assisted arm was similar to the control arm (12 mm vs. 10.5 mm). Therefore peritumoral DCIS did not appear to affect the R0 resection rate. ▶ **Table 4** shows the residual tumor burden detected in the reoperation. No other tumor component could be detected in 6/9 patients, a further DCIS component was detected in 2/9 patients and invasive as well as in-situ carcinoma were detected in 1 of the 9 patients.

Complications

The surveillance period for surgical complication was 14 days. No major complications were reported for either group. Overall, 5 patients developed a hematoma which did not require further treatment (3 in the ultrasound-assisted arm, 2 in the control arm).

▶ **Table 4** Overview of the tumor-free margin distance and residual tumor burden in patients for whom reoperation was recommended.

patient and study arm (ultrasound/control)	minimal distance to invasive tumor (mm) (initial surgery)	minimal distance to DCIS (mm) (initial surgery)	number of reoperations (n)	residual tumor burden (mm), (reoperation)
1 ultrasound	3	< 1	1	0
2 ultrasound	< 1 (caudal)	< 1 (caudal)	1	0
3 control	5	< 1 (cranial)	1	0
4 control	0 (caudal)	0 (caudal)	1	1 (DCIS)
5 control	< 1 (nipple)	< 1 (nipple)	2	70 mm (DCIS)
6 control	0 (ventral)	10	1	0
7 control	0 (ventral)	0 (ventral)	1	13 (IDC), 16 (DCIS)
8 control	5	< 1 (cranial)	1	0
9 control	10	< 0.1 (cranial)	1	0

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

Discussion

A key oncological objective in breast cancer surgery is to achieve tumor-free margins. For both palpable and non-palpable lesions, removal of the optimal resection volume is easy to plan using preoperative imaging, but difficult to perform during surgery. The surgeon knows the tumor's location from preoperative imaging and must apply this information to the surgical site. Although wire marking can help define the correct resection volume, it is still a "blind" procedure for the surgeon. The aim of this study (MAC 001) was to investigate the value of ultrasound-assisted tumor surgery, with regard to the R0 resection rate in patients diagnosed with breast cancer after core needle biopsy. In our study, intraoperative ultrasound-assisted visualization of the tumor decreased the reoperation rate by 28 %, a statistically significant reduction.

A similar outcome was reported in a study by Moore et al [10]. A decrease in the reoperation rate leads to an improvement in the quality of life of the patient, cosmetic outcomes and a reduction in costs for the healthcare system. In our study, ultrasound-assisted surgery also resulted in a trend towards a lower weight and smaller volume of the resected specimen compared with the control arm. Although these outcomes were not significant ($p > 0.05$), we consider them to be relevant favorable factors for an improved postoperative cosmetic result, reduced tissue trauma and therefore a better quality of life. Our cosmetic results were subsequently confirmed in the COBALT trial by Haloua et al. which compared ultrasound-assisted surgery with palpation-guided surgery [11].

No serious complications were reported in the MAC 001 trial. Small hematomas not requiring treatment were documented in approximately 10 % of patients in both arms. No infections requiring antibiotics were reported. The results of this trial confirm the findings of similar studies, although these studies had different inclusion criteria and different intraoperative ultrasound techniques [12 – 16]. Therefore, it seems feasible that ultrasound-assisted surgery leads to better results than conventional conservative surgery without ultrasound techniques.

A resection volume determined solely using palpation after prior core needle biopsy may not be valid due to the resulting swelling of tissue. Preoperative wire localization can determine orientation but does not allow direct visualization of the tumor. In contrast, intraoperative ultrasound shows the exact location of the tumor. According to data from Krekel et al., intraoperative ultrasound can even significantly reduce the reoperation rate for palpable breast cancer [17, 18]. This confirms our hypothesis that it is not possible to accurately palpate the exact extent of a tumor following core needle biopsy.

In the ultrasound-assisted arm of our study, more patients had a peritumoral DCIS component, yet a higher R0 resection rate was achieved. Although DCIS is difficult to diagnose with ultrasound, the DCIS component had no negative effect on the R0 resection rate. Similar outcomes have been reported in other studies [17, 19, 20]. We attribute this to the observation that the tumor contained in the resection specimen removed under ultrasound guidance is centrally located. In our study, excisions of tumors marked with wire and without ultrasound guidance resulted in a significantly more often decentralized tumor site than those removed with ultrasound guidance. Although there was no significant difference in mean tumor size between treatment arms, the resection volume was substantially smaller in the ultrasound-assisted arm despite a higher R0 resection rate. It seems clear that the central location of the tumor in the resected specimen represents a significant predictive factor for obtaining tumor-free surgical margins.

The technique of ultrasound-assisted surgery is described differently in current publications. In the COBALT trial by Krekel et al., the tumor volume was first determined intraoperatively by color marking and ultrasound was used to repeatedly control the visualization during resection. In the present MAC 001 study, our ultrasound technique did not use color marking, but did incorporate a repetitive visualization check. Other studies that have used ultrasound to mark tumor boundaries on the skin have also shown

a reduction in R1 status [19, 21]. We favor immediate intraoperative visualization.

In this context, the surgeon should be aware that ultrasound underestimates the real size of breast cancer tumors [1]. Stachs et al. [24] published a paper stating that the accuracy of tumor sizing with different ultrasound techniques is most accurate using strain elastography followed by 3 D ultrasound compared to B-mode. The question is whether this underestimation is relevant or not for the measurement of tumor free margins during surgery. However, strain elastography should be considered for further trials.

From our perspective, two things should always be considered in the application of ultrasound-assisted surgery.

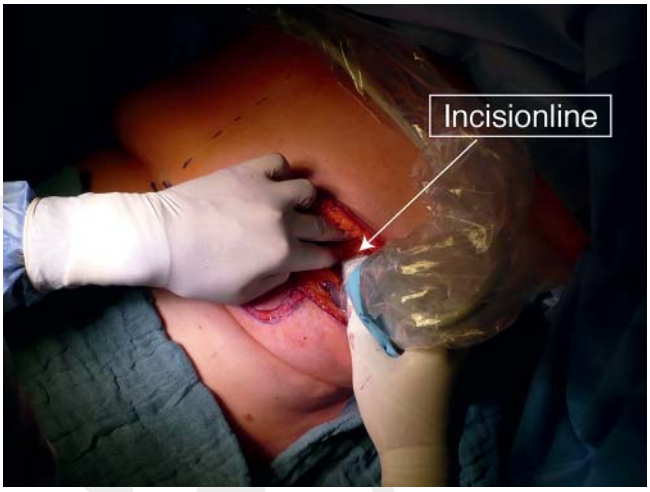
1. The tumor should be preoperatively examined with ultrasound by the surgeon. The surgeon can then decide whether wire marking should be used.
2. If the tumor is not clearly represented on ultrasound following core needle biopsy, e. g., small tumors, we recommend a combination of preoperative wire localization and ultrasound-assisted surgery. In general, wire marking should be used for lesions that are difficult to locate on ultrasound as there is a risk that the tumor cannot be located during surgery.

▶ **Table 4** shows a detailed examination of the patients with closed resection margins. Of the 9 patients for whom reoperation was necessary, residual tumor was detected in 3. The tumor reached the ink-stained border in 2 of these patients and in the other patient an extensive DCIS component of 70 mm was present. In the other 6 patients where the tumor had not reached the ink-stained edge, no further residual tumor was found during reoperation. These results may represent a challenge for the interdisciplinary tumor board when determining the indication for reoperation based on individually adapted risk and, at the same time, following the guidelines.

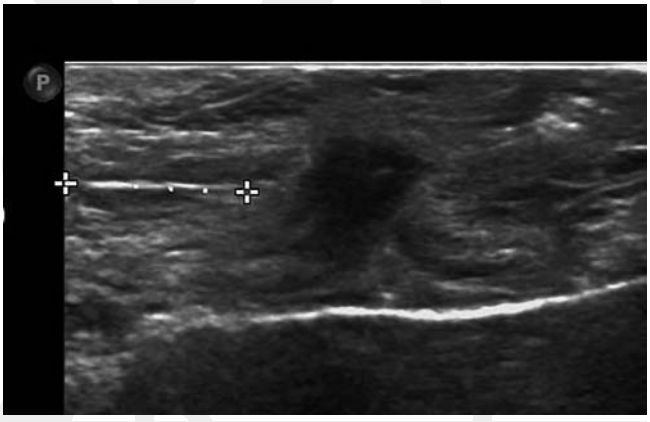
Our study has several limitations. Firstly, the overall number of included patients was rather low and the distribution of the patients into both arms was not 1:1, but was rather skewed towards the experimental arm.

After an interim analysis, the study was discontinued before arriving at the recruitment target to start a modified study with extended inclusion criteria. In the modified study, patients are included regardless of tumor biology or multifocality.

Another limitation of MAC 001 is that the ultrasound technique during surgery was not described exactly step-by-step in the study protocol. We believe that an optimal surgical result can be achieved by standardizing the ultrasound technique performed during the procedure. This standardization has been included in the modified protocol. The intramammary lesion and the transducer are positioned so that there is 1 cm of free distance between the tumor and the transducer's edge. The edge of the transducer serves as the border at which the surgeon incises the specimen all the way down to the pectoral fascia (▶ **Fig. 2, 3**). This technique is repeated in all four directions (cranial, caudal, nipple, and peripheral). As the ultrasound transducer is used as a ruler, one can measure the thickness of the macroscopically tumor-free margin with great precision. This is followed by a specimen ultrasound for which a free margin of at least 5 mm is desired



▶ **Fig. 2** Intraoperative ultrasound technique.



▶ **Fig. 3** Tumor with 1 cm free distance to the edge of the probe.

when taking the data of Olsha et al. and Eggemann et al. into account [22, 23].

Considering the current data, it is astonishing that so little attention has been paid to ultrasound-assisted surgery. A likely reason for this could be the lack of training in the field of ultrasound. Additionally, a survey showed that the financial cost of a high-resolution ultrasound device in the operating room limits the application of this technique.

In summary, ultrasound-assisted tumor surgery significantly increases the possibility of tumor free margins in breast-conserving breast cancer surgery compared with conventional surgery using wire marking for localization. Which individual subgroups may derive the most benefit and whether different types of intraoperative ultrasound techniques are more effective should be explored in future studies.

Conflict of Interest

The authors declare that they have no conflict of interest.

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