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Ultrasound-guided breast-conserving surgery compared to conventional breast-conserving surgery

Ultraschallassistierte versus konventionelle Tumorchirurgie bei brusterhaltender Therapie des Mammakarzinoms

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ABSTRACT

Purpose The goal of breast-conserving surgery is to achieve negative tumor margins, since insufficient marginal distance is associated with more local and distant recurrences. This study investigates whether IOUS (intraoperative ultrasound) can reduce the re-resection rate compared to standard breast surgery, regardless of tumor biology and focality.

Materials and Methods The present study is a monocentric, prospective, randomized, and non-blinded parallel group study conducted between 7/2015 and 2/2018. Patients with sonographically visible breast cancer were randomized into two study arms: 1) breast-conserving surgery with IOUS; 2) conventional arm.

Results 364 patients were included in the study and underwent surgery. Tumor biology, size, and focality were equally distributed in both groups (p = 0.497). The study arms did not differ significantly in the proportion of preoperative wire markings (p = 0.084), specimen weight (p = 0.225), surgery duration (p = 0.849), and the proportion of shavings taken intraoperatively (p = 0.903). Positive margins were present in 16.6 % of the cases in the IOUS arm and in 20.8 % in the conventional arm (p = 0.347). Re-operation was necessary after intraoperative shavings in 14.4 % of cases in the US arm and in 21.3 % in the conventional arm (p = 0.100).

Conclusion Although the present study showed a clear difference in the rate of positive tumor margins with IOUS compared to conventional breast surgery without IOUS, this was not statistically significant in contrast to the current literature. This could be due to the high expertise of the breast surgeons, the precise wire marking, or the fact that the IOUS technique was not standardized.

ZUSAMMENFASSUNG

Ziel Das Ziel einer brusterhaltenden Operation stellen negative Tumorränder dar. In dieser Studie wird untersucht, ob intraoperativer Ultraschall (IOUS), unabhängig von der Tumorbiologie und -fokalität, die Zweitoperationsrate im Vergleich zur Standardoperation senken kann.

Material und Methoden Die vorliegende monozentrische, prospektive, randomisierte und unverblindete Parallelgruppenstudie wurde zwischen 7/2015 und 2/2018 durchgeführt. Patientinnen mit sonografisch sichtbarem Mammakarzinom wurden in zwei Studienarme randomisiert: 1) brusterhaltende Operation mit IOUS; 2) konventioneller Arm.

Ergebnisse 364 Patientinnen wurden eingeschlossen und brusterhaltend operiert. Tumorbiologie, -größe und Fokalität waren in beiden Gruppen ähnlich (p = 0,497). Es gab keinen signifikanten Unterschied hinsichtlich der präoperativen Drahtmarkierungen (p = 0,084), des Resektatgewichts (p = 0,225), der Operationsdauer (p = 0,849) oder der intraoperativ entnommenen Shavings (p = 0,903). Positive Ränder waren in 16,6 % der Fälle im US-Arm und in 20,8 % der Fälle im konventionellen Arm vorhanden (p = 0,347). Eine Zweitoperation war nach intraoperativ entnommenen Shavings in 14,4 % der Fälle im US-Arm und in 21,3 % der Fälle im konventionellen Arm erforderlich (p = 0,100).

Schlussfolgerung Obwohl die vorliegende Studie einen deutlichen Benefit durch Hinzunahme des IOUS im Vergleich zur konventionellen Brustchirurgie zeigte, war dieser im Gegensatz zur aktuellen Literatur statistisch nicht signifikant. Ursächlich könnten die hohe Expertise der Brustchirurgen, die präzise präoperative Drahtmarkierung und die nicht standardisierte IOUS-Technik sein – es wurde nur „freier Rand“ im Ultraschall verwendet.

Introduction

Since the oncological safety of breast-conserving surgery with adjuvant radiotherapy has been confirmed by many randomized controlled trials [1, 2], quality of life following breast-conserving therapy can be improved [3] if adequate tumor-to-breast ratio as well as surgical expertise are present. However, breast-conserving surgery is always associated with the risk of tumor-involved margins (R1 classification), resulting in re-surgery.

The rate of re-excision is highly variable in the literature and is reported to be between 12–35 % in large population-based studies [4, 5]. Re-operation in a patient delays adjuvant treatment and is associated with reduced cosmetic outcome, increased complications, physical discomfort, emotional distress, and financial burden on the healthcare system [6, 7, 8]. The main problem, however, is a higher rate of local and distant recurrence, which increases with the number of operations until a complete resection (R0) with negative margins is reached [9, 10].

The goal of primary surgery is to completely remove the tumor [7] while avoiding excessive resection of breast tissue to achieve a good cosmetic and oncologically safe result [8].

With the continuous improvement of imaging techniques and mammography screenings, almost half of all tumors are detected before they are palpable [11]. Non-palpable breast cancer must be marked preoperatively to ensure complete removal of the breast lesion. Ultimately, even palpable tumors cannot be reliably assessed in terms of their volume due to post-biopsy swelling and hematoma. The gold standard is to mark the tumor volume with wires placed under sonographic or mammographic guidance, followed by specimen ultrasound or radiography [12]. However, other techniques are increasingly being used, such as radioactive seed localization, magnetic seeds, radiofrequency identification tags, or radar reflector-based localization [12, 13, 14, 15].

Intraoperative orientation is purely tactile when using wire or similar localization techniques, without directly visualizing the target volume during surgery. Ultrasound guidance allows direct visualization of the lesion and the tumor volume in real-time and therefore might have the potential to reduce re-surgery [16, 17, 18, 19, 20, 21, 22].

The present study was designed to clarify whether, in the clinical routine and independent of tumor biology, focality, or tumor-associated microcalcifications, the rate of primary tumor-free margins can be increased by using intraoperative ultrasound (IOUS).

Materials and methods

The present study is a monocentric, prospective, randomized, and non-blinded parallel-group study conducted between 7/2015 and 2/2018.

Patients with core needle biopsy-confirmed and sonographically visible invasive breast cancer who underwent primary breast conservation surgery were included in the study regardless of tumor size, biology, focality, and tumor palpability. Compared to other studies that investigated IOUS, cases with microcalcifications that could exceed the size of the tumor were also included.

Exclusion criteria were multicentric findings with indication for mastectomy, neoadjuvant treatment, and sonographically inconclusive findings.

Written informed consent to participate in the study was obtained from all patients. The study was approved by the local ethics committee (x/xx).

Study objectives

The primary study objective was to compare the rate of tumor-involved or positive margins (R1) in both study arms. At the time of the study, positive margins were defined as margins ≤ 1 mm for the invasive cancer, or ≤ 2 mm for an extensive ductal carcinoma in situ (DCIS). In these cases, a re-operation was indicated. Secondary outcome measures were comparison of volume and weight of the resected tissue as well as surgery duration.

Randomization

Patients were randomized by the study center to one of the two study arms in the operating room shortly before surgery started:

- Study arm 1 (US-assisted): ultrasound-guided surgery under repetitive ultrasound visualization of the target volume regardless of other wire marking according to the study protocol.
- Study arm 2 (conventional): conventional surgery with wire marking (in case of non-palpable lesions, satellites, or microcalcifications) without intraoperative sonographic visualization of the tumor volume.

Statistics

Patient data was collected in a REDCap database. Statistical analysis was performed using R, Version 4.1.1. Patients were randomized into one of two groups. Three subjects were randomized to study arm 2 but received treatment according to study arm 1 by mistake. The statistical analysis followed ITT (intention-to-treat), i. e., patients were sorted by the group into which they were randomized.

Continuous variables are characterized by mean and standard deviation (SD), for nominal variables numbers and percentages are shown. Differences between the two groups are assessed by t-test for approximately normally distributed variables and by Wilcoxon-Mann-Whitney rank test for variables with skewed distributions. Nominal variables are compared by (generalized) Fisher's exact test as implemented in R. All tests are two-sided and a significance level of 5 % is chosen.

Surgery

All surgeons were qualified as "senior breast surgeons" according to the German Cancer Society and Onkozert and trained in breast ultrasound (at least DEGUM II level). Preparation for surgery was independent of the study arm and was determined during an interdisciplinary conference.

In the case of non-palpable lesions, satellites, or microcalcifications, wires were placed either in the center of small lesions or at the edges of larger or extensive tumors, irrespective of the study arm.

During surgery, the ultrasound probe was wrapped in a sterile protective sheath. In the ultrasound-assisted study arm, the target volume was visualized and resected under repetitive ultrasound visualization in B-mode. IOUS was used to determine the free resection margin by the surgeon, but the exact technique for IOUS and specimen sonography was not standardized in detail. Only "free margin" on ultrasound was used.

In both study groups, the surgical specimens were suture-marked three-dimensionally for pathological work-up and sonography of the specimen was performed by the surgeon. Radiography of the resected tissue as well as macroscopic reporting were performed thereafter. In the case of imaging or macroscopically positive or close margins, shavings were taken intraoperatively. The weight of the resected volume for the study was determined by the pathologists.

Results

Study population

374 patients were considered for the study and underwent breast-conserving surgery between 7/2015 and 2/2018. 10 of these patients had to be excluded based on the exclusion criteria. Thus, 364 patients were available for the ITT analysis, i. e., 181 in US-assisted study arm 1 and 183 in study arm 2.

The study population did not differ significantly with respect to age (61.2 years (SD 10.4) vs. 59.8 years (SD 10.8), p = 0.227) or proportion of patients with previous breast surgeries (9.4 % vs. 9.8 %, p = 1.000).

The proportion of different tumor biologies pre- and postoperatively was comparable between the groups (▶ **Table 1**).

In 286 patients, the invasive ductal carcinoma (NST) of the preoperative core-needle biopsy was confirmed by postoperative histology, as was the invasive lobular carcinoma (ILC) in 31 patients. In 14 patients, the results of core-needle biopsy and final histology alternated between invasive ductal and invasive lobular carcinoma or vice versa. In 237 patients, DCIS was found in the postoperative histology but had not been reported in the core-needle biopsy (▶ **Table 2**).

The distribution of TNM stages between the study arms was well-balanced (T stage p = 0.848, N stage p = 0.446, M stage p = 0.623) (▶ **Table 1**). The two study groups did not differ regarding the histological extent of the invasive (17.4 mm (SD 9.0) vs. 18.8 mm (SD 10.3), p = 0.172) or the noninvasive tumor (15.0 mm (SD 17.3) vs. 16.4 mm (SD 19.4), p = 0.662) and the focality (p = 0.497). The tumor size only differed significantly using mammography in the two study arms (17.1 mm (SD 9.4) vs. 19.5 mm (SD 9.5), p = 0.029), with a greater length in the conventional arm (▶ **Table 3**).

The number of preoperative wire markings (p = 0.084), weight of the resected tissue (p = 0.225), and duration of surgery (76 min. (SD 25) vs. 75 min. (SD 27), p = 0.849) were similar in both study arms. In the conventional arm, skin was resected significantly more often (156 of 183 (85.2 %) vs. 139 of 181 (76.8 %) p = 0.045).

There was no difference between the groups in specimen sonography regarding margins (6.2 (SD 3.7) vs. 5.8 (SD 3.3), p = 0.450), but there was a difference in the specimen radiograms: the margin was significantly larger in the US-assisted group (8.8 mm (SD 4.4) vs. 8.1 mm (SD 5.7), p = 0.026).

There was no difference in the number of shavings taken intraoperatively (136 of 181 (75.1 %) vs. 139 of 183 (76.0 %), p = 0.903). When comparing the shavings taken directly intraoperatively, an additional tumor was found histologically more frequently in the conventional arm (21 of 134 (15.7 %) versus 17 of 132 (12.9 %), p = 0.600), but the difference was not significant. Positive margins (R1) would have been present without additional shavings in 16.6 % of cases in the US arm and in 20.8 % of cases in the conventional arm (p = 0.347).

Involved tumor margins (after removal of shavings) were present in 14.4 % of cases in the US arm and 21.3 % in the conventional arm (p = 0.100).

Eleven adverse events were documented during the further course, irrespective of the group (post-operative bleeding, hematoma, wound healing disorder and fistula formation).

Discussion

New findings from the present study

Compared with previous studies, the present study was unique in the way that no restrictions were placed on tumor biology, size and focality or microcalcifications during recruitment.

In this population, IOUS reduced the rate of positive margins and led to a clear reduction of R1 status and re-operation rate in the IOUS arm, but the difference was not significant.

A skin spindle was taken significantly more often in the conventional arm without IOUS (p = 0.045). This demonstrates the value of ultrasound in estimating the distance between the tumor and the skin in terms of avoiding excessive resection of breast and skin tissue.

Comparison to previous literature

It is known that in subcollectives, positive margins can be reduced by the additional use of ultrasound in both palpable and non-palpable tumors [18, 21, 23, 24] in breast-conserving surgery.

In the present study, positive margins were present postoperatively in 14.4 % of cases in the IOUS arm and in 21.3 % in the conventional arm (p = 0.100). There is a difference with a lower R1 rate with the addition of ultrasound both in the initial resected tissue and in the final postoperative histology after removal of shavings, but this was not statistically significant.

▶ **Table 1** Patient characteristics.

	Study arm 1 (IOUS) mean (SD) or number of patients	Study arm 2 (control group) mean (SD) or number of patients	p-value
Patients	181	183	–
Age [years]	61.2 (10.4)	59.8 (10.8)	0.227#
Previous breast surgeries			1.000‡
Yes	17	18	
No	164	165	
T-stage			0.848‡
T1	2	0	
T1a	6	8	
T1b	30	29	
T1c	90	92	
T2	52	51	
T3	1	2	
T4b	0	1	
N-stage (n = 363)			0.446‡
N0	145	140	
N1	10	16	
N1a	19	21	
N1c	2	0	
N2	1	1	
N2a	4	4	
M-stage (n = 355)			0.623‡
M0	176	175	
M1	1	3	
Tumor biology (CNB)**			–
NST	154	152	
ILC	18	15	
DCIS	1	0	
Others	9	16	
Histology of resected tissue**			–
NST	150	144	
ILC	23	21	
DCIS	115	122	
Others	21	30	

#t-test
‡Fisher's exact test
**Multiple answers possible

This difference is in line with the previous prospective study by Hoffmann et al. [18], which showed in a small group of 47 patients that the additional use of IOUS significantly increased the rate of negative margins in breast-conserving surgery compared to conventional wire-marked surgery (95 % vs. 65 %, p = 0.026). However, only patients with unifocal invasive ductal carcinoma with a tumor size of ≤ 3 cm were included.

In the study by Rahusen et al. [25], 26 patients were randomized to the US arm and 23 patients to the wire-labelling arm. Duration of surgery and specimen weight were similar in the two arms,

▶ **Table 2** Tumor type before and after surgery.

Number of patients		Type of tumor postoperatively (histology) (multiple answers possible)			
		NST	ILC	DCIS	Other
Type of tumor according to biopsy (CNB) (multiple answers possible)	NST	286	12	214	17
	ILC	2	31	8	13
	DCIS	1	0	1	1
	Other	6	1	15	21

but close resection margins were less frequent in the US arm (7 % vs. 27 %, p = 0.007).

In their large mono-center randomized controlled trial, Hu et al. [24] showed in 520 patients that in the case of sonographically clearly visible lesions, positive margins occurred significantly less frequently using IOUS alone than after preoperative wire marking alone (4.6 % vs. 19.4 %, p < 0.001). However, only focal lesions were included.

In their systematic review and meta-analysis in 2022, Banys-Paluchowski et al. [23] were able to show that IOUS is associated with a higher rate of negative margins and lower rate of re-operations in the review of 22 prospective and 19 retrospective studies in non-palpable lesions.

In the present study, we observed a lower rate of positive margins with the use of the IOUS before shavings were taken intraoperatively. There was no difference between the groups in the percentage with shavings (p = 0.903). However, histologically more tumor remnants were found in the shavings in the conventional arm than in the US-assisted arm (12.9 % vs. 15.7 %, p = 0.600).

A point of criticism of the present study is that the additional margin shavings taken intraoperatively were not only in the direction of the intraoperative problematic margin.

In the study by Hu et al. [24], intraoperative re-excision was performed significantly more frequently in the wire-labeled than in the ultrasound-only study arm (24.0 % vs. 11.1 %, p < 0.001). A striking feature of intraoperative shavings was that the narrow incision margins were correctly identified in 91.7 % of cases in the US arm, compared to only 33.9 % in the wire group.

Eggemann et al. also performed shavings more frequently in the wire-based study arm compared to the US group (26.5 % vs. 10.0 %, p = 0.010) and correctly identified the correct, i. e. narrow, incision margin by ultrasound in all cases, whereas this was only achieved correctly in 27.8 % of the cases in the wire arm [26].

This is also reflected in the evaluation of the present study. Due to the professional expertise of the surgeons (DEGUM II/III), close margins were often correctly assessed during specimen sonography in both study arms and shavings were mostly removed in the correct critical direction.

The diversity of included tumor biologies, focality, and microcalcifications certainly represents a special feature of the present study.

A subgroup analysis with regard to tumor biology is not possible due to the small number of cases in the individual subgroups and overlaps in tumor biology, but it would be useful in a follow-up study with a larger number of cases.

Although the proportion of different tumor biologies preoperatively and postoperatively was comparable between the groups, 238 patients had concomitant DCIS in the postoperative histology (▶ **Table 3**), which makes the R0-resection rate much less likely and the low reoperation rate in this collective even more valuable.

Concomitant DCIS on imaging remains a problem and the most frequent limitation for primary negative margins [27]. Further research and studies are urgently needed here to show surgeons the margins of DCIS pre- and intraoperatively.

Secondary study objectives

The study arms did not show statistical significance in terms of the weight of the resected volume (p = 0.225) and the duration of surgery (76 min. (SD 25) vs. 75 min. (SD 27), p = 0.849). This might also be due to the precise preoperative wire marking, with the wires being placed right in the center of small lesions or marking the borders of larger tumors, and to the experience of the surgeons (Onkozert + DEGUM II/III), who can both interpret and integrate the various imaging modalities into the planning and implementation of the surgery. Previous studies are inconsistent regarding a difference in the weight of the specimen and surgery duration when IOUS is added [18, 24, 26, 28, 29].

Limitations of the study

The main limitation – regarding a possible subgroup analysis – is the small number of cases. With a larger number of cases, subgroup analyses according to tumor biology could certainly provide further insight into which collectives would benefit most from IOUS.

Another weak point of the present study is that there was no explicit specification on what technique to use for sonographically guided intraoperative tumor resection. Thus, it was up to each surgeon to decide how intraoperative ultrasound was used for tumor resection.

When visualizing the tumor intraoperatively with US, the primary resection margin should already be free of tumor in all directions by 10 mm in IOUS to avoid shavings. However, the “ultrasound as a ruler technique” requires an individual learning curve,

▶ **Table 3** Results.

	Study arm 1 (IOUS) mean (SD) or number of patients	Study arm 2 (control group) mean (SD) or number of patients	p-value
Focality			0.715‡
Unifocal (imaging)	164	168	
Multifocal (imaging)	17	15	
Focality			0.497‡
Unifocal (histology)	160	166	
Multifocal (histology)	21	17	
Tumor size in ultrasound [greatest length in mm] (n = 362)	15.0 (7.5)	16.3 (8.0)	0.110#
Tumor size in mammography [greatest length in mm] (n = 301)	17.1 (9.4)	19.5 (9.5)	0.029#
Histological total size of			
invasive tumor [mm] (n = 361)	17.4 (9.0)	18.8 (10.3)	0.172†
DCIS [mm]	15.0 (17.3)	16.4 (19.4)	0.662†
Preoperative wire marking			0.084‡
Yes	136	122	
No	45	61	
Skin resection			0.045‡
Yes	139	156	
No	42	27	
Duration of surgery [min]	76 (25) (min. 23, max. 146)	75 (27) (min. 25, max. 190)	0.849†
Weight of primary resected specimen [g] (n = 352)	62.8 (43.2)	68.6 (48.3)	0.225‡
Specimen sonography Closest margin [mm] (n = 331)	6.2 (3.7)	5.8 (3.3)	0.450†
Specimen radiogram Closest margin [mm] (n = 334)	8.8 (4.4)	8.1 (5.7)	0.026†
R1 without shavings			0.347‡
Yes	30	38	
No	151	145	
Shavings intraoperatively			0.903‡
Yes	136	139	
No	45	44	
Tumor cells in shavings			0.600‡
Yes	17	21	
No	115	113	
R1 status (shavings included)			0.100‡
Yes	26	39	
No	155	144	

#t-test
†Wilcoxon-Mann-Whitney rank test
‡Fisher's exact test

appropriate training, and a high-resolution ultrasound machine in the operating room.

The fact that the present study involved very experienced surgeons and sonographers is also reflected in the very low rate of positive margins after primary breast-conserving surgery in both groups.

Conclusion for clinical action

In the present study of breast cancer surgeries regardless of tumor biology and microcalcification, and thus in an unselected population of routine clinical practice, we found a lower rate of positive margins and skin resection with ultrasound-guided tumor resection compared with surgery after preoperative wire marking alone.

Intraoperative ultrasound should be part of the curriculum for every surgically active breast surgeon. Surgeons should be encouraged to work on their ultrasound skills. The study shows that, with sonographic expertise, the use of ultrasound guidance does not prolong the duration of surgery.

Future studies should investigate the intraoperative sonographic examination technique in a standardized way, IOUS after neoadjuvant therapy [29] as well as the use of other marking techniques plus IOUS with intraoperative ultrasound alone.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Clinical Trial

Registration number (trial ID): NCT02840864 | ClinicalTrials.gov (http://www.clinicaltrials.gov/) | Type of Study: monocentric, prospective, randomized, and non-blinded parallel-group study

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