Intraoperative Ultrasound: Improved Resection Rates in Breast-conserving Surgery

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Abstract. *Aim: The objective of this study was the investigation of a possible improvement of tumor resection rate, i.e. R0 vs. R1 resection when intraoperative ultrasound evaluation of tissue margins is used during breast-conserving surgery (BCS). Patients and Methods: A total of 250 cases were evaluated retrospectively. The impact of ultrasound analysis onto clean margin rates was evaluated. A subgroup analysis assessed histology, stage, and neoadjuvant therapy with respect to R0 resection rate and ultrasound evaluation. Results: Of 250 BCS cases 84, (33.6%) underwent intraoperative ultrasound and 166 (66.4%) did not. Clean primary surgical margins (R0) were demonstrated for 218 (87.2%) patients after histological analysis. R0 resection was achieved in 81 (96.4%) patients in the ultrasound group compared to 137 (82.5%) in the control group. The difference between the two groups is significant. Conclusion: This study revealed a significant increase in R0 resection rates when intraoperative ultrasound was used to evaluate surgical margins.*

Breast cancer is the most common cancer of the women in the Western world. Great progress has been made in the treatment of breast cancer, leading to a good prognosis in cases of nodal negative cancer. Diagnostic options include a clinical workup, mammography, magnetic resonance imaging (MRI) and ultrasound. These methods are often used in combination in order to both detect tumors and estimate their size and exact location (1-3). Low- and high-risk tumors are differentiated *via* histological workup after biopsy removal. Nonetheless, a full pathological analysis and classification *via* union for international cancer control (UICC) remains the gold standard. Apart from hormone, antibody and chemotherapy, surgical removal of the tumor plays as a vital role in breast cancer treatment. In particular, breast-conserving surgery (BCS), for the removal of small lesions, is a major surgical option in modern breast cancer treatment (4, 5). In countries with an effective screening program, roughly 90% of tumors may be treated by surgery when diagnosed. Benign tumors, as well as ductal carcinoma *in situ* (DCIS) and lobular carcinoma *in situ* (LIN/LCIS) can also be removed with BCS. For multi centric precancerous conditions, radiotherapy combined with extended surgery may become necessary. Malignant breast cancer requires an individually adjusted surgical approach. When adhering to certain clinical and histological parameters, BCS is a viable option with a survivability identical to the one occuring after total mastectomy (6-9). Moreover, BCS in combination with preoperative chemotherapy and postoperative radiotherapy is possible 70-80% of the time (10). Surgical tumor excision with healthy margins dramatically reduces patient morbidity in both a psychological and physical manner, as well as increasing overall postoperative quality of life (11).

BCS has the goal of maintaining the overall shape of the breast while removing the tumor with histologically clean margins. At least 1 mm, more for invasive carcinoma, of healthy tissue is required as a safety margin in order to be considered an R0 resection. In order to eradicate residual tumor cells, successful BCS with R0 resection always requires subsequent radiotherapy. Intraoperative radiotherapy is also an option. Chemo, antihormone and antibody- therapy also play a role in breast cancer treatment, although a specific excursion into the details of these procedures is beyond the scope of this study. It is clear that a wide array of treatment options is available for the successful treatment of small malignant breast cancer lesions, one of which is the complete removal of neoplastic tissue *i.e.* an R0 resection.

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Sonographic investigation of excised tissue is a procedure that is widely used at the University of Cologne, Germany. Naturally, the complete removal of neoplastic tissue during surgery, resulting in R0 resection and margin optimization is of vital prognostic importance and some smaller studies have also addressed this issue (12). Intraoperative ultrasound is a standardized method used to ensure appropriate margins of resected tissue. The tissue sample is sonographically analyzed by physicians in the breast cancer treatment centers who will immediately determine margins around all surfaces of the sample. Thus, the surgeon is informed if clean margins are not achieved and subsequent further resection may become necessary.

This study investigates the impact of intraoperative tumor sonography on the rate of R0 resection. The goal was to compare two patient groups scheduled for BCS. One group underwent sonographic evaluation of the removed tissue during surgery; the other group served as a control group and did not undergo intraoperative ultrasound analysis.

Patients and Methods

A total of 250 cases were evaluated retrospectively in order to determine the impact of intraoperative sonography on R0 resections. Patients with histologically proven breast cancer which allowed for BCS during the year 2007 were selected at the Department of Gynecology at the University of Cologne. With the exception of having to qualify for BCS surgery, selection was random. Overall, 245 patients were selected, five of whom had breast cancer in both breasts, thus being entered into the case pool twice. Histological analysis, wire marking, neoadjuvant therapy and surgeries were performed at the Department of Gynecology at the University of Cologne. Grading, hormone receptor (HR) status and margin evaluation were performed by the Institute of Pathology at the University of Cologne. Evaluation was based on the following parameters: date of birth, surgical procedure, histology, stage, HR status, palpability, focality, neoadjuvant chemotherapy, wire marking, margins and ultrasound analysis of the resected tissue. Patients who underwent a mastectomy in 2007 were eliminated from the study. This study used the standard TNM classification as well as the commonly used grading system (13).

Several types of surgical methods may be applied during BCS, including segmental and quadrant resection. Adequate surgical approaches were determined and taken by an experienced surgeon and combined with mastopexia or reduction plastic surgery if necessary. Guide wire markings were introduced when required.

Neoadjuvant therapy. Preoperative treatment was either chemotherapy according to the Cologne protocol with 4 cycles of epirubicin (90 mg/m^2) and cyclophosphamide (600 mg/m^2) (EC) and 4 cycles of Taxotere (docetaxel, 100 mg/m^2) or antihormone therapy with Femara (letrozol 2.5 mg/d).

Ultrasound. Sonography was performed intraoperatively by an experienced physician. Both palpable and non-palpable tumors may require ultrasound verification of their location and extent. In this study, sonographic analysis of the tumor was performed shortly after excision while the patient was still under general anesthesia. This allowed immediate feedback between the surgeon and the physician performing the ultrasound analysis. The removed tissue was marked as shown in Figure 1 in order to allow correct orientation of the tissue surfaces, *i.e.* ventral, dorsal, lateral surface *etc*. Following intraoperative marking *via* suture material, the sample was sent to the breast cancer center where it was sonographically analyzed. Patient data, such as tumor location, size *etc*., was documented and communicated as well. Naturally, only tumors which were detectable sonographically were included in the ultrasound group. A standardized procedure was used during the sonographic analysis of the sample in order to minimize the impact of different ultrasound techniques on the results.

The resected tissue was introduced into a water bath and then scanned using a high resolution 2D and 3D ultrasound probe (6-16 MHz). The tumor was identified and represented at two levels. A 3D probe was also used in order to more accurately evaluate the tumor with regards to infiltration, and extent of growth. Results were communicated to the surgeon *i.e.* tumor size, tumor location and surgical margins on all six surfaces of the resected tissue. This allowed immediate adjustment of the resected area in case a margin was too small or not clear. Figures 2 and 3 show ultrasound images collected during tissue analysis.

Statistics. Statistical analysis was performed using the Statistical Program for the Social Sciences Version 16 (IBM SPSS Statistics, Germany). Clinical, tumor biological and histopathological factors were analyzed. A Pearson's chi-squared test and *t*-test were used in order to evaluate the significance of clinical results.

Results

A total of 250 BCS cases were evaluated, of which 84 (33.6%) underwent intraoperative ultrasound and 166 (66.4%) did not. Out of 245 patients included in this retrospective study, the age at diagnosis had a large range (27-81 years). The median age was 55±11 years; 19 (7.6%) patients were below the age of 40 years, 137 (37.6%) between the age of 41 and 59 years and 94 (37.6%) were above the age of 60 years. The age distribution did not differ significantly between the ultrasound and the non-ultrasound (control) groups ($p>0.05$).

Tumor stage. Overall, most patients had a medium to high tumor stage: tumors in 74% were pT1c stage or above. The ultrasound group included 95.2% patients with a tumor stage above pT1a, while that in 88.8% of the control group showed a stage above pT1a. Detailed tumor stage distributions are shown in Table I.

Histology. The majority of the tumors were invasive ductal carcinoma (81.2%) followed by invasive lobular lesions (14%). 83.3% of patients that underwent an ultrasound analysis, had invasive ductal lesions and 10.7% had invasive lobular tumors. Invasive ductal carcinoma had a similar occurrence in the ultrasound group (83.3%) as in the control (80.1%) group. Detailed tumor histology distributions are shown in Table II.

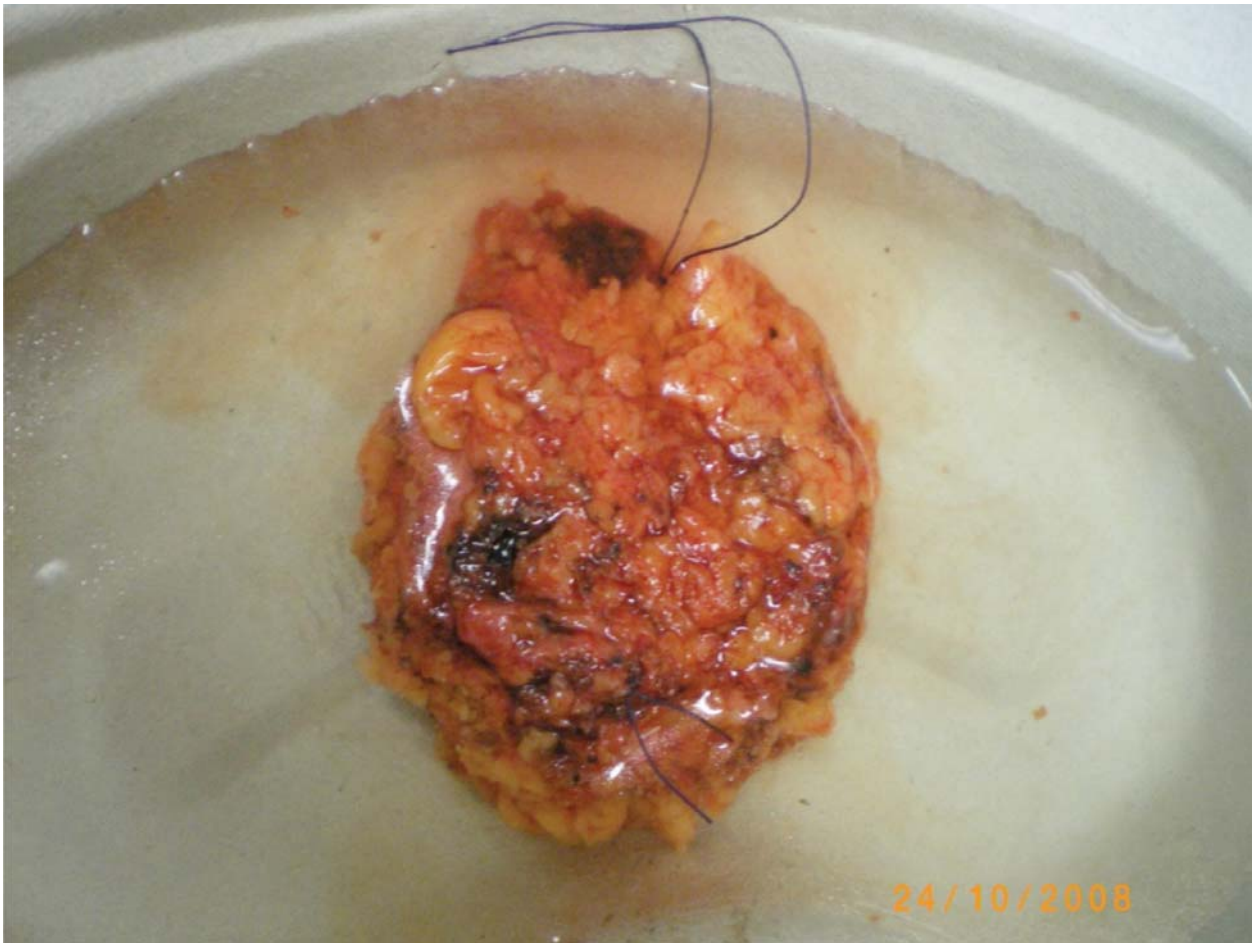

Figure 1. *Tissue resection with suture markings.*

Grading. Carcinoma grading was similar in both the ultrasound and the control group: 77.4% of the patients in the ultrasound group had a moderately differentiated G2 grade tumor, while 71.7% of the control did (Table III).

HR status/HER+. Tumors in the ultrasound group had a positive estrogen receptor status in 90.5% of the cases, while the status in the control group was 81.9%. A positive progesterone receptor status in the ultrasound group was found in 89.3% of the cases, while that in the control group was 83.1%. A positive HER2+ status was found in 27.4% cases of the ultrasound group, that in the control group was 33.7%.

Neoadjuvant therapy. 81.0% of the ultrasound group, did not receive any neoadjuvant therapy, while 72.3% of the control group did not receive any. Further details are listed in Table IV. 4% of the patient collective showed a complete remission after therapy.

Surgical approach. The most common surgical method was the segmented resection, which was used in 97.6% of the ultrasound group, and in 81.3% of the control group; 2.4% of BCSs were quadrant resections in the ultrasound group and 18.7% of the control group.

Resection. Clean margins (R0) were achieved in 87.2% of all surgeries; 12.8% of all cases required a second resection or mastectomy due to R1 results. The analysis of R0 resection margins is limited to invasive carcinoma since ductal carcinomas are generally not detectable *via* ultrasound. Table V shows a summary of resection outcome.

Impact of sonography on rates of clean surgical margins. Overall, clean primary surgical margins (R0) could be shown in 218 (87.2%) of all patients after histological analysis. R0 resection was achieved in 96.4% (81) patients in the ultrasound group compared to 82.5% (137) in the control group. The

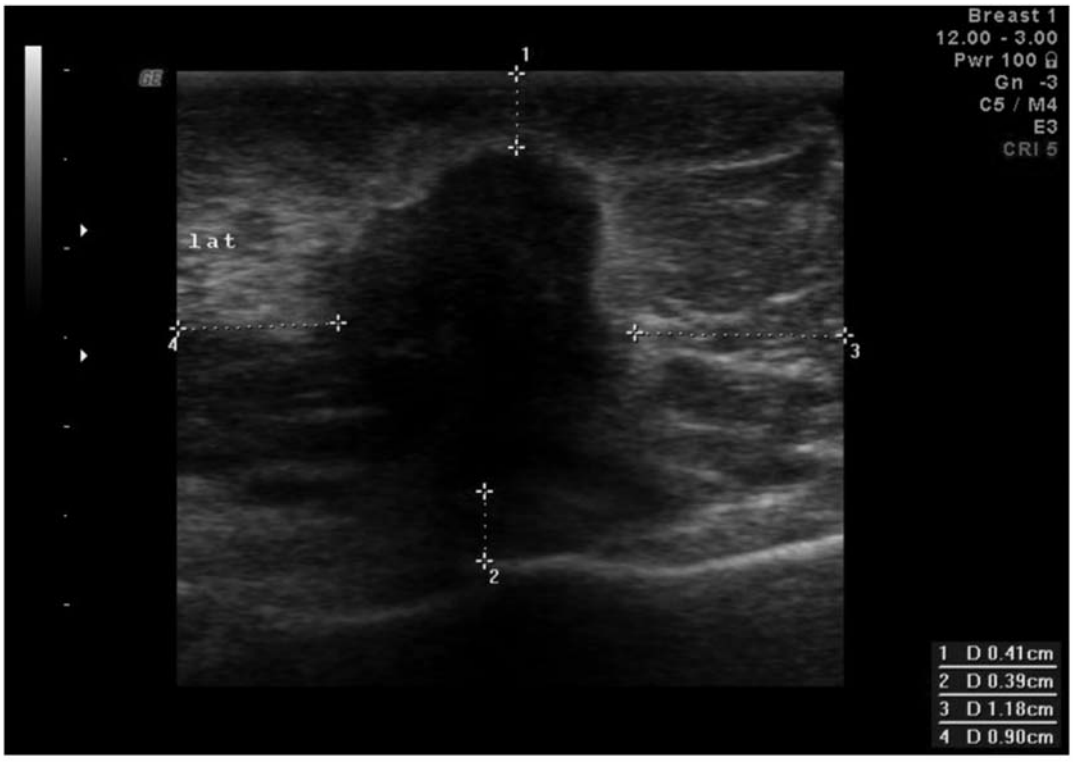

Figure 2. *2D Ultrasound of centrally located tumor with surgical margin measurements 1-4.*

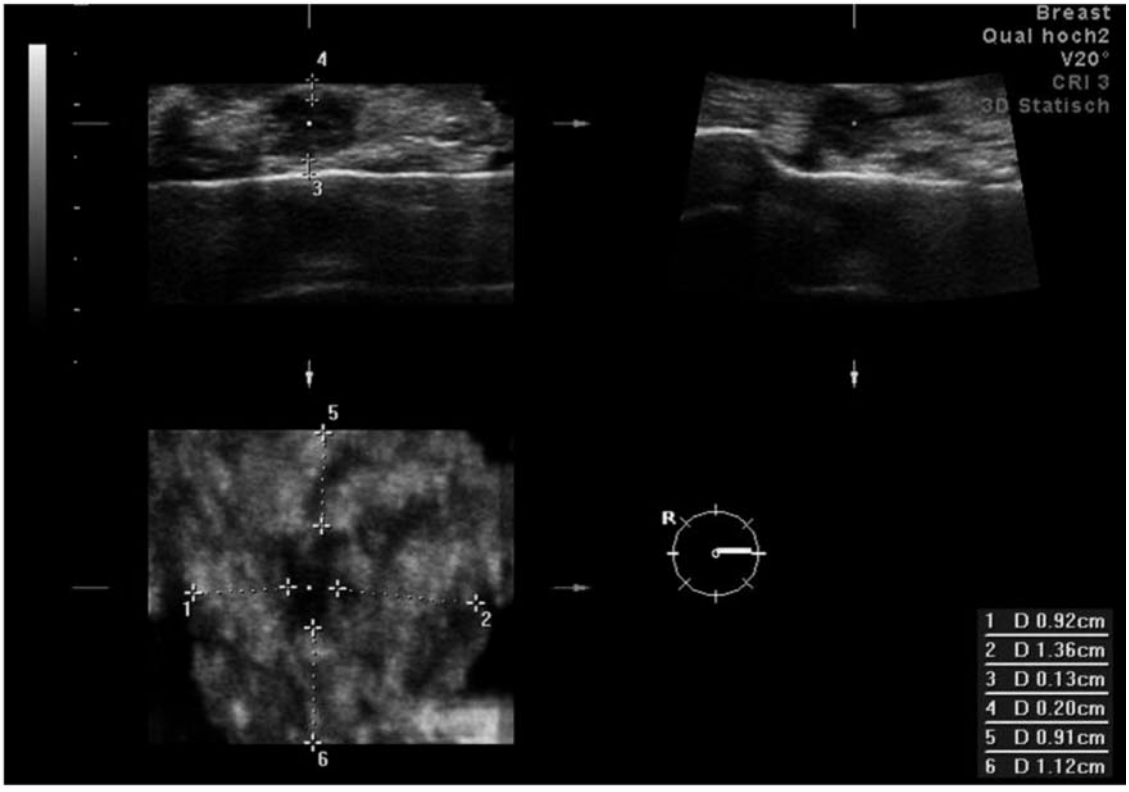

Figure 3. *3D Ultrasound of a tumor with surgical margin measurements 1-6.*

Table I. *Tumor stage distributions in the ultrasound (US) and non-ultrasound (control) groups.*

Tumor stage	US	Control	Total
pT0	1 (1.2%)	9 (5.4%)	10 (4%)
pT1a	3 (3.6%)	8 (4.8%)	11 (4.4%)
pT1b	21 (25%)	21 (12.7%)	42 (16.8%)
pT1c	47 (56%)	80 (48.2%)	127 (50.8%)
pT2	11 (13%)	45 (27.1%)	56 (22.4%)
pT3	1 (1.2%)	3 (1.8%)	4 (1.6%)
Total	84 (100%)	166 (100%)	250 (100%)

Table II. *Tumor histology distribution in the ultrasound (US) and non-ultrasound (control) groups.*

Histology	US	Control	Total
Invasive ductal	70 (83.3%)	133 (80.1%)	203 (81.2%)
Invasive lobular	9 (10.7%)	26 (15.7%)	35 (14%)
Tubular	4 (4.8%)	5 (3.0%)	9 (3.6%)
Invasive mucinous	1 (1.2%)	1 (0.6%)	2 (0.8%)
Medullary	0 (0%)	1 (0.6%)	1 (0.4%)
Total	84 (100%)	166 (100%)	250 (100%)

Table III. *Tumor grade distribution in the ultrasound (US) and non-ultrasound (control) groups.*

Grading	US	Control	Total
G1	12 (14.3%)	12 (7.2%)	24 (9.6%)
G2	65 (77.4%)	119 (71.7%)	184 (73.6%)
G3	6 (7.1%)	31 (18.7%)	37 (14.8%)
Missed grading	1 (1.2%)	4 (2.4%)	5 (2.0%)
Total	84 (100%)	166 (100%)	250 (100%)

difference between the two groups is significant (Pearson's chi squared test p=0.002; Fisher's exact test p=0.001).

Subgroup analysis. Histology: The histological analysis with regards to the rate of clean margins showed that intrasurgical ultrasound analysis was advantageous for both the invasive-ductal and the invasive lobular carcinoma. R0 resection for invasive ductal carcinoma for the ultrasound group was achieved for 95.7% compared to 85.7% in the control group (p<0.05). R0 resection for the invasive-lobular carcinoma for the ultrasound group was at 100% compared to 61.5% in the control group (p<0.028). The other histological outcomes as listed in Table II could not be compared since all were R0 resections.

Table IV. *Neoadjuvant therapy regimens in the ultrasound (US) and non-ultrasound (control) groups.*

Neoadjuvant therapy	US	Control	Total
None	68 (81.0%)	120 (72.3%)	188 (75.2%)
Chemotherapy	13 (15.5%)	40 (24.1%)	53 (21.2%)
Anti-hormone	3 (3.6%)	6 (3.6%)	9 (3.6%)
Total	84 (100%)	166 (100%)	250 (100%)

Table V. *Resection outcome summary in the ultrasound (US) and non-ultrasound (control) groups.*

Resection margins	US	Control	Total
R0	81 (96.4%)	137 (82.5%)	218 (87.2%)
R1	3 (3.6%)	29 (17.5%)	32 (12.8%)
Total	84 (100%)	166 (100%)	250 (100%)

Subgroup analysis. Stage: This analysis showed a trend that intraoperative ultrasound proved to be advantageous for the subgroup pT1c. This trend showed that the ultrasound group only led to 4% R1 resections while the control yielded a 11% R1 resections (p=0.18); significance could not be established.

Subgroup analysis. Neoadjuvant therapy: Overall, patients that did not receive neoadjuvant treatment (R0=97%) profited significantly from ultrasound analysis of resected tissue (p=0,007) when compared to patients with neoadjuvant therapy (R0=84.2%). No significant difference was established for subgroups with anti-hormone and chemotherapy,

Discussion

Despite a large number of improvements in diagnostics and treatment in the field of breast cancer, complete removal of all neoplastic tissue whenever possible remains highly important. BCS was established as the gold standard for localized tumors. If optimally performed, any surgery should result in tumor removal without having to revisit the surgical area in any type of follow-up procedure *i.e.* revision surgery. Nonetheless, due to the microscopic nature of some neoplastic entities, remaining tumor tissue may sometimes not be noticed until the removed specimen is investigated histologically. Hence, revision surgery may sometimes become necessary. In order to minimize this scenario, ultrasound analysis of the resected tissue has proven to be an

easily performed, cheap and readily available instrument in order to further reduce the rate of revision surgeries due to R1 resection.

This retrospective study analyzed 250 cases with regards to the resection classification R0 and R1, with and without intraoperative ultrasound analysis. Ultrasound tissue analysis was conducted on 84 out of the 250 cases during surgery. It was shown that R0 resection during BCS could be achieved significantly more often if intrasurgical ultrasound was performed, with 96.4% of the ultrasound group achieving an R0 resection with clean margins compared to 82.5% of the control group ($p<0.05$). The difference is significant. Olsha *et al*. also suggested that intraoperative ultrasound may lower the reoperation rate, as well as improving the localization of neoplastic tissue within the resected area, *i.e*. improving R0 resection rates (12).

Several subgroups were also analyzed. Resection of both invasive ductal and invasive lobular carcinoma was improved when intrasurgical ultrasound analysis was performed, with almost a 10% increase in R0 resection for the ultrasound group. Unfortunately, it was not possible to demonstrate a significant difference in the subgroup in regard to tumor stage. With regards to neoadjuvant treatment on the other hand, a significant improvement of resection quality was shown. Without neoadjuvant treatment, R0 resection with ultrasound was achieved in 97% compared to 84.2% of the control group ($p<0.05$). When neoadjuvant therapy was applied, no difference between groups could be shown. This is most likely due to the decrease in ultrasound detection of tissue after neoadjuvant treatment.

Limitations. The Authors are aware that the patient collective is a rather non-homogenous group of individuals that did not allow identical initial conditions for all examined cases. Tables I through IV show different subgroups and their distributions with regards to a variety of breast cancer properties. Attempts were made to achieve a similar distribution between the compared subgroups.

In conclusion, in order to optimize the surgical outcome during BCS, intraoperative ultrasound should be recommended. It was possible to increase the R0 resection rate by 10% when compared to a control group without ultrasound analysis. Ultrasound is a cheap and readily available tool that does not interfere with established surgical protocols. It should, therefore, be used whenever available in order to optimize resection outcomes.

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