Original Study

The Use of Intraoperative Ultrasound During Breast Conserving Surgery

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Abstract

This is a retrospective study examining the use of intraoperative ultrasound (IOUS) in breast conserving surgery and the impact of IOUS on margin positivity and re-excision rates and factors contributing to breast surgeon utilization of IOUS. Conducted in patients with preoperative diagnosis of breast cancer undergoing breast-conserving surgery by breast surgeons at multiple centers within a single healthcare system. There was no significant difference in re-excision rates between IOUS and WGL or among the 4 surgeons. Ultrasound-certified surgeons were more likely to utilize IOUS, and re-excision rates trended higher for WGL.

Objectives: The purpose of this study is to evaluate the utilization of intraoperative ultrasound (IOUS) for tumor localization in breast-conserving surgery and to examine its impact on margin positivity and re-excision rates. Additionally, the study seeks to identify factors contributing to surgeon utilization of IOUS. **Methods:** A retrospective chart review was conducted of patients with preoperative diagnosis of breast cancer undergoing breast-conserving surgery by breast surgeons at multiple centers within a single healthcare system. Characteristics such as lesion size, palpability, histology, receptor status, and use of neoadjuvant chemotherapy were recorded. Re-excision rates were determined based on localization technique and surgeons' status of breast ultrasound certification. **Results:** A total of 671 cases were performed, with 322 meeting study inclusion. 57 cases utilized IOUS, 250 utilized preoperative wire-guided localization (WGL), 10 used both methods and 5 cases used neither method. There was no significant difference in re-excision rates between IOUS and WGL or among the four surgeons. Ultrasound-certified surgeons were more likely to utilize IOUS, and re-excision rates trended higher for WGL, which may be clinically significant. **Conclusion:** Increasing familiarity with and utilization of IOUS during breast-conserving surgery may be clinically advantageous over traditional localization techniques. Ultrasound certification may lead to increased use of IOUS among surgeons.

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Introduction

Modern-day treatment for breast cancer is both local and systemic, with the number of breast-conserving surgery (BCS) procedures exceeding those of mastectomies nationwide. With widespread use of screening mammograms as well as neoadjuvant chemotherapy (NACT), breast surgeons are tasked with excising smaller and often non-palpable lesions while conserving a maximal amount of healthy tissue. Traditionally, preoperative wire-guided localization (WGL) using mammographic or sonographic techniques has been utilized immediately prior to surgery, requiring an additional procedure with a radiologist which can lead to scheduling delays and patient discomfort, among other disadvantages.[1-6]

The use of intraoperative ultrasound (IOUS) as an alternative localization technique has been demonstrated to provide the numerous advantages in the performance and outcomes of BCS. Notably, IOUS allows for real-time visualization and 3-dimensional localization of lesions to better achieve negative margins, as compared to manual palpation, WGL, or other techniques that are often more expensive. IOUS has been shown to be superior to palpation-guided BCS.[2] In addition, Rahusen et al. were among the first to compare IOUS and pre operative WGL, demonstrating a higher achievement of negative surgical margins in cases utilizing IOUS.[7] Since then, IOUS has continued to produce at least equivalent outcomes to WGL.[1] IOUS has been of particular interest with its reported feasibility for the excision of smaller, non-palpable breast lesions,[3]

Subtitle: Breast Surgery Use of Intraoperative Ultrasound

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including after NACT,[4] as well as its additional advantages in terms of patient comfort, cosmetic outcomes, and time- and cost-savings through the minimization of other hospital services, among many other things.[1-6]

Choice in localization technique is influenced by a lesion's characteristics, such as size and palpability, as well as surgeons' experience and institutional resources. To date, the literature mainly focuses on the effect of lesion characteristics on the surgical success across various localization techniques, but it does not consider the effects of surgeon-related characteristics on surgical outcomes. Previous studies have noted that the success of IOUS is dependent on operator training and comfort,[1,3,4] but there are no existing criteria to evaluate surgeons' expertise with IOUS. One possible method to objectively measure a surgeon's IOUS skills is successful achievement of the Breast Ultrasound Certification offered by the American Society of Breast Surgeon (ASBrS), which aims to recognize individual surgeons who meet criteria for the proper performance and clinical application of breast ultrasound and ultrasound-guided procedures within their practices.[8]

The primary aim of our study is to determine the impact of IOUS compared to WGL on margin positivity and re-excision rates in BCS and further stratify for lesion-related characteristics, such as palpability and NACT status. Our secondary aim is to evaluate if surgeon attainment of the ASBrS Breast Ultrasound Certification is associated with increased use of IOUS as a localization technique.

Materials and Methods

Institutional Review Board approval from Rutgers Cancer Institute of New Jersey was obtained for this study. A retrospective chart review was conducted of all patients undergoing BCS by any of 4 surgeons at 4 breast centers within a single healthcare system between 1/2018 and 12/2019. Patients with a preoperative cancer diagnosis confirmed via biopsy prior to lumpectomy were included in the study. Patients without a preoperative cancer diagnosis as well as non-BCS procedures, such as mastectomy, were excluded from this study. The type of localization technique employed, namely WGL and/or IOUS, was noted. The localization technique was categorized as WGL if a wire was placed preoperatively by the radiology department. The localization technique was categorized as IOUS if the surgeon utilized IOUS without preoperative radiology assistance. Presenting characteristics, including patient age at time of surgery, lesion histology and palpability, receptor status, and NACT status, were recorded. The surgeon characteristic of presence or absence of ASBrS Breast Ultrasound Certification was also noted. Primary outcome of re-excision rates due to positive surgical margins was measured and compared among the different groups. Statistical methods used for analysis were Pearson's chi-squared test and logistical regression.

Results

A total of 671 surgeries were performed within the study time period. Of these, 322 lumpectomies were performed for a preoperative cancer diagnosis, thus meeting study inclusion. The average age of patients included in this study was 62 years old (age range, 24-92 years). Final surgical pathology consisted mostly of invasive ductal carcinoma (IDC) (191/322, 59.3%), followed by ductal carcinoma in situ (DCIS) (63/322, 19.6%). Majority of the invasive breast cancer cases reflected a receptor status that was hormone positive, HER2 negative (170/322, 52.8%). Across all cases, 128 (128/322, 39.8%) of tumors were palpable at presentation, and 66 (66/322, 20.5%) of cases utilized neoadjuvant chemotherapy (NACT). Of the 4 surgeons included in this study, 2 had active ASBrS Breast Ultrasound Certification at the time of this study. Table 1 summarizes the overall patient and tumor characteristics and compares these values for the US-certified and non-certified groups of surgeons.

Of the 322 lumpectomies eligible for inclusion, 250 (250/322, 77.6%) were performed using WGL only, 57 cases (57/322, 17.7%) used IOUS only, 10 (10/322, 3.1%) used both IOUS and WGL, and 5 (5/322, 1.6%) used neither method. When localization technique utilization was stratified by the surgeon group, US-certified surgeons were far more likely to perform IOUS over non-certified surgeons (39/127, 30.7% vs. 28/195, 14.4%, $P = .0004$, 2-tailed test). On multivariate analysis looking at parameters of palpability and NACT status, US-certified surgeons trended toward use of IOUS at higher rates than non-certified surgeons. Conversely, US-certified surgeons had a lower utilization rate of WGL than non-certified surgeons (86/127, 67.7% vs. 174/195, 89.2%, $P = < .0001$, 2-tailed test). These utilization rates are featured in Table 2.

Re-excision rates were stratified by localization method comparing IOUS versus WGL. For all cases, there was no statistical significance between the re-excision rates for IOUS and WGL overall (7/67, 10.5% vs. 46/260, 17.7%, $P = .21$, 2 tailed test), although these values trended towards a lower re-excision rate for IOUS as compared to WGL. However, there was no statistical significance when further stratifying by palpability and NACT status. Table 3 compares re-excision rates for IOUS and WGL across these parameters.

Re-excision rates were also stratified by surgeons' ultrasound certification status. The re-excision rate of cases that did not utilize NACT localized by WGL for US-certified surgeons was lower than non-certified surgeons (8/67, 11.9% vs. 34/141, 24.1%, $P = .044$, 2 tailed test). The re-excision rates for non-palpable tumors using WGL also trended lower for ultrasound-certified surgeons as compared to non-certified surgeons but did not reach statistical significance (7/65, 10.8% vs. 24/113, 21.2%, $P = .076$, 2 tailed test). Re-excision rates among surgeon groups are presented in Table 4.

Discussion

WGL involves preoperative placement of a wire by a radiologist under mammographic or sonographic guidance. This procedure occurs outside of the main operating suite and is often performed just prior to definitive surgery. Several studies have discussed the disadvantages of WGL, such as patient discomfort, limitation in the number of operative cases that could be scheduled in a day, delayed operative start times, as well as possible additional costs associated with utilization of the radiology department. Moreover, a larger volume of breast tissue is often removed with WGL, leading to poorer cosmetic outcomes and decreased patient satisfaction.[1-3,5-7,9,10]

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Table 1 Patient and Tumor Characteristics

	All Surgeons	US-certified Surgeons	Non-certified Surgeons
	Nean (Range)	Mean (Range)	Mean (Range)
Patient age	62.2 (24-92)	65.3 (37-87)	60.1 (24-92)
	n (%)	*n* (%)	*n* (%)
Total cases	322 (100)	127 (39.4)	195 (60.6)
Final diagnosis			
Invasive Ductal Carcinoma (IDC)	191 (59.3)	79 (24.5)	112 (34.8)
Ductal Carcinoma in Situ (DCIS)	63 (19.6)	21 (6.5)	42 (13.0)
Invasive Lobular Carcinoma (ILC)	18 (5.6)	8 (2.5)	10 (3.1)
Mixed IDC and ILC	7 (2.2)	3 (0.9)	4 (1.2)
Other	43 (13.4)	16 (5.0)	27 (8.4)
Tumor palpable at presentation	128 (39.8)	46 (14.3)	82 (25.5)
Administration of NACT	66 (20.5)	30 (9.3)	36 (11.2)
	n (%)	*n* (%)	*n* (%)
All diagnoses with receptor reportability	244 (75.8)	106 (32.9)	138 (42.9)
Receptor status			
Hormone +/HER2 -	170 (52.8)	80 (24.8)	90 (28.0)
Triple Negative	34 (10.6)	15 (4.7)	19 (5.9)
Triple Positive	29 (9.0)	8 (2.5)	21 (6.5)
Hormone -/HER2 +	11 (3.4)	3 (0.9)	8 (2.5)

Table 2 Localization Usage for US-certified vs. non-certified surgeons

	US-Certified Surgeons	Non-Certified Surgeons	
Localization Method Usage	***n*** **(%)**	***n*** **(%)**	***P*** **Value**
IOUS	39 (30.7)	28 (14.4)	.0004
Wire	86 (67.7)	174 (89.2)	<.0001
Nonpalpable tumors			
IOUS cases	18 (22.2)	3 (2.7)	<.0001
WGL cases	65 (80.3)	113 (100.0)	<.0001
Palpable Tumors			
IOUS cases	21 (45.7)	25 (30.5)	.0862
WGL cases	21 (45.7)	61 (74.4)	.0011
Neoadjuvant chemotherapy			
IOUS cases	10 (33.3)	5 (13.9)	.0605
WGL cases	19 (63.3)	33 (91.7)	.0051
No Neoadjuvant chemotherapy			
IOUS cases	29 (29.9)	23 (14.5)	.0029
WGL cases	67 (69.1)	141 (88.7)	<.0001

Table 3 Re-excision Rates Comparing IOUS and WGL Localization Methods

	% Re-excised IOUS	% Re-excised WGL	*P* Value
All cases	10.5	17.7	.21
Palpable tumors	13.0	18.3	.62
Nonpalpable tumors	4.8	17.4	.21
Neoadjuvant chemotherapy	6.7	7.7	1.00
No Neoadjuvant chemotherapy	11.5	20.2	.17

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Table 4 Re-excision Rates Comparing US-Certified and Non-Certified Surgeons

	US-Certified Surgeons	Non-Certified Surgeons	*P* Value
Palpable tumors	15.2	18.3	.808
% re-excised IOUS cases	14.3	12.0	1.000
% re-excised WGL cases	9.5	21.3	.332
Nonpalpable tumors	9.6	21.2	**.048**
% re-excised IOUS cases	5.6	0.0	1.000
% re-excised WGL cases	10.8	21.2	.076
Neoadjuvant chemotherapy	6.7	8.3	1.000
% re-excised IOUS cases	10.0	0	1.000
% re-excised WGL cases	5.3	9.1	1.000
No neoadjuvant chemotherapy	13.4	22.6	.074
% re-excised IOUS cases	10.3	13.0	1.000
% re-excised WGL cases	11.9	24.1	**.044**

Ultrasound has been widely studied as an invaluable tool in the field of breast surgery, and in recent decades, it has gained popularity for use intraoperatively as a method of localization for excision of both benign and malignant breast lesions. In terms of localization, ultrasound grants the surgeon visualization of the 3-dimensional borders of a lesion in real-time. In contrast, WGL relies on static two-dimensional images produced during wire insertion aimed to target the lesion or biopsy marker. IOUS can also be used to more precisely excise suspicious margins, eliminating the tissue sacrifice involved with a more systematic cavity shave of the margins.[3] With reduced excision volumes, cosmetic outcomes and thus patient satisfaction is improved.[4] This may be particularly helpful with the excision of larger lesions, as surgeons are traditionally more cognizant of the volume of breast tissue removed.[1] Furthermore, IOUS has proven to be efficacious across a variety of lesion presentations, demonstrating success regardless of the lesion's palpability,[2,11,12] which is especially favorable in tumors treated with NACT.[4] This can be achieved by placement of newer "echodetectable" metal biopsy clips that remain sonographically visible despite a time delay from biopsy procedure with the clip placement to definitive surgery, including after NACT.[4] Beyond the reduced cost of omitting the preoperative wire placement by radiology at the time of initial surgery, cost is further reduced by avoiding re-excision, as IOUS may produce better surgical outcomes in many circumstances. Finally, use of IOUS eliminates the patient discomfort associated with preoperative wire placement.[1-3,5-7,9,10]

The accuracy of IOUS in obtaining negative surgical margins has previously been compared to other methods of localization, specifically palpation-guided localization,[2,11,12] WGL,[1-3,6,7,9] or radioguided occult lesion localization (ROLL).[9] In our study, the overall re-excision rate of 10.5% (7/67) for IOUS was comparable to other studies, with their rates ranging between 2.4% and 19%,[6,13-15] and lower than the reported total re-excision rate for all breast surgeons participating in the Mastery of Breast Surgery Registry (18.4%). With regards to direct comparison of localization techniques, our study indicated that although it did not reach statistical significance, the use of IOUS trended toward lower re-excision rates compared to WGL (7/67, 10.5% vs. 46/260, 17.7%, $P = .21$, 2-tailed test), consistent with other studies that also demonstrated superiority of IOUS over WGL, with rates of close or positive margins necessitating additional surgery ranging from 21.3% to 45% with WGL versus 3.7% to 11% with IOUS.[7,9,18]

When stratifying for palpable lesions localized by IOUS, our study demonstrated a re-excision rate of 13.0% (6/46) comparable to the existing literature showing re-excision rates of 3.5% to 11%.[9,11,12,16,17] For non-palpable lesions localized by IOUS, our study produced a re-excision rate of 4.8% (1/21), consistent with the lower end of already published results (3%-20.8%).[13,18,19] However, for lesions treated with NACT, our study reported a re-excision rate of 6.7% (1/15) with use of IOUS, which was lower than the 12.0% rate of return to surgery (6.8% with breast-conserving re-excision and 5.2% with secondary mastectomy) reported in the 2014 study from Ramos et al. for lumpectomies utilizing IOUS after NACT. Notably, Ramos et al. highlighted the utility of an "echodetectable" non-ferromagnetic marking clip (MReye Breast Localization Coil) placed prior to treatment with NACT, which was still sonographically detectable after significant shrinkage of the lesion due to partial or complete pathologic response.[4] However, most metallic marking clips placed at the time of the diagnostic core needle biopsy are too small to be readily visualized with IOUS. While our study did not specify whether IOUS was used to visualize the lesion itself versus the biopsy clip for post-NACT cases, presumably either could have been used as the target to guide surgical excision, thus obviating the need for preoperative wire placement.

With the advent of newer fiducial marker technologies allowing for sonographic visibility, IOUS can be more frequently utilized to target both smaller non-palpable lesions as well as post-NACT lesions exhibiting partial or complete response. More recent wireless localization options and products have emerged to offer patients a non-wire localization procedure by radiology, such as the Magseed system (Endomag limited, Cambridge, UK), SAVI SCOUT system (Cianna Medical, Aliso Viejo, CA, USA), the Faxitron LOCalizer system (Hologic Inc., Santa Clara, CA, USA), and MOLLI (Molli Surgical Inc, Toronto, ON, Canada). These systems involve image-guided placement of a miniature tag near a previously placed biopsy clip that can be detected with the assistance of a handheld reader during surgery. This is especially useful for lesions only visible on mammogram (such as those with calcifications) or MRI (with MRI-

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visible enhancement), which cannot be readily visualized by IOUS at the time of surgery. While these wireless options can decouple the time of tag placement and the time of surgery, a separate preoperative radiology procedure is still required. In contrast, sonographically visible biopsy clips placed at the time of original biopsy will not require a separate localization prior to surgery. For example, HydroMARK markers placed at the time of diagnostic core needle biopsy utilize hydrogel technology that hydrate tissue surrounding the metallic clip to maintain long-term sonographic visibility. By utilizing these types of biopsy clips upfront, IOUS can be more readily utilized for BCS involving both non-palpable lesions and lesions after NACT. While not currently available for use during stereotactic or MRI-guided biopsies, placement of HydroMARK biopsy clips during these procedures can be a promising alternative for localization of the target lesion with IOUS use at the time of BCS.

Distinct from the existing literature, our study also examined surgeon-related factors that may influence choice of localization technique in addition to surgical outcomes. Although many studies discuss operator-dependence related to IOUS,[1,3,4] none suggest an objective measurement for technical "mastery" beyond familiarity and experience. Thus, by using successful attainment of the Breast Ultrasound Certification from ASBrS as an indicator of IOUS mastery, we were able to stratify and better analyze the above parameters of localization technique choice and subsequent surgical outcomes.

Surgeons who were ASBrS Breast Ultrasound certified were far more likely to utilize IOUS compared to their colleagues (39/127, 30.7% vs. 28/195, 14.4%, $P = .0004$, 2 tailed test). This can be explained by comfort, familiarity, and preference for IOUS over other localization techniques when the characteristics of the lesion allow for use of any method. However, it should be noted that absence of the formal Breast Ultrasound Certification does not necessarily indicate lack of familiarity or comfort with IOUS. When analyzing re-excision rates regardless of palpability or NACT status, there was no statistically significant difference in re-excision rates between surgeon groups when using IOUS, as demonstrated in Table 4.

Of note, the only significant difference in re-excision rates between US-certified and non-certified surgeons was for WGL in cases which did not use NACT (11.9%, 8/67 vs. 24.1%, 34/141, respectively, $P = .044$, 2 tailed test). Although not statistically significant, re-excision rates for non-palpable tumors using WGL trended towards significance, with ultrasound-certified surgeons achieving a lower rate of 10.8% (7/65) vs. 21.2% (24/113) for non-certified surgeons ($P = .076$, 2 tailed test). One possible explanation for these improved WGL re-excision rates for US-certified surgeons is that both categories had smaller sample sizes as compared to non-certified surgeons. With larger or more comparable sample sizes between groups, the comparison may move towards a truer representation of re-excision rates. Another explanation is that confounding factors may be present, such as better pre-operative visibility for the 21 non-palpable WGL cases or 19 non-NACT cases for US-certified surgeons.

IOUS has been touted as "less complex than other [localization] techniques"[4] and overall "easy to learn."[2] Recently, the analysis of IOUS has expanded to include ultrasound-guided wire placement by the breast surgeon intraoperatively[1] and even a combination of WGL and IOUS for increased surgical success.[18-22] Of note, 3 cases were included in our study where the surgeon placed a wire intraoperatively using IOUS. These cases were classified as IOUS, as the wire placement circumvented the radiology department. Although these surgeries were intended to be localized with IOUS, when the lesion was initially being localized in the operating room, the surgeon determined that the lesions were small and could lose localizability once the ultrasound probe was removed. Thus, the intraoperative placement of a wire using ultrasound guidance by the surgeon themself proved to be an advantageous method of localization. Additional studies should evaluate the success of this method in comparison to traditional pre-operative WGL by radiology.

Several limitations existed within our study. The patient characteristics of race and ethnicity were omitted from this report, as the previous electronic medical records system at our institution was inconsistent in the inclusion of these items. Race and ethnicity are important factors in the discussion of breast cancer treatment and outcomes and would have allowed for more robust reporting. Nonetheless, as choice of BCS localization technique is primarily determined by lesion characteristics and visibility, we feel that the absence of race and ethnicity reporting does not detract from the results of this study. Given the retrospective nature of this study, histologic characteristics were not evenly distributed among surgeons or type of localization technique utilized. Additionally, of the 322 lumpectomies that qualified for this study, only 57 utilized IOUS; thus, a higher number of IOUS cases would increase the power and perhaps statistical significance of the comparison to WGL. For the surgeons without ASBrS Breast Ultrasound Certification, there were no other measures in place to assess familiarity and comfort with IOUS. Thus, the inclusion of additional surgeon-related factors may be helpful in further analyzing surgical outcomes. Previous studies evaluated the volume of breast tissue excised, often as a surrogate for cosmetic outcomes, but patient satisfaction was not measured objectively.[4,21,23] Finally, a limitation arose from the healthcare system in which this study takes place, which is not currently equipped for a larger transition to IOUS usage.

Conclusion

In conclusion, IOUS as a method of intraoperative localization during breast surgery is a viable tool with numerous advantages over traditional localization techniques. These benefits include financial savings, patient comfort, and improved surgical outcomes. In order to become more prevalent in the practice of breast surgical oncology, healthcare systems must be willing to invest in IOUS training and technology.

Clinical Practice Points

Ensuring that surgeons are trained in the use of intra-operative ultrasound is advantageous to the patient and the provider because it leads to higher rates of ultrasound use during breast-conserving surgery and, in turn, lower re-excision rates. Additionally, ultrasound is a more comfortable method of localization for the patient so incentivizing providers to receive ultrasound training can

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also alleviate patient discomfort associated with breast-conserving surgery. Ultrasound use instead of wire localization also minimizes the amount of time the patient spends in the pre operative preparation stage of the procedure. Finally, ultrasound is a cheaper method of localization because it utilizes less specialized equipment and trained staff, which is also advantageous for patients.

Author Disclosure

Nicole Fosko: data curation; investigation; writing original draft. Yelizaveta Gribkova: data curation; investigation; formal analysis; writing original draft, review & edit. Kelly Krupa: conceptualization; investigation; methodology; writing original draft, review & edit. Kavita Jain: data curation; review & edit

Dirk Moore: formal analysis. Chunxia Chen: formal analysis. Lindsay Potdevin: conceptualization; methodology; review & edit. Shicha Kumar: conceptualization; methodology; review & edit. Firas Eladoumikdachi: conceptualization; methodology; supervision; review & edit. Maria Kowzun: conceptualization; methodology; supervision; review & edit

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