Original Article

Comparison of ultrasound guided surgery and radio-guided occult lesions localization (ROLL) for nonpalpable breast cancer excision

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Background: There is little literature comparing intraoperative ultrasound (IOUS) with radio-guided occult lesions localization (ROLL) in nonpalpable invasive tumors in breast conserving surgery (BCS). There is a need to compare these two methods in terms of safety and efficacy.

Methods: This is an observational cohort study. All patients treated with BCS for nonpalpable invasive breast cancer using IOUS from March 2016 to March 2020 were included and compared with a historical reference control group operated on using ROLL from March 2013 to March 2017. For each detection method, the ability to locate tumors intraoperatively, tumor and surgical specimen sizes, total resection volume (TRV), optimal resection volume, excess of healthy tissue resected (ETR), margin status, re-excision rate, surgical time, complications and costs were studied.

Results: One hundred and fifty-eight were included, 83 with IOUS and 75 with ROLL. The mean tumor size is equivalent in both groups (11.88 mm IOUS *vs.* 12.29 mm ROLL, P=0.668). TRV is significantly lower with IOUS (24.92 *vs.* 60.32 cm^3, P<0.001), and the ETR is also significantly lower in the IOUS group (21.74 *vs.* 58.37 cm^3, P<0.001). The rate of positive margins did not differ (10.98% *vs.* 12.16%, P=1), nor did re-excision rate (10.98% *vs.* 8.11%, P=0.597). Complication rate did not differ (12.2% IOUS *vs.* 10.81% ROLL, P=0.808). Surgical time was shorter in IOUS (45.5 *vs.* 57 min, P>0.05).

Conclusions: IOUS in BCS for nonpalpable invasive breast cancer is more accurate than ROLL because it decreases excision volumes with the same rate of free margins and re-excision. Also, IOUS is a more efficient and comfortable technique, and just as safe as ROLL.

Keywords: Breast cancer; breast conserving surgery (BCS); nonpalpable tumors; ultrasonography; intraoperative ultrasound (IOUS)

Submitted Jan 19, 2023. Accepted for publication Jul 20, 2023. Published online Sep 14, 2023.
doi: 10.21037/gs-23-27
View this article at: https://dx.doi.org/10.21037/gs-23-27

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Introduction

Breast cancer is the most common cancer among women worldwide (1). Lifetime risk of developing breast cancer is estimated to be one in eight women (12%) (2).

Breast conserving surgery (BCS) with adjuvant radiotherapy is the standard local treatment for early-stage breast cancer (3). The goal of BCS is to remove all the tissue affected by the tumor lesion, with tumor free resection margins and thus prevent local recurrence.

Non-palpable tumors represent most lesions that we detect in breast cancer today (50–60%) (3). They require some technique for their intraoperative detection and excision. It is a challenge to be able to accurately localize very small and non-palpable lesions intraoperatively. Breast surgeons currently have a wide variety of techniques for the intraoperative detection of non-palpable tumors. Wire localization (WL) is still considered the gold standard for intraoperative tumor localization, and it is the most widely used detection technique today (80%) (3,4). Other techniques that have been most used to date are radio-guided occult lesions localization (ROLL), radioactive I125 seeds, magnetic seeds, radiofrequency seeds, carbon clips and intraoperative ultrasound (IOUS). There is no clear evidence to advise one technique over another (3-5).

ROLL is the second most used method in recent years, and the most used in our center in the last decade. It was developed at the European Institute of Oncology (IEO) in Milan in 1996. In 1999, the same group from Milan published that the ROLL technique was superior to WL in terms of more adequate location of the lesion and excision of lower volume (6). The great advantage of this technique is that it also allows the detection of the sentinel lymph node with the injection and drainage of the Technetium 99m. Sentinel node detection with Tc99m is the most widespread and currently used SLN detection technique in breast cancer.

In 2016, we introduced IOUS in our center as a reference technique for detecting non-palpable breast tumors. It consists of performing an ultrasound in the operating room to locate the lesion and excising under direct visualization. This technique allows us to know where the tumor is in depth and in the rest of the planes. IOUS allows us for studying the intraoperative margins in real time. For non-echo visible lesions, radiological markers such as hydrophilic clips can be used.

There are several studies published since 1988 on the use of IOUS in breast cancer compared to the WL (4,7-12), which conclude that IOUS is an accurate and effective tool for locating breast tumors and that it facilitates surgical excision, achieving smaller volumes, lower rate of positive margins and re-excisions (13-16), better cosmetic outcomes and patient's satisfaction (17,18). There are very few studies comparing IOUS with ROLL (19,20).

Ultrasound is an operator-dependent technique, and therefore requires prior training by the surgeon. It has been calculated that the learning curve necessary to perform ultrasound-guided surgery is 11 procedures (21).

The aim of this study is to evaluate the efficacy of the IOUS in obtaining good volumes of resection and margins compared to ROLL. We present this article in accordance with the STROBE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-27/rc).

Highlight box

Key findings

- Intraoperative ultrasound (IOUS) in breast conserving surgery (BCS) for nonpalpable invasive breast cancer is more accurate than radio guided occult lesions localization (ROLL).

What is known and what is new?

- Is known that there are a lot of techniques for the intraoperative detection of non-palpable tumors. Wire localization (WL) is still considered the gold standard for intraoperative tumor localization. There is no clear evidence to advise one technique over another.
- This manuscript adds that IOUS decreases excision volumes with the same rate of free margins and re-excision than ROLL. Also, IOUS is a more efficient and comfortable technique, and just as safe as ROLL.

What is the implication, and what should change now?

- In the future IOUS will be considered a necessary tool in modern breast units that want to offer optimal surgery. More studies are needed to validate its superiority over other techniques and a randomized study between both techniques would be necessary.

Methods

Patients and study design

This is an observational cohort study. We compare two techniques used in our center for the intraoperative detection of nonpalpable tumors in BCS: IOUS and ROLL. All patients undergoing BCS for nonpalpable tumors with IOUS, between March 2016 and March 2020, were included in the study. These were compared with a historical cohort of patients who also underwent BCS for nonpalpable tumors with ROLL, from January 2013 to

January 2017.

Nonpalpable tumors with infiltrating carcinoma, T1–T2, N0–N1 were included. Tumors with only *in situ* component, palpable, multifocal disease, or candidates for neoadjuvant treatment or oncoplastic techniques were excluded.

Regarding immunohistochemical subtype classification, tumors were considered Luminal A-like if ER or PR was positive and Ki 67 was ≤20%, Luminal B-like if ER or PR positive and Ki 67>20%. Triple negative when ER, PR and human epidermal growth factor receptor 2 (HER2) were negative. HER2 positive when HER2 was positive, independently of ER or PR status.

The following variables have been studied: lesion detection rate, tumor and surgical specimen sizes, total resection volume (TRV), optimal resection volume (ORV), excess of healthy tissue resected (ETR), rate of affected margins, re-excision rate, surgical time and complications.

The anatomopathological analysis of the margins has been conducted by expert pathologists in breast pathology intraoperatively and in a deferred study in all the samples. All cases were performed by four dedicate breast surgeons at the Hospital Universitari General de Catalunya.

Excision methods

In the ROLL excision, the injection of the Technetium 99m is performed into the tumor prior to the surgical procedure under ultrasound guidance in the Radiology department. On the operating room, the tumor is located with a gamma probe (Europrobe 3) by Nuclear Medicine Department. Once surgical piece is removed, the resection bed is checked with the gamma probe and the sample is sent to the Pathology department for intraoperative analysis of the margins.

In the IOUS excision, the surgeon conducts a preoperative visit to check that the lesion or clip is clearly visible by ultrasound and to prepare the surgical strategy to follow. At this visit, an ultrasound is performed by the same surgeon, who leave the exact location of the tumor or clip in writing, indicating in which quadrant is it located, how far from the areola and the depth. Once inside the surgery room, the detection of the tumor or the clip is ultrasound guided prior to anesthetic induction. The skin is marked with ink to guide the incision more precisely, making a cross with the two axes that intersect in the center of the tumor. The surgeon then proceeds to perform the lumpectomy, always checking the location of the lesion or the clip and the safety margins. The surgeons insert the probe in the incision multiple times to determine the deep and the distance from the lesion to the margins. Once tumor has been removed, the specimen is verified by ultrasound and the margins are measured, before sending it to the pathological study. In case of ultrasound margins close to the lesion (<5 mm), suspicious close margin ampliation is performed.

Ultrasonography equipment used in the study are: Multifrequency Wideband linear array probe (7–17 mHz), Mindray DCN3 in the pre-surgery visit and General Electric LogiqP9 in the operating room.

Surgical time study

Time of surgery is defined as time in minutes from the beginning to the end of the anesthetic induction. The cost of operative time was calculated by multiplying individual operative time by a cost price per hour. We have based ourselves on the study by Haloua *et al.* (22), in which they calculate a price of 17 euros per minute of surgery (€1,020/h).

Volume calculation

TRV was calculated using the three diameters of the surgical specimen (a, b, c) applying the formula: 4/3 * pi * r3.

We assume that the tumor is spherical [Radius = 1/2 × diameter (a, b, c)] and the surgical specimen is ellipsoid [Volume = 4/3 pi (a × b × c)] (20). ORV was calculated using the tumor radius plus optimal tumor-free margin of 1 cm, converting this value to a spherical volume using the formula 4/3π (r + 1 cm) 3. TRV was compared to the ORV (23). The calculated resection ratio (CRR) was defined to determine the amount of ETR. It's calculated by dividing TRV by ORV.

Statistical analysis

Patients were assigned either to IOUS or ROLL group according to the guidance method used for surgery in each case.

Median and interquartile range (IR) were reported for continuous variables and number and percentage for categorical variables. Pearson Chi-square test and Fisher exact test (when any count cell was less than 5) were used for categorical variables. For continuous nonparametric variables a Mann-Whitney-Wilcoxon test was used.

Homogeneity was assessed comparing baseline characteristics [age, histology, tumor, node,

metastasis (TNM), hormonal receptors, HER2, immunohistochemistry] of the 2 groups. Mean (volume) and secondary (ETR, margins, re-interventions and complications) outcomes were compared between the two groups. Multivariate regression analysis was performed using volume as a dependent variable.

P values less than 0.05 were considered to indicate statistical significance. The following statistical software and packages were used for statistical calculations and plotting: R (version 2020), Tidyr [2020], Dplyr [2021], Ggplot2 [2016], KableExtra [2020] and Knitr [2020].

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics committee of Hospital Universitari General de Catalunya (No. 2019/72-GIN-HUGC). Individual consent was obtained for this study.

Results

A total of 302 patients operated for nonpalpable tumors with BCS were identified. One hundred and forty-four cases were excluded due to: lack of data, multifocal disease, advanced staging, no presence of infiltrating carcinoma in the tumor. One hundred and fifty-eight cases were included, 83 operated on with IOUS (52.5%) and 75 by ROLL (47.5%). Patient and tumor characteristics are compared in *Table 1*.

Both groups were equivalent in terms of the mean size of the lesion (11.88 mm IOUS *vs.* 12.29 mm ROLL, P=0.668). Total resection volume and excess healthy breast tissue resected volume were significantly lower in the IOUS group: TRV 24.92 cm^3 IOUS *vs.* 60.32 cm^3 ROLL, P<0.001 (*Figure 1*), ETR 21.74 cm^3 IOUS *vs.* 58.37 cm^3, P<0.001.

There were no differences in the rate of margins affected by infiltrating carcinoma in both groups (10.98% IOUS *vs.* 12.16%, P=1), either in the re-excision rate: 12.68% (n=9) IOUS *vs.* 11.11% (n=6) ROLL, P=0.597.

No differences were observed in the rate of complications [12.2% (n=10) IOUS *vs.* 10.81% (n=8) ROLL, P=0.808]. In all cases (n=18) we refer to minor complications (seromas or hematomas).

Summary of the results are presented in *Table 2*.

The ultrasound-guided surgery group presented a shorter surgical time than the ROLL group (45.5 *vs.* 57 min, P<0.05). The difference was 11.5 minutes more on average for the ROLL group.

When cost is considered and considering a price of 17 euros per minute of surgery (22) price of the ROLL/SNOLL would increase by 195.5 euros compared to IOUS.

Discussion

Our results are favorable to IOUS versus ROLL in terms of less total resection volume, less amount of healthy breast tissue removed and less surgical time. We do not get significant differences in the rate of positive margin, re-excision, or complications.

There is enough literature to state that IOUS is a safe and effective method for the BCS in nonpalpable tumors (3,4,22,24). The use of IOUS has increased in recent years as it has proven to be a good method which obtain optimal excision volume, with negative resection margins and minimal sacrifice of surrounding healthy tissue, compared with other methods such as the WL.

The smallest volume resection in BCS is important to achieve a more precise surgery in terms of obtaining a better aesthetic result while preserving oncological safety. We observe that in the literature most of the studies conclude that IOUS is the technique that obtain smaller volumes, especially when compared with the WL (4,23,25). However, there is quite disparity of data from different authors. It is difficult to compare studies that include palpable tumors with those that only include non-palpable lesions, or to compare with studies that include cases of carcinoma *in situ* without an infiltrating component. Another factor to consider is that most studies do not reflect whether the size of the surgical piece presented includes margins made intraoperatively or not, a factor that may contribute to a larger volume.

We can see how there is an evolution over time where the ultrasound volumes presented in the different articles mentioned are being reduced. This is probably due to the evolution of the technique and the learning curve. Our results in volume of surgical piece with ultrasound are a bit lower than those presented in most studies, this is mainly explained by the fact that we have not included palpable tumors, and they are included in many studies.

There is evidence in the literature that relates a smaller volume of resected tissue with a better aesthetic result and less scar (17,18,26). This has a significant impact on body image, the main cause of psychological disorders and affectation of self-esteem, sexual health, and quality of life in women (18). The relationship between a greater degree of breast asymmetry after conservative surgery for

Table 1 Patient and tumor characteristics of two groups

Characteristics	Ecoguided, n (%)	ROLL, n (%)	P value
Cases	83 (52.53)	75 (47.46)	
Age, years (mean)	57.4	59.4	0.316
TNM			
T1a	11 (13.58)	6 (8.45)	0.44
T1b	22 (27.16)	18 (25.35)	0.855
T1c	38 (46.91)	40 (56.34)	0.26
T1Mi	0 (0)	2 (2.82)	0.217
T2	9 (11.11)	5 (7.04)	0.417
N0	61 (79.22)	60 (82.19)	0.683
N1A	9 (11.69)	6 (8.22)	0.589
N1B	2 (2.60)	2 (2.74)	1
N1Mi	5 (6.49)	2 (2.74)	0.443
NX	0 (0)	3 (4.11)	0.104
Histological type			
Ductal	63 (77.78)	65 (87.84)	0.137
Lobulillar	5 (6.17)	4 (5.41)	1
Other	13 (16.05)	5 (6.76)	0.083
Estrogen receptors			
Positive	73 (89.02)	72 (97.3)	0.06
Progesterone receptors			
Positive	71 (86.59)	71 (95.95)	0.051
HER2			
Positive	6 (7.32)	4 (5.48)	0.751
Immunohistochemical profile			
Ki >20%	30 (36.59)	28 (37.84)	1
Luminal A	40 (48.78)	35 (47.30)	0.734
Luminal B	31 (37.80)	33 (44.59)	0.378
Triple negative	8 (9.76)	2 (2.70)	0.158
HER2 positive	6 (7.32)	4 (5.48)	0.751

The lesion was found in 100% of the cases included in both groups (P=1). ROLL, radio guided occult lesions localization; TNM, tumor, node, metastasis; HER2, human epidermal growth factor receptor 2.

breast cancer with higher rates of depression has also been described (26). Considering the significant impact of the cosmetic result, IOUS has enormous potential to improve the quality of life after BCS (18).

It has been shown for years that achieving negative margins in conservative surgery entails a lower rate of loco-regional recurrences and increases overall survival (27). It is the only prognostic factor that depends on surgeon (28). There are several studies that compare the rate of affected margins with the different techniques with very different

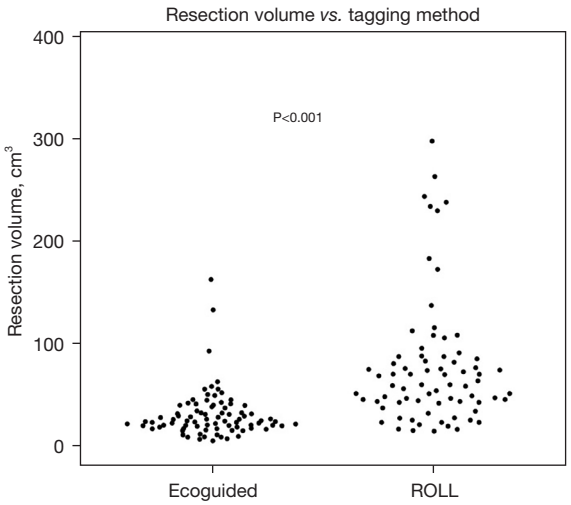

Figure 1 Total resection volume. ROLL, radio guided occult lesions localization.

results (*Table 3*, *Table 4*).

Many studies show the superiority of IOUS in terms of lower rate of affected margins and fewer re-excisions compared to other techniques, especially with WL although with quite different results (4,10,14,18,28). They also demonstrate that including ultrasound in the surgical process optimizes the surgeon's ability to obtain satisfactory margins in BCS.

In our study, the results show that IOUS has the same rate of margins affected by infiltrating carcinoma as ROLL even removing less volume. These results are consistent with what has been published to date in terms of the rate of affected margins with IOUS (4,21). When reading our results in terms of volumes, it would be expected that ultrasound would have a higher rate of affected margins than ROLL by obtaining a much smaller surgical specimen volume, but we

Table 2 Summary of the results

Characteristics	General, mean [range]	Ecoguided, mean [range]	ROLL, mean [range]	P value
Age (years)	58 [49.5–67]	56 [49–64]	59.5 [50.25–67]	0.316
Tumoral size (mm)	12 [8–17]	12 [8–16]	12 [9–17]	0.668
Volume removed (mm^3)	39.41 [22.7–63.33]	24.92 [19.15–38.49]	60.32 [43.36–87.17]	<0.001
Excess tissue (mm^3)	36.69 [19.65–61.23]	21.74 [16.84–35.66]	58.37 [40.72–82.77]	<0.001
Affected margins, n (%)	18 (11.60)	9 (10.98)	9 (12.33)	1
Reinterventions, n (%)	15 (12.00)	9 (12.68)	6 (11.11)	0.597
Complications, n (%)	18 (11.54)	10 (12.20)	8 (10.81)	0.808

ROLL, radio guided occult lesions localization.

Table 3 Rate of affected margins ROLL *vs.* Wire

Author	Year	ROLL (n)	Wire (n)	Affected margins ROLL, %	Affected margins Wire, %
Rampaul (29)	2004	48	47	0	0
Medina-Franco (30)	2008	50	50	11.1	37.5
Moreno (31)	2008	51	59	6,5	13.5
Mariscal Martínez (32)	2009	66	68	10.6	17.6
Krekel (20)	2011	32	117	25	21.3
Postma (33)	2012	162	152	14	12
Carrera (34)	2017	81	80	45.7	45

ROLL, radio guided occult lesions localization.

Table 4 Rate of affected margins IOUS *vs.* Wire

Author	Year	IOUS (n)	Wire (n)	Affected margins IOUS, %	Affected margins Wire, %
Rahusen (35)	2002	26	23	11.11	45.45
Knauer (36)	2007	299	61	19.06	37.70
Krekel (20)	2011	52	117	3.70	21.30
Barentsz (15)	2012	120	138	6.67	6.52
Eggemann (12)	2016	90	68	12.20	13.20
Esgueva (21)	2019	148	66	5.40	15.15

IOUS, intraoperative ultrasound.

did not observe significant differences. This is because the difference in volume is at the expense of the ETR.

There are some studies that show that IOUS is a cost-effective adjunct in the treatment of breast lesions (22). There is not much literature with complete cost-effectiveness studies given its complexity, but some authors conclude that ultrasound-guided surgery is a cheaper method than other techniques (22,36). The price of ultrasound-guided surgery with SN is equivalent to the price of the ROLL procedure, but in cases where we do not need the sentinel node technique, such as in cases of lymphadenectomy, this cost difference is very favorable for IOUS. Therefore, it is an efficient instrument in BCS.

In terms of learning the technique, ultrasound-guided surgery requires the training of breast surgeons, but the learning curve for the IOUS techniques is short (21). Training is important since it is decisive in surgical precision and determine the surgical time. IOUS provides a live view of the lesion, allowing the surgeon to control more depth and margins in surgery than with any other marking technique. IOUS is a useful tool to consider for optimal and objectively measurable tumor excision.

Also, IOUS is not subject to the problems arising from the use of radioactive substances, there is no risk of complications related to the procedure, is a painless technique that does not cause any type of discomfort to the patient, it reduces pre-surgery psychological stress for the patient, does not affect surgical scheduling and does not require the intervention of other specialists. Therefore, it is a more accessible and comfortable technique for both the patient and the surgeon. IOUS is cheap, time-efficient, simple, and improves the accuracy and quality of classical surgery (37).

Conclusions

In conclusion, we believe that in the future IOUS will be considered a necessary tool in modern breast units that want to offer optimal surgery, and mandatory for breast young surgeons. Even so, more studies are needed to validate its superiority over other techniques and a randomized study between both techniques would be necessary.

Patients will be followed up to assess whether there may be an increased risk of local recurrence due to the smaller amount of tissue removed, although it is unlikely since, as we have mentioned, multiple studies make it clear that while the margins are negative, there seems to be no impact on the risk of local tumor recurrence as long as correct adjuvant radiotherapy treatment is performed.

Acknowledgments

This study was made possible thanks to all the patients who wanted to participate.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-23-27/rc

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-23-27/dss

Peer Review File: Available at https://gs.amegroups.com/article/view/10.21037/gs-23-27/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-23-27/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics committee of Hospital Universitari General de Catalunya (No. 2019/72-GIN-HUGC). Individual consent was obtained for this study.

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Cite this article as: Argacha P, Cortadellas T, Acosta J, Gonzalez-Farré X, Xiberta M. Comparison of ultrasound guided surgery and radio-guided occult lesions localization (ROLL) for nonpalpable breast cancer excision. Gland Surg 2023;12(9):1233-1241. doi: 10.21037/gs-23-27