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Learning curves in intraoperative ultrasound guided surgery in breast cancer based on complete breast cancer excision and no need for second surgeries

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ABSTRACT

Background: Intraoperative ultrasound guided surgery (IOUS) is an effective surgical technique for breast cancer with advantages over wire localization guided surgery (WL), enabling smaller lumpectomies without compromising margins. Nevertheless, it has had a slow implementation, maybe due to lacking a learning curve. Also differences in costs are not clearly reported. The aim of the study is to assess differences in volume of healthy breast tissue excised, to establish a learning curve and to prove it is cost saving.

Patients and methods: From February 2009 to April 2013, women diagnosed with invasive breast cancer eligible for IOUS or WL breast conserving surgery were recorded into a prospectively maintained database. Both groups were compared for differences in margin status, second surgeries and excess of healthy tissue resected, defined by the calculated resection ratio (CRR). A raw cost study was assessed. IOUS learning curve was analyzed using Cumulative sum control chart (CUSUM).

Results: The study included 214 patients, 148 (69.16%) in the IOUS group and 66 (30.84%) in the WL group. IOUS showed significantly smaller surgical volumes ($p = 0.02$), smaller CRR ($p = 0.006$), higher rate of negative margins ($p = 0.017$) and less surgical time ($p = 0.006$) than WL. Learning curves based on complete tumor excision and no need for second surgeries showed that 11 cases were enough to master the technique. Around 900€ per surgery was saved using IOUS vs. WL.

Conclusion: IOUS decreases excision of healthy breast tissue while increasing negative margin rates compared to WL. IOUS can be easily implemented; 11 cases are enough to acquire skills for performing the technique. Savings can be up to 900€ per surgery.

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Introduction

Approximately one third of breast cancers are diagnosed at non-palpable stages [1], mainly due to the use of screening methods for breast cancer and better diagnostic imaging. Intraoperative ultrasound guided surgery (IOUS) has extensively shown to be a more effective tool compared to wire localization (WL) [2] and palpation-guided surgery (PGS) [3]. It improves rates of negative margins

[4,5], reducing the need of second surgeries [6].

Another advantage of IOUS is the potential for resecting less volume of healthy breast tissue (HBT). The randomized COBALT study showed a reduction in the volume excised when using IOUS as compared to PGS (38 cm³ vs. 57 cm³, $p = 0.002$) [7]. Similar results were achieved in the study by Slijkhuis [8] with resected volumes of 39 and 56 cm³ in the IOUS and control group respectively ($p = 0.001$). Assessing surgical volumes will provide us with how much tissue has been resected. The problem with surgical volume lies in the differences between size of the initial tumors, the bigger the initial tumor, the bigger the volume excised. To outperform this problem, the calculated resection rate (CRR) was

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Abbreviations

IOUS	Intraoperative ultrasound guided surgery
WL	Wire localization guided surgery
PGS	Palpation guided surgery
HBT	Healthy breast tissue

described [9]. It calculates the excess of HBT removed, regardless of the initial tumor size. In both studies, when IOUS was performed, the CRR scored lower without compromising margins [7,8].

Even with these advantages, the IOUS technique has been slowly implemented into clinical practice. One of the reasons may be the need for training and the lack of a learning curve to acquire those skills. Krekel [10] analyzed three surgeons performing ten procedures for palpable lesions. After two supervised procedures, optimal resection volumes were reached, and after 8 procedures they mastered IOUS. In the USA, the American College of Radiology (ACR) along with the American Society of Breast Surgeons (ASBrS) holds a qualification for surgeons performing IOUS. In Europe several courses on IOUS are being held but there is no established qualification [11]. It is important to point out that in all new surgical techniques the key relies on the cases needed to learn how to do the procedure and how it will be evaluated. Once the procedure is successfully performed then it is necessary to identify quality measures that evaluate the outcomes and ways to improve the technique with appropriate feedback.

In a decade of increasing health costs, it is also important to evaluate cost-effectiveness of different techniques. There are few studies addressing costs and, although IOUS seems to be cost saving, these studies are small and lack statistical power [12–14].

The aim of the study was to assess differences in volume of health breast tissue excised between IOUS and WL, to establish a learning curve of IOUS and to prove that it is cost saving.

Material and methods

From February 2009 to April 2013, all women diagnosed with invasive breast cancer - T1-T2, N0-N1 undergoing breast conserving surgery (BCS) guided either by WL or IOUS for non-palpable or palpable tumors at the Breast Cancer Center at the Hospital Universitario Vall d'Hebrón were included in a prospectively maintained database. Patients were excluded if they had received neoadjuvant chemotherapy or had pure intraductal carcinoma.

Techniques described in the manuscript are standard surgical treatment for breast cancer, that is why there was no need for ethical approval on the techniques. Ethical approval was obtained for study publication of the data.

Radiological imaging

All patients underwent a mammogram and breast and axillary ultrasound at diagnosis. Magnetic Resonance was used if tumor size could not be assessed by mammogram, for patients <45 years or if a multifocal/multicentric tumor was suspected. At the time of the diagnostic core biopsy, a single marker was placed at the site of the tumor when the lesion was difficult to see under US. There were two different markers depending on the time period of diagnosis. Until June 2011 a metallic marker clip (TuMark[®], Somatex Medical Technologies, Germany) was used. After that time an ultrasound-visible hydrogel polymer containing a central permanent metal marker was placed (Hydromark[®], Mammotome, OH, USA). A two-view mammogram was obtained to assess the clip placement in

all cases.

Surgical treatment

The selection of the localization method was left to the discretion of the surgeon. All procedures were done under general anesthesia, along with the planned treatment for the axilla (sentinel lymph node biopsy or/and axillary lymph node dissection if indicated). The surgical time was defined as the minutes between the start of the surgery until the complete closing of the wounds.

Ultrasound guided surgery

The surgical technique for patients included in the IOUS starts with the localization by US of the tumor/clip by the breast surgeon in the outpatient clinic in the preoperative visit. US was performed using an Esaote MyLab25Gold (Genova, Italy). In the operation room, the probe was placed in a sterile cover for its use in the surgical field. Once the tumor/clip has been localized, the skin is marked to guide the incision. IOUS guides the excision with negative margins. Ex vivo, US verifies the complete excision of the tumor and distances to each margin were recorded. At that time, additional re-excisions were done if the distance of the tumor to the margin was <5 mm by US [15]. Specimen was sent to Pathology for intraoperative assessment of margins. Titanium clips were placed at the lumpectomy site for radiotherapy treatment. The IOUS technique has been reported in more detail elsewhere [16].

Most of the patients underwent conventional BCS, a few of them underwent level I oncoplastic techniques (round block mainly). Patients with level II techniques were not included in the study as volume of health breast tissue excised is not an aim in this type of surgery and it was one of the objectives of the study.

Pathological examination

Intraoperative assessment of margins was performed by a dedicated breast pathologist in all cases. It consisted mainly in macroscopic examination of tumor margins. No frozen section was performed. If intraoperative margin assessment was positive, re-excision of margins was performed at the time of surgery. Re-excision in a second surgery was evaluated if final pathology revealed close (≤ 2 mm) or positive margins.

When measuring tumor volume, the maximum diameter from any of the imaging tests was taken into the formula: $V = (r^3 \times \pi)4/3$ [17]. For the surgical specimen, the three dimensions were obtained from the Pathology report and taken into the formula: $V = (a \times b \times c \times \pi)4/3$ [18]. Optimal resection volume (ORV) was considered as the volume of the specimen that would result after adding 1 cm of free margin to the tumor diameter. Excess volume resection was defined as the calculated resection ratio and calculated by dividing the volume of each specimen by the ORV.

Postoperative treatments

All patients received whole breast radiation therapy. Systemic therapy was left to the discretion of the treating oncologist. Patients with positive hormone receptor tumors underwent hormone therapy treatment.

Statistical analysis

Data were analyzed using STATA 14 (Stata Corp, TX, USA). Groups were compared using the *t*-Student test, one-way analysis of variance or Mann-Whitney test when appropriate. Data included patient and tumor characteristics (Age, date of surgery, localization

within the breast, type of surgery, axillary status, immunohistochemical tumoral characteristics, presence of lymphovascular invasion, size, physical exam, breast imaging tests, cost of each interventions/test, type of marker used at the time of the biopsy, need of mammogram of the surgical specimen, need for second surgeries, locoregional recurrence rate and death). To avoid confounding factors multivariate regression was performed if any baseline category presented $p < 0.15$.

The CUSUM (Cumulative sum control chart) test was applied [19] for the learning curve measurements, considering that the complete resection of the tumor without second surgeries was a success. This statistical tool represents the accumulated sum of successes and failures in a procedure between two decision levels, upper and lower CUSUM. Upper CUSUM (H1) is reached when the number of failures exceeds what is expected. Lower CUSUM (H0) is reached when the optimal balance successes/failure is obtained. Between H1 and H0 there is a “shadow area” that comprises cases that are performed without mastering the technique but without reaching the accumulated failure level.

To evaluate costs of the techniques, data were taken from the Spanish Health Department Report [20]. Survival analysis was performed with Log-Rank and Kaplan-Meier tests.

Results

Patient and tumor characteristics

214 patients were included: 148 in the IOUS group (69.2%) and 66 in the WL group (30.8%). There were no differences in patient age, tumor type or tumor stage among groups (Table 1). Multivariate regression did not show differences for age ($p = 0.16$), tumor size ($p = 0.41$), histology ($p = 0.12$), Ki67 ($p = 0.35$), re-excision rate

($p = 0.57$) or palpable tumors ($p = 0.11$).

Specimen volumes and CRR

Median initial tumor volumes were 3.19 cm^3 for the IOUS and 1.64 cm^3 for the WL group ($p = 0.05$). Mean specimen volume was smaller in the IOUS group compared with the WL group (43.24 cm^3 vs. 55.68 cm^3 , $p = 0.02$). IOUS also obtained smaller CRR (1.88 vs. 2.56, $p = 0.006$).

Margin status and second surgeries

Negative margins were achieved in 94.5% in the IOUS group versus 84.78% in the WL ($p = 0.017$). Intraoperatively, after US assessment of margins, 65 patients (87%) underwent a re-excision decided by the surgeon in the IOUS group, while 14 patient (53%) in the WL group. ($p = 0.001$). In the final pathology, 8 patients (5.4%) had positive margins in the IOUS group compared to 10 patients (15.15%) in the WL group ($p = 0.02$), with a relative risk of 3.13 (IC 95% 1.17–8.33). Eighteen patients out of 214 (8.41%) underwent a second surgery, 8 patients (5.40%) in the IOUS group (including 4 patients with mastectomy and 4 with BCS) vs. 10 patients in the WL group (including 6 with mastectomy and 4 with BCS), ($p = 0.02$). Mastectomy as the final treatment was performed in 4/148 patients (2.70%) in the IOUS group vs. 6/66 patients (9.09%) in the WL group, ($p = 0.04$).

Surgical time

There was a significant difference in the duration of surgery between groups, with an average of 40.58 min in the IOUS compared to 53.86 min in the WL group ($p = 0.006$). Neither the

Table 1
Baseline characteristics.

Characteristics	IOUS	WL	p
N	148	66	
Age, average (range)	56.74 (32–86)	60.14 (39–90)	0.11
Initial tumoral size mm (range)	16.09 (1–50)	14.5 (1–50)	0.75
T			0.15
T1	118 (79.73%)	58 (87.88%)	
T2	30 (20.27%)	8 (12.12%)	
Histological type, n (%)			0.08
Ductal	138 (94.52%)	56 (87.50%)	
Lobulillar	6 (4.11%)	6 (9.38%)	
Others	2 (1.37%)	2 (3.13%)	
Estrogen Receptors, n (%)			0.18
Positive	130 (87.84%)	62 (93.94%)	
Negative	18 (12.16%)	4 (6.06%)	
Progesterone Receptors, n (%)			0.65
Positive	112 (75.68%)	48 (72.73%)	
Negative	36 (24.32%)	18 (27.27%)	
HER2 Status, n (%)			0.47
Positive	6 (4.11%)	4 (6.45%)	
Negative	136 (93.15%)	56 (90.32%)	
Indeterminate	4 (2.74%)	4 (6.45%)	
Ki 67, n (%)			0.09
<20%	88 (59.46%)	46 (71.88%)	
≥20%	60 (40.54%)	18 (28.13%)	
Volumes cm^3 (range)	43.24 (4.3–104.7)	55.68 (15.7–311)	0.02
CRR	1.88 (0.2–6.87)	2.56 (0.5–11.71)	0.006
Intraoperative margin re-excision	74 (50%)	26 (42.42%)	0.09
Intraoperative re-excision indication			0.001
By surgeon	65 (87.83%)	14 (53.85%)	
By pathology	9 (12.17%)	12 (46.15%)	
Palpable tumors			0.16
Yes	87 (58.78%)	32 (48.48%)	
No	61 (41.22%)	32 (51.52%)	

time spent in placing the wire prior to surgery at the Radiology Department or localizing the tumor/clip before surgery were included. Adding these additional times, still IOUS had lower surgical duration (42.03 vs. 72.73 min, $p = 0.0001$). A lineal regression to assess the evolution of surgical time showed that for every additional surgery the time was shortened by 3.2 s (Fig. 2), ($p < 0.01$).

Learning curve

The graphics of each surgeon participating in the study are represented in Fig. 1. The evolution of each surgeon is displayed as a green dotted line limited by two red dotted lines that are H1 and H0 as described in materials and methods. Surgeons are intended to begin in the zero position and evolve towards H0 line. When this lower limit is crossed the technique is mastered. Surgeon 1 achieves H0 rate at 9 cases. After that, he goes back into the shadow zone, which means that after achieving proficient results he goes back into the area where he does not master the technique, though surgical outcomes may be correct. It is important to note that Surgeon 1 never crosses H1, implying that the outcomes do not cross the limit that meets failure at performing the technique. Surgeon 5 does not reach H0 during the period study and remains in the shadow area during the study, but he never crosses H1 limit. Surgeon 6 Reaches H0 at the very first case. The rest of all surgeons reach H0 in 7–17 procedures. If we calculate the average number of BCS for the six breast surgeons, the mean number of procedures to master this technique is 11.

Cost analysis

An overall gross cost study was performed by calculating the cost for each patient and the mean cost for each group (IOUS vs. WL). The average cost for the IOUS group was 3841.33€ (IC 95% 3626.35–4056.31) vs. 4742.30€ (IC 95% 4133.54–5351.05) for the WL group ($p = 0.002$).

Follow up

Median follow up was 51.22 months (range, 36.07–62.51 months) for IOUS and 69.85 months (range, 26.45–98.58 months) for WL group. There were no differences in disease free survival ($p = 0.25$) or overall survival ($p = 0.92$) between both groups.

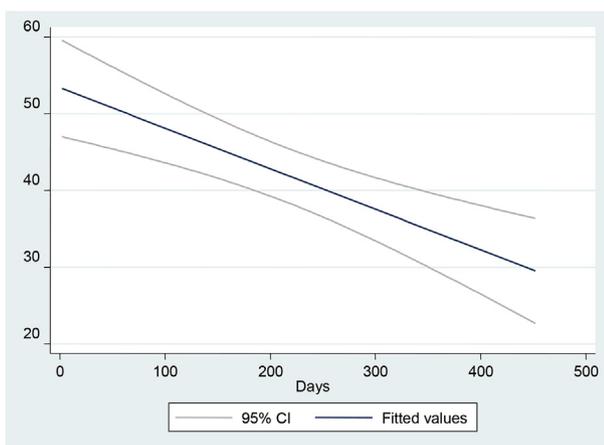


Fig. 1. Surgical time evolution. This fitted lineal regression graphic reflects the evolution in time of the surgical time. We have estimated for additional day during the study period, surgery was shortened by 3.2 s in average ($p < 0.001$).

Discussion

Margin status and second surgeries

Achieving clear margins remains an important goal in breast surgery, as it is an important predictor of local recurrence after BCS [21,22]. This study shows a reduction of positive margins with IOUS vs. WL, with almost a threefold reduction (5.4 vs. 15.15%). This is concordant to other published studies [8,23]. The IOUS technique allows the surgeon to assess margins by US intraoperatively and this influences the negative margins at the final pathology. When surgeons perform a re-excision intraoperatively, significantly decreases the rate of positive margins at final pathology as it has been shown in our study [15]. The proportion of involved margins for IOUS in our study is quite similar (3.8–6.7%) to other studies [9,24], and much lower than WL guided surgery, with rates of up to 47.7% [25]. This has been also reported in a meta-analysis by Ahmed et al., [2] that shows that IOUS has lower risk of involved margins (OR = 0.52 (95% IC 0.38–0.71)) when compared to WL.

Consequently, the need of second surgeries decreases using IOUS with an absolute reduction of 9.75% (5.4 vs. 15.15%). Second surgeries significantly affect cosmetic and patients' satisfaction worsening outcomes [26,27]. Mastectomy rates are also three times higher for the WL group (2.7 vs. 9.09%).

Surgical volumes and CRR

Our study confirms that IOUS reduces the volume of the surgical specimen resecting less HBT. Moreover, this reduction does not affect the rate of complete excision of the tumor and neither has an impact on local recurrence rates. Volume excised is a surrogate marker for the cosmetic outcome, with lumpectomies over 100 cm³ resulting in worse cosmetic outcomes [27]. In our data only 2 specimens were bigger than 100 cm³ in the IOUS group (both smaller than 105 cm³) while 6 specimens exceeded that volume (maximum of 311 cm³) in the WL group. A mean of 43.24 cm³ for IOUS and 55.68 cm³ for WL was found in our study, similar to Slijkhuis [8] (39 vs. 56, $p = 0.02$) and Krekel [3] (38 vs. 57, $p = 0.002$). These differences were not seen in the meta-analysis [2] probably because they included only two studies from 1999 with 53 patients.

One of the limitations when comparing surgical volumes appears when initial tumor sizes are different within groups. CRR avoids this differences taking into account only the excess of HBT resected. Our data show that the CRR is significantly lower (1.88 vs 2.56) with the use of IOUS, consistent with previous studies [3]. Nevertheless there are other reported studies where [28], the CRR was bigger in the IOUS group than in the WL group (4.3 vs 3.3, $p = 0.018$), probably explained by the fact that US was only used to mark on the skin the tumor localization prior to surgery.

Learning curve

Implementation of IOUS technique has not been successful even after multiple studies showing its advantages over WL. There is a controversy on how many procedures need to be done to master the technique [10], with only observational information published lacking statistical power.

The CUSUM method is a robust test that incorporates outcome information as soon as it is available [29]. It is also important to determine robust parameters to be analyzed when assessing outcomes by this method. Complete tumor excision and avoiding second surgeries due to involved margins are two of the main goals of the technique. Most of the surgeons reached mastering level in 7–17 cases, with an average of 11 cases. Importantly, none of the

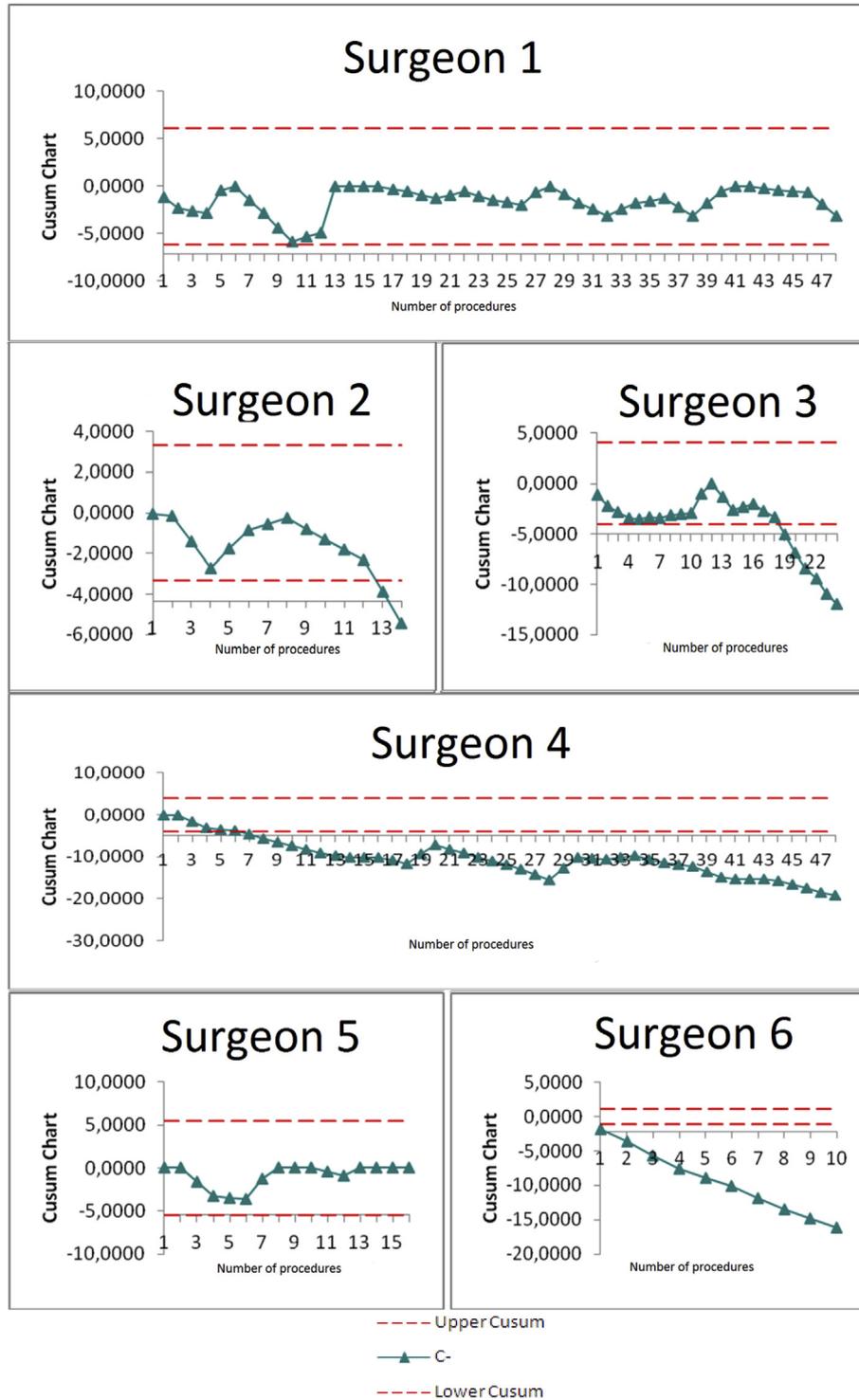


Fig. 2. CUSUM charts.

surgeons reached the H1 level where the failure rate exceeds the success rate.

Other researchers have measured the competence by observational studies that recorded rates of CRR by 3 surgeons performing 10 cases of IOUS surgery and found this number to be enough to master the technique [10]. We consider that CUSUM gives more statistical strength to the results and the ability to real-time data monitor performance of each surgeon, making it possible to find and solve problems (if any) at a very early stage.

Other authors have tried to measure the learning curve through surveys, where most of the surgeons felt comfortable performing IOUS in less than 10 cases, with an average training in ultrasound for 10.2 h [30].

Surgical time

Although previous studies have not found significant differences in duration of surgery, our study showed shorter surgeries for IOUS

with a mean absolute reduction of 13.28 min [2,3,28]. This decrease may be due to the fact that IOUS confirms tumor resection ex-vivo right at the surgical field just after excision. The WL specimen needs to be sent to the radiology department increasing the time and this extra time is part of the surgery as the patient is still under anesthesia.

Cost study

There is a lack of cost-efficiency studies comparing IOUS vs. WL, probably due to their complexity, as not only direct costs are included, but also indirect ones and its equivalence in QALYs (Quality-adjusted life year). A raw cost study was performed and showed that an average of 900.97€ per surgery may be saved with the use of IOUS. If all of the patients in our study had undergone IOUS, the savings would have raised up to 59,464€.

Other groups have reported differences in costs without statistical significant differences. The most exhaustive study [31] did not find statistical differences between groups, though they claim that the cost difference between PGS and IOUS was –154€ (95% CI –388 to 81) and that IOUS is cost saving for centers with >30 patients per year due to the decrease in the re-excision rate.

Conclusions

IOUS is an effective technique in the surgical treatment of early stage breast cancer as it enables to excise less HBT while obtaining lower rates of involved margins or second surgeries. Better implementation may be expected, as there is a short learning curve and each breast surgeon can monitor complete tumor excision and rates of free margins. In addition, it may save costs compared to WL.

Declarations of interest

None.

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