Radio-guided vs. clip-guided localization of non-palpable mass-like lesions of the breast from a screened population: a propensity score-matched study

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Running head: Clip vs. ROLL for nonpalpable nodules

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Synopsis for Table of Contents

Non-palpable breast cancers require an accurate localization for proper lumpectomy. ROLL and ultrasound localization of a clip marker are equally effective to reduce involved margins and re-interventions. ROLL allows more tailored resections for mass-like breast lesions.

Abstract

Background and Objectives: An accurate localization is mandatory to tailor breast lumpectomy in non-palpable cancers. The aim of this study was to compare radio-guided localization (ROLL) vs. ultrasound localization of a titanium clip with collagen (TCC) in non-palpable mass-like breast cancers.

Methods: 273 consecutive patients were reviewed: 64 patients were localized by TCC and 209 patients by ROLL. Propensity score-matched analysis was performed. Margins status and re-intervention rates were compared. Adequacy of resection was expressed as the calculated resection ratio (CRR) considering lesion size. Loco-regional and distant recurrence rates were assessed with ROLL vs. TCC.

Results: No differences were found with ROLL vs. TCC in clear margins (90.6% vs. 89.1%, OR 0.74, p=0.64) or re-operations (6.7% vs. 1.6%, p=0.529). ROLL allowed more tailored resections compared to TCC (adjusted CRR 1.7 vs. 2.7, p=0.0008), particularly in lesions with associated extensive intraductal component (respectively CRR 3.0 vs. 4.5, p=0.017). Loco-regional recurrence occurred in 1.9% of ROLL patients vs. 3.2% of TCC cases (p=0.628).

Conclusions: ROLL and TCC are equally effective to excise non-palpable mass-like breast cancers with clear margins, providing similar loco-regional control. However, ROLL allows more tailored breast resections, particularly in lesions with associated extensive intraductal component.

Keywords: Breast Cancer; Radio-guided Occult Lesion Localization; Clip; Non-palpable breast lesions; Breast-conserving surgery

Introduction

Non-palpable breast cancers have increased over time due to the wide adoption of screening mammography and improved patients' awareness [1-3]. The standard of care for surgical treatment of these lesions is breast-conserving surgery [4]. Today the surgeon should perform a tailored resection to ensure clear margins with smaller resection volumes, in order to associate a reduced risk of local relapse with a satisfactory cosmetic outcome [5]. Despite huge advances in breast cancer management and the recent revolution of the concept of adequate margin, re-interventions still range from 20 to 50% [6, 7]. To minimize reoperations rate, an accurate preoperative localization was considered mandatory to accurately plan surgery of non-palpable lesions [8].

However, yet no localization technique proved to be superior [8, 9]. Comparisons between techniques have been often performed without considering the type of non-palpable lesion, although microcalcifications and mass-like lesions could require different localization methods to optimize surgery, related to their different clinical features such as visibility on mammography or ultrasound (US). Therefore, lesion type may impact the choice of localization technique. We have previously described the usefulness of the preoperative localization of a titanium clip embedded with a collagen plug (TCC), positioned after biopsy and visible on US, as a stand-alone technique in non-palpable breast cancer surgery [10].

The aim of the present study was to compare the US localization of TCC vs. US radio-guided occult lesion localization (ROLL) in terms of clear margins, re-interventions and resection volumes in non-palpable mass-like breast cancers from a screened population.

Materials and methods

Study population and case selection

From January 2016 to January 2018, 273 consecutive patients affected by non-palpable mass-like unifocal breast cancer with clinically negative axillary nodes, diagnosed by screening mammography with or without US, and with indication of breast-conserving surgery, were included. All the patients were treated at the Breast Unit of ICS Maugeri Hospital, a high-volume tertiary center directly involved in extensive mammographic screening programs in northern Italy. Mass-like lesions included any nodule, mammographic opacity, or parenchymal distortion. Patients affected by microcalcifications without any associated mass-like lesion, candidated to total mastectomy, or patients treated by neoadjuvant chemotherapy were excluded from the study. All patients underwent breast-conserving surgery with preoperative localization of the lesion. In all cases where the breast lesion was almost completely removed by the core biopsy, a TCC (MammoMARK, Devicor Medical Products, Leica Biosystems, IL, USA) was positioned in the biopsy cavity immediately after the procedure. In these cases, preoperative localization was always performed by looking for TCC on US. In the remaining case in which the residual lesion after biopsy was clearly visible on US, thus excluding the need for a TCC, localization was performed by ROLL under US guidance.

End-points and outcomes evaluation

The following outcomes were assessed between TCC and ROLL patients:

1) Rate of clear margins

2) Rate of re-interventions

3) Resection volumes and excess of resected breast tissue

4) Surgery time

5) Loco-regional recurrence rate, distant metastases rate and cancer-related death rate

Clear margins were defined as no ink on tumor in case of invasive cancer, and 2 mm of free margin in case of ductal carcinoma in situ (DCIS) [11, 12]. In case of positive margins, the extent of involvement (focal vs. extensive) and the number of involved margins were reported. After surgery, all cases were discussed in the multidisciplinary meeting. The standard approach in case of positive margins was a re-operation: specifically, a re-excision of the breast parenchyma surrounding the surgical cavity was considered in case of a single margin involvement or multiple focally involved margins; in case of extensive involvement of multiple margins, or whether multifocality was observed, a total mastectomy was proposed. However, if a single focally positive margin was observed on final pathology, in selected cases with associated favorable features no further surgery was proposed, provided that adjuvant therapy was administered.

To accurately calculate resection volumes, the three dimensions of surgical specimen and of tumor were recorded after surgery. As previously reported, both cancer and specimen were considered as ellipsoids [5, 10]. The optimal resection volume (ORV) was defined as the tumor volume plus 1 cm of macroscopically clear tissue on all margins, by the following formula:

$$ORV = \frac{4}{3}\pi\left(\frac{a}{2}+1\right)\left(\frac{b}{2}+1\right)\left(\frac{c}{2}+1\right)$$

where a, b and c are the three tumor diameters expressed in cm. The total resection volume (TRV) was calculated by the formula:

$$TRV = \frac{4}{3}\pi\left(\frac{d}{2}\cdot\frac{e}{2}\cdot\frac{f}{2}\right)$$

with d, e and f being the three specimen dimensions. Finally, the calculated resection ratio (CRR) expressed the amount of excess of resected breast tissue and thus a parameter to evaluate the adequacy of resection, has been obtained with the formula:

$$CRR = \frac{TRV}{ORV}$$

Margins status, re-interventions and CRR were also separately analyzed comparing ROLL and TCC in lesions with or without extensive intraductal component (EIC), to verify the impact of EIC on performance of the two localization techniques.

Updated follow up data were retrieved by the prospectively-maintained institutional database of the Breast Unit. In case of missing follow up, data were obtained from recent outpatient routine clinical evaluations, or by phone interview. Loco-regional recurrence was defined as the occurrence of ipsi-lateral breast cancer or nodal disease proven on core biopsy. Distant metastasis was defined as the occurrence of distant lesions with computed tomography and positron emission tomography characteristics highly suggestive of malignancy. Cancer-related death was defined as the breast-cancer specific mortality.

Localization techniques and surgery

In TCC group, patients underwent preoperative localization of the clip with US, being in supine position with the upper limb abducted, thus resembling the same setting of the operating room. A mark was placed on the skin overlying the position of TCC. During surgery, a skin incision followed the mark and resection was performed excising breast tissue from skin deep to pectoralis major's fascia [10]. Then, an X-ray on the specimen was obtained to check the removal of the clip, its centricity into the specimen, and the macroscopic adequacy of margins. In ROLL group, 15-25 MBq of 99mTc-labelled human serum albumin nanocolloids (Nanocoll, GEHC, Italy) in 0.2 mL saline were injected into the lesion under US guidance on the day before surgery [13, 14]. The needle tip was positioned at the center of the lesion using a linear probe (7.5-10 MHz), and radiotracer was then injected. Then, a scintigraphy was performed to assess the adequacy of procedure. During surgery, a gamma probe (Bluetooth Neoprobe Gamma Detection System) was used to localize the lesion projection on breast skin, where the incision was made. Resection was then guided by the

gamma probe, to repeatedly check the inclusion of the lesion into the specimen. After lesion removal, the gamma probe was used to assess possible residual signal in the resection cavity. In all cases, the sentinel lymph node was detected with the radioisotope technique. All the procedures were performed by the same surgical equipe.

Statistical analysis

For all patients clinical and pathological variables were collected in a prospectively-maintained database. Differences between TCC and ROLL patients were assessed to verify the heterogeneity of the study population. Due to the non-random design of the study and the patient selection in assigning localization technique, a propensity score-matched analysis was performed, matching patients according to preoperative variables. TCC and ROLL patients were matched in a 1:1 ratio and compared with a logistic regression model adjusted for post-operative variables significantly associated with the outcomes, to avoid any bias. Variables were reported as means ± standard deviations or as absolute numbers and percentages. Categorical variables were compared using χ^2 test or Fisher exact test (two-tailed), while continuous variables were compared using Student's T test. Bartlett's test for homogeneity of variances was performed on mean CRRs with ROLL vs. TCC. Statistical significance was set at $p<0.05$. Data analysis was performed using STATA software (v. 13, StataCorp, Austin, USA).

Results

Variables distribution between TCC and ROLL

Sixty-four (23.4%) patients underwent localization by TCC, while the remaining 209 patients (76.6%) were localized by ROLL. Baseline characteristics of TCC and ROLL patients are reported in Table 1. A BI-RADS score 5 was observed in 18.8% of TCC patients and 40.2% of ROLL cases (p=0.005). Lesions localized by TCC were more frequently associated to grade 1 compared to ROLL group (40.6% vs. 20.1%, p=0.001). A slight increase in axillary dissections was observed among ROLL patients compared to TCC cases (14.4% vs. 4.7%, p=0.047). All the other variables were balanced between the two groups.

Margin status, re-intervention rates and operative times

Negative margins were observed in 90.9% of ROLL patients and in 89.1% of TCC patients (OR 1.19, 95%CI 0.38-3.75, p=0.77, Table 2). No differences in type of margin involvement or number of involved margins were found between ROLL and TCC, although a non-significant increase in multiple involved margins was observed with ROLL (31.6% vs. 0% with TCC, p=0.146). A re-intervention was performed in 6.7% of ROLL patients vs. 1.6% in TCC cases (p=0.529). Eleven patients with positive margins on final pathology (5 ROLL patients and 6 TCC patients) did not undergo re-excision. Operative time was similar between TCC and ROLL (respectively 65 ±14.2 min vs. 62.9 ±27.8 min, p=0.562). No complications related to the localization technique occurred in both groups.

Resection volumes and adequacy of resections

A significantly lower mean resection volume was found with ROLL compared to TCC (43.9 ±37.2 cm^3 vs. 56.8 ±44.1 cm^3, p=0.021). Accordingly, mean CRR was lower with ROLL compared to TCC, being respectively 2.8 (±2.3) vs. 3.7 (±3.4), p=0.016.

Performances of ROLL vs. TCC in lesions with or without associated extensive intraductal component

EIC was present in 73 ROLL patients (34.9%) and in 13 TCC patients (20.3%), p=0.031. Among patients with lesion-associated EIC, clear margins were obtained in 82.2% of ROLL patients vs. 92.3% of TCC cases (p=0.684). No differences were observed in total resection volumes (p=0.534) or re-interventions (p=0.815). However, mean CRR was significantly lower in ROLL patients (3.0 ±2.1 vs. 4.5 ±1.6, p=0.017). No significant differences were observed between ROLL and TCC in patients without associated EIC. All these data are reported in Table 3.

Adjuvant treatments and oncologic outcomes

Radiotherapy was proposed in 91.4% of ROLL patients vs. 85.9% of TCC cases (p=0.231). No differences were observed also in administration of hormone therapy (respectively in 85.6% vs. 82.8%, p=0.555) or chemotherapy (8.1% vs. 6.2%, p=0.791), as reported in Table 1. Mean follow up was 14.7 ±8.8 months in ROLL group and 16.6 ±8.7 months in TCC group (p=0.131). Loco-regional recurrence occurred in 1.9% of ROLL patients and in 3.2% of TCC cases (p=0.628). Distant metastases (p=0.138) and cancer-related death (p=1.000) rates were similar between ROLL and TCC patients, as reported in Table 2.

Propensity score-matched analysis and multivariate logistic regression

After propensity-score matching, no differences were found in margins status with the two localization techniques, with ROLL associated to 90.6% negative margins vs. 89.1% with TCC after matching patients (p=0.77). After multivariate analysis, adjusted OR was equal to 0.74 (95%CI 0.21-257,

p=0.64). No variable emerged as independently predictive of involved margins. About resection volumes, unadjusted mean CRR was 1.8 (±1.1) with ROLL vs. 2.7 (±1.1) with TCC (p=0.003). After multivariate analysis, a significantly lower adjusted mean CRR was observed with ROLL compared to TCC (respectively 1.7 vs. 2.7, p=0.0008, Table 4, Figure 1), thus ROLL was independently associated to more tailored resections. Notably, CRR was also independently associated to lesion size (p=0.003) and presence of DCIS (p=0.02). Furthermore, CRRs showed a wider variance with a higher dispersion using TCC compared to ROLL (p=0.0002, Figure 2).

Discussion

Optimizing the surgical strategy of non-palpable breast lesions by an accurate localization is highly required not to lose the benefits of breast-conserving surgery [15]. In this study, ROLL and US localization of TCC were compared in a large-population study of non-palpable mass-like breast cancers.

Mass-like lesions such as nodules or distortions have been often analyzed together with microcalcifications in several previous studies comparing different localization techniques, but these lesions do not share the same clinical and pathological features and may differently benefit of available localization strategies [16-19]. Therefore, type of lesion may affect the choice of localization technique by surgeons and radiologists: for microcalcifications a stereotactic wire-guided localization (WGL) of US localization of TCC might be preferable, while for non-palpable mass-like lesions US ROLL could be overwhelmingly used, since nodules are excellently visible on US [20, 21]. Thus, analyzing together different types of non-palpable lesions may result in significant biases. Due to such concern, we decided to perform a separate analysis for non-palpable mass-like lesions, clearing the study population from microcalcifications to properly compare the two localization techniques.

In the present study, ROLL and TCC were associated to similar involved margin rates (respectively 9.1% vs. 10.9%) and similar re-intervention rates (6.7% vs. 1.6%). A discrepancy between involved margins and re-intervention rates could be observed, since 11 patients on 26 with involved margins were not re-operated. All these patients had only a focal involvement of a single margin and presented with favourable features (age >50 years, Luminal A lesions, no axillary involvement), therefore after discussion of each case in the multidisciplinary meeting of the Breast Unit, a re-excision was avoided.

In 16 patients (5.9%) sentinel lymph node biopsy was not performed, because these patients were

affected by pure ductal carcinoma in situ undergoing breast-conserving surgery, therefore axillary staging was not routinely recommended [22]. However, the other 13 patients affected by intraductal cancer received sentinel node biopsy, due to associated high-risk features predictive of upstaging to invasive disease on post-operative histopathology [23].

Interestingly, ROLL significantly reduced resected volumes and improved adequacy of resection, with an adjusted mean CRR equal to 1.7 vs. 2.7 with TCC (p=0.0008) considering confounder factors. Interestingly, by analyzing specifically lesions with associated EIC, a significantly higher mean CRR emerged with TCC compared to ROLL (4.5 vs. 3.0, p=0.017), while margins status and re-interventions were similar. Conversely, no difference was observed between the two techniques among lesions without EIC, being mean CRR comparable. In other words, the presence of associated EIC revealed to have a strong impact on the observed difference in CRR between ROLL and TCC. This finding may be related to the lack of an intraoperative guidance during TCC-guided surgery, thus the surgeon may be prone to excise more than needed in treating lesions with associated microcalcifications/EIC. Accordingly, lesion size and presence of DCIS emerged as independent predictors of higher CRR on multivariate analysis after propensity score matching. Since CRR itself normalizes the volume of resection on lesion size, a correlation between higher size and higher CRR means that surgeons performed wider excisions if they faced wider lesions or DCIS. Despite this tendency and the higher proportion of patients with EIC (34.9% vs. 20.3%, p=0.031), ROLL allowed a more tailored surgery compared to TCC, and standardization of surgery thanks to ROLL was demonstrated by the lower dispersion of mean CRR (p=0.0002). Indeed, intraoperative guiding with ROLL, by continuously checking with the probe the position of the lesion, allowed to tailor the resection in real-time, conversely to TCC-guided surgery [24, 25].

No difference was observed in oncologic outcomes between ROLL and TCC patients, and in particular loco-regional recurrences were less frequent among ROLL patients (1.9% vs. 3.2%, p=0.628), despite their lower volumes of resection. Thus, TCC-guided surgery was associated to

excessive breast resections without a benefit in loco-regional control. Anyway, these findings should be cautiously taken into account because follow up was quite short, being no more than 24 months. HER2-positive and triple-negative breast cancers are associated to early events, but Luminal cancers (the majority of cases in this series) are more frequently late-recurring, thus possible recurrences may be missed in the present study [26].

No differences were observed in surgery time between ROLL and TCC (respectively 65 vs. 62.9 minutes) despite operative time included also the intraoperative X-ray of specimen to check the position of the clip among TCC patients. Notably, presence and position of TCC within the surgical specimen was not checked by ex vivo US. TCC-guided surgery only relies on localization of the clip without any intraoperative guiding as in case of ROLL. Therefore, to increase the confidence of the surgeon to have completely excised the lesion, a further check by looking for the metallic core of the clip into the specimen by X-ray was always performed. X-ray unequivocally confirmed the presence of the clip within the specimen and allowed the surgeon to check macroscopically for the adequacy of margins and the centricity of the TCC.

Several previous studied compared various localization techniques, demonstrating that ROLL may improve localization and excision, with adequate resection volumes, better cosmetic outcome and shorter procedure time, but without a consolidated significant difference with other techniques in terms of accurate localization [27-33]. A recent meta-analysis endorsed by the Cochrane Collaboration on 11 randomized controlled trials compared the effectiveness of ROLL vs. radioactive seed (RSL) and WGL: ROLL and RSL proved to be equivalent to WGL in terms of successful excision, although ROLL confirmed to be associated with improved cosmesis [8]. Both WGL and RSL have well known drawbacks, such as displacement, fracture or patient's discomfort in case of WGL, and an additional procedure before surgery to insert the seed, as well as radioactivity handling and disposal concerns, in case of RSL [8]. Only a few studies have evaluated US localization of clip markers, providing encouraging results compared with WGL; however, an accurate assessment of such

technique in terms of adequacy of resection volumes specifically in different lesion types is still lacking, especially compared with ROLL [34, 35].

Most of previous studies were designed before the recent definition of adequate margins for invasive cancer and DCIS, and frequently patients with benign or uncertain lesions were included, conversely to the present study [8, 27-33]. Furthermore, adequacy of resection has been often evaluated on specimen volumes or weight, or patients' cosmetic satisfaction, without accurately correlating resection volumes with lesion size by CRR. A proper and standardized evaluation of resected volumes should be imperative in this kind of studies, since adequacy of resection is a main end-point for breast-conserving surgery of non-palpable cancers, and current imprecisions and heterogeneity in volumes measurement have led to inconsistent or controversial results [36, 37].

A limitation of the present study is its retrospective and non-random design, which could have potentially affected distribution of baseline variables between groups. However, only BI-RADS and grading resulted to be significantly different, and a propensity score matching with multivariate analysis was performed to avoid bias. Furthermore, the relatively short follow up could have biased the loco-regional recurrence rates between ROLL and TCC patients.

Conclusions

Our findings suggest that ROLL and US localization of TCC are equally effective to excise non-palpable mass-like breast cancers with clear margins, providing similar loco-regional control, if wisely used in a tertiary referral center. However, ROLL is associated to significantly reduced resection volumes, allowing to perform more tailored and standardized breast resections particularly if extensive intraductal component is present.

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Tables

Table 1. Variables distribution between ROLL and TCC groups

	ROLL (n = 209)	TCC (n = 64)	Total (n = 273)	p Value
Age at diagnosis (years)	62.1 (±11.5)	64.2 (±8.4)	62.6 (±10.9)	0.177
BI-RADS				
<4	11 (5.3%)	4 (6.2%)	15 (5.5%)	0.005
4	114 (54.5%)	48 (75.0%)	162 (59.3%)	
5	84 (40.2%)	12 (18.8%)	96 (35.2%)	
Lesion size (mm)	11.3 (±5.5)	10.6 (±5.2)	11.1 (±5.4)	0.368
Histological type				
DCIS	22 (10.5%)	7 (10.9%)	29 (10.6%)	0.711
Invasive ductal	161 (77.0%)	46 (71.9%)	207 (75.9%)	
Invasive lobular	19 (9.1%)	7 (10.9%)	26 (9.5%)	
Others/No residual lesion	7 (3.3%)	4 (6.3%)	11 (4.0%)	
pT stage				
pTis	22 (10.5%)	7 (10.9%)	29 (10.6%)	0.775
pT1	175 (83.7%)	52 (81.3%)	227 (83.2%)	
pT2	12 (5.8%)	5 (7.8%)	17 (6.2%)	
pN stage				
pN0/pNmic	170 (81.3%)	58 (90.6%)	228 (83.5%)	0.876
pN1	17 (8.1%)	5 (7.8%)	22 (8.0%)	
pN2	7 (3.3%)	0 (0.0%)	7 (2.6%)	
SLNB not performed	15 (7.2%)	1 (1.6%)	16 (5.9%)	
Axillary Dissection				
No	179 (85.6%)	61 (95.3%)	240 (87.9%)	0.047
Yes	30 (14.4%)	3 (4.7%)	33 (12.1%)	
Grading				
G1	42 (20.1%)	26 (40.6%)	68 (24.9%)	0.001
G2	136 (65.1%)	36 (56.3%)	172 (63.0%)	
G3	31 (14.8%)	2 (3.1%)	33 (12.1%)	
Biological portrait				
Luminal A	131 (62.7%)	41 (64.1%)	172 (63.0%)	0.419
Luminal B	55 (26.3%)	20 (31.3%)	75 (27.5%)	
HER2-positive	13 (6.2%)	1 (1.6%)	14 (5.1%)	
TNBC	10 (4.8%)	2 (3.1%)	12 (4.4%)	

Extensive intraductal component				
No	136 (65.1%)	51 (79.7%)	187 (68.5%)	0.031
Yes	73 (34.9%)	13 (20.3%)	86 (31.5%)	
Radiotherapy				
No	18 (8.6%)	9 (14.1%)	27 (9.9%)	0.231
Yes	191 (91.4%)	55 (85.9%)	246 (90.1%)	
Hormone therapy				
No	30 (14.4%)	11 (17.2%)	41 (15.0%)	0.555
Yes	179 (85.6%)	53 (82.8%)	232 (85.0%)	
Chemotherapy				
No	192 (91.9%)	60 (93.8%)	252 (92.3%)	0.791
Yes	17 (8.1%)	4 (6.2%)	21 (7.7%)	

Table 2. Margins status, re-interventions and oncologic outcomes between ROLL and TCC groups

	ROLL (n = 209)	TCC (n = 64)	Total (n = 273)	p Value
Margin status				
Negative (no ink on tumor)	190 (90.9%)	57 (89.1%)	247 (90.5%)	0.632
Involved	19 (9.1%)	7 (10.9%)	26 (9.5%)	
Type of involved margin				
Focally involved	16 (84.2%)	7 (100.0%)	23 (88.5%)	0.539
Extensively involved	3 (15.8%)	0 (0.0%)	3 (11.5%)	
Number of involved margins				
1	13 (68.4%)	7 (100.0%)	20 (76.9%)	0.146
>1	6 (31.6%)	0 (0.0%)	6 (23.1%)	
Re-intervention				
No	195 (93.3%)	63 (98.4%)	258 (94.5%)	0.529
Yes: Re-lumpectomy	9 (4.3%)	1 (1.6%)	10 (3.7%)	
Yes: Total mastectomy	5 (2.4%)	0 (0.0%)	5 (1.8%)	
Loco-regional recurrence				
No	205 (98.1%)	62 (96.8%)	267 (97.8%)	0.628
Yes	4 (1.9%)	2 (3.2%)	6 (2.2%)	
Distant metastasis				
No	208 (99.5%)	62 (96.8%)	270 (98.9%)	0.138
Yes	1 (0.5%)	2 (3.2%)	3 (1.1%)	
Cancer-related death				
No	209 (100.0%)	64 (100.0%)	273 (100.0%)	1.000
Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Mean follow up (months)	14.7 (±8.8)	16.6 (±8.7)	14.9 (±8.8)	0.131

Table 3. Performance of ROLL vs. TCC among lesions with or without associated extensive intra-ductal component (EIC)

	EIC (n = 86)			**No EIC (n = 187)**		
	ROLL (n = 73)	**TCC (n = 13)**	**p Value**	**ROLL (n= 136)**	**TCC (n = 51)**	**p Value**
Margin status						
Negative (no ink on tumor)	60 (82.2%)	12 (92.3%)	0.684	130 (95.6%)	45 (88.2%)	0.092
Involved	13 (17.8%)	1 (7.7%)		6 (4.4%)	6 (11.8%)	
Total resection volume (cm^3)	46.3 (±34.8)	52.4 (±9.7)	0.534	42.6 (±38.7)	45 (±35.4)	0.699
CRR (mean)	3.0 (±2.1)	4.5 (±1.6)	0.017	2.8 (±2.4)	2.3 (±1.9)	0.183
Re-intervention						
No	64 (87.7%)	13 (100.0%)	0.815	131 (96.3%)	50 (98.0%)	1.000
Yes: Re-lumpectomy	6 (8.2%)	0 (0.0%)		3 (2.2%)	1 (2.0%)	
Yes: Total mastectomy	3 (4.1%)	0 (0.0%)		2 (1.5%)	0 (0.0%)	

Table 4. CRR according to localization technique after propensity score matched analysis

	ROLL	TCC	p Value
CRR (unadjusted mean)	1.8 (±1.1)	2.7 (±1.1)	0.003
CRR (adjusted mean)	1.7 (±1.2)	2.7 (±1.2)	0.0008
Multivariate analysis	**Estimate/OR**	**95%CI**	**p Value**
Lesion size	-0.04	-0.06-(-0.01)	0.003
Age at diagnosis	0.007	-0.006-0.02	0.3
Grading			
G1 vs. G3	-0.38	-0.88-0.12	0.14
G2 vs. G3	-0.27	-0.72-0.18	0.24
pT stage			
DCIS vs. pT2	-0.82	-1.52-(-0.12)	0.02
pT1 vs. pT2	-0.51	-1.16-0.14	0.12
BI-RADS			
BI-RADS <4 vs. 5	-0.24	-0.81-0.34	0.41
BI-RADS 4 vs. 5	0.22	-0.13-0.56	0.21

Figure Captions

Fig. 1 Mean adjusted CRRs after breast-conserving surgery between ROLL and TCC in mass-like non palpable breast cancers. CRR: calculated resection ratio; ROLL: radio-guided occult lesion localization; TCC: titanium clip with collagen.

Fig. 2 Dispersion of CRRs between ROLL and TCC in mass-like non palpable breast cancers. On the *vertical axis* distributions of frequency are reported, while the *horizontal axis* represents CRRs. CRR: calculated resection ratio; ROLL: radio-guided occult lesion localization; TCC: titanium clip with collagen.