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REVIEW

Comparison of Radioguided Occult Lesion Localization (ROLL) and Wire Localization for Non-Palpable Breast Cancers: A Meta-Analysis

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Four randomized trials encompassing 449 patients of non-palpable breast cancer undergoing with radio-guided occult lesion localization (ROLL) or wire guided localization (WGL). In the fixed effects model, accurate localization, peri-procedural complications, and reoperation rate were comparable between two techniques. Risk of having positive resection margins following WGL was higher. Duration of localization and surgical excision was shorter for ROLL. Volume and weight of the excised occult breast lesion was similar in WGL and ROLL groups. *J. Surg. Oncol.* © 2011 Wiley Periodicals, Inc.

KEY WORDS: occult breast cancer; non-palpable breast cancers; localization techniques; wire guided localization; radioguided occult lesion localization

INTRODUCTION

The introduction of the national breast screening program and the subsequent routine use of mammography and ultrasonography have resulted in more precise delineation of impalpable breast lesions [1,2]. More than 25% of radiologically suspicious breast lesions are non-palpable; accurate localization is required with respect to diagnostic core biopsy or surgical excision [3–5]. Precise localization of non-palpable lesions is an essential step to guarantee cancer clearance without compromising cosmetic results. Various modalities have been trialed for accurate localization of non-palpable breast lesions; each with some advantages and risks. The first method reported in 1966 [6] involved bent-wire implanted under fluoroscopic control through a needle placed in the occult breast lesion. The use of needles combined with hook-wire was later proposed in 1976 for the preoperative marking of impalpable breast lesions [7]. Since then a large number of localization interventions have been reported; these include positioning of a needle hook wire [8–13], dye injection [14], using radiological and clinical measurements [15], perforated grids [16], stereotactic methods [17,18], carbon localization [19] and intra-operative ultrasonography [20]. In addition, the use of magnetic resonance imaging [21], computerized axial tomography [22] and radioactive seed localization have been described [23] with variable success. The majority of preoperative approaches for impalpable breast lesion localization are associated with significant failure rates and complications, resulting in only a handful being used routinely.

Wire guided localization (WGL) is currently the most commonly used localization method for non-palpable breast cancers. WGL is an effective method of preoperative localization; however it too has several disadvantages. Wire placement is technically challenging and may pose significant difficulty, particularly in dense breast tissue. The procedure can be demanding on the patient as the wire must be keep in place until the time of operation; sometimes with significant pain and discomfort. The wire may become displaced, migrate or be transected [24–27] especially during mobilization of the patient and replacement may have to be repeated with the help of mammography or ultrasonography. Repositioning can be complicated by bruised tissue within the previously punctured tumor site. Local complications of wire insertion can include pneumothorax [28] and the physical presence of a wire within the operation zone can result in a more complicated incision and make the procedure of surgical excision with clear margins technically cumbersome. Radioguided occult lesion localization (ROLL) is a relatively new [29,30] preoperative localization technique for non-palpable early breast cancers. In ROLL, a radiotracer solution is injected adjacent to the lesion under ultrasonographic or stereotactic guidance. This allows for subsequent surgical biopsy or wide local excision to be performed under the guidance of a hand held gamma-ray detection counter. ROLL has steadily gained popularity in impalpable lesion localization due to its minimal side effects and technical ease. Preliminary results assessing the use of the ROLL technique have been very encouraging [3,8,31–33] but it is still not the preferred localization technique for non-palpable breast cancers. The objective of this article is to systematically analyze the published randomized controlled trials on the efficacy of both ROLL and WGL in the preoperative localization of non-palpable breast cancers in order to achieve a combined conclusion and recommend its utilization as a preferable technique if available evidence supports this.

METHODS

Relevant studies (irrespective of type, language, blinding, sample size, or publication status) on the effectiveness of ROLL and WGL in localization of non-palpable breast cancers are included in this

Conflict of interest: none to declare.

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review. The Cochrane Breast Cancer Group (CBCG) Controlled Trial Register, the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, Medline, EMBASE, and Science Citation Index were searched using the medical subject headings (MeSH) terms ''occult breast cancers,'' ''non-palpable breast cancers,'' ''breast screening,'' ''breast ultrasonography,'' ''breast magnetic resonance imaging,'' and ''mammogram'' were used in combination with ''occult lesion localization techniques,'' ''wire guided localization,'' ''radioguided occult lesion localization,'' and ''image guided localization.'' The ''related article'' function was used to widen the search criteria. All abstracts, comparative studies; non-randomized trials and citations scanned were reviewed in order to get the maximum results by comprehensive literature search. A filter for identifying relevant studies recommended by The Cochrane Collaboration [34] was used to filter out irrelevant studies in Medline and EMBASE. The references of the included studies were searched to identify further trials. Two authors independently identified the relevant studies for inclusion; extracted data related to the outcomes and secured data on a Microsoft Excel spread sheet.

Analysis of the data was aided by a software package; RevMan 5.0.1 [35] provided by The Cochrane Collaboration. The odds ratio (OR) with 95% confidence interval (CI) was calculated for binary data variables, and the mean difference (MD) with 95% CI for continuous data variables. If the mean values were not available for continuous outcomes, median values were used for the purpose of meta-analysis. If the standard deviation was not available, it was calculated according to the guidelines of The Cochrane Collaboration [34] either from range values or *P*-values. This involves assumptions that both groups have the same variance, which may not be true. The random-effects model [36] and the fixed-effect model [37] were used to calculate the combined outcome in both binary and continuous variables. In case of heterogeneity only the results of the random-effects model were reported. Heterogeneity was explored using the χ^2 test, with significance set at $P < 0.05$, and quantified [38] using I^2, with a maximum value of 30% identifying low heterogeneity [39]. The Mantel–Haenszel method was used for the calculation of OR under the fixed effect model, and the DerSimonian/Laired method was used for the calculation of OR under the random effect model [34]. In a sensitivity analysis, 0.5 was added to each cell frequency for trials in which no event occurred in either the treatment or control group, according to the method recommended by Deeks et al. [40]. The estimate of the difference between both techniques was pooled depending upon the effect weights in results determined by each trial estimate variance. The forest plot was used for the graphical display of results from the meta-analysis. The square around the estimate stands for the accuracy of the estimation (sample size) and the horizontal line represents the 95% CI.

RESULTS

Quorum diagram to explain the study methodology and literature search is given in Figure 1. Four randomized controlled trials [43–46] encompassing 449 patients undergoing either ROLL or WGL were retrieved from the electronic databases for systematic review. The ROLL group comprised a total of 218 patients and WGL group 231 patients. The specific technique's used for ROLL and WGL in these studies can be viewed in Table I. The characteristics of these trials are given in Table II. Variables used to achieve a combined outcome are given in Table III.

Methodological Quality of Included Studies

The methodological quality of included trials is explained comprehensively in Table IV. It was evaluated by the published guideline of SIGN (Scottish Intercollegiate Guidelines Network) and Rangel et al. [41,42]. The Mantel–Haenszel fixed effect model was used to compute robustness and susceptibility to any outlier among these trials. The allocation concealment and blinding of investigator, assessor, and statistician were not clearly reported, consequently the methodological quality of all four trials may be considered inadequate. All trials scored between 11 and 14 out of 19 indicating a moderate strength of each individual trial.

Accurate Localization Rate

There is no heterogeneity [$\chi^2 = 0.01$, df = 1 ($P < 0.93$); $I^2 = 0\%$] amongst the three trials [43,44,46] which contributed in the combined outcome. Therefore, in the fixed effects model (OR, 1.57; 95% CI, 0.25–9.84; z = 0.87; $P < 0.38$; Fig. 2), both techniques are equally effective in the localization of impalpable breast lesions.

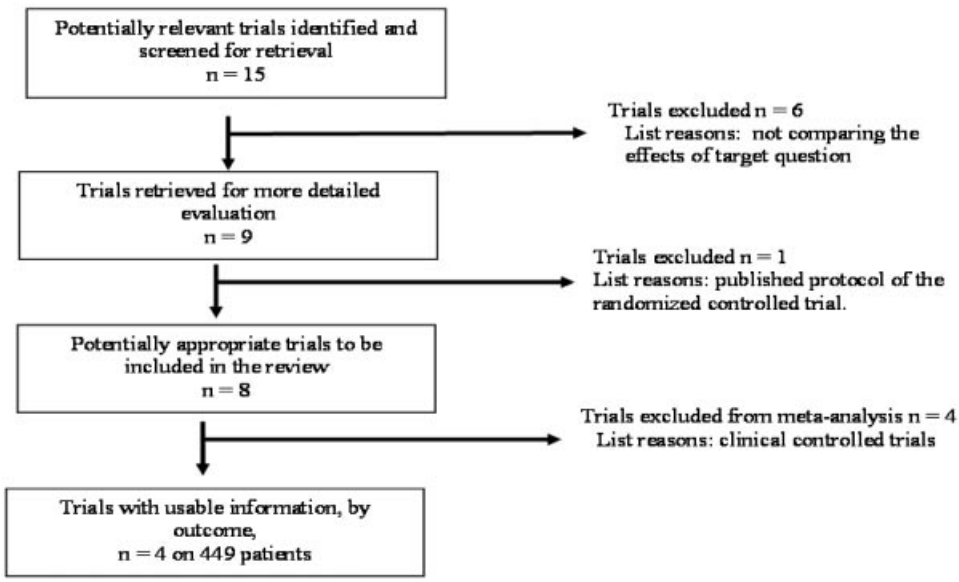

Fig. 1. Quorum diagram showing study methodology.

TABLE I. Protocols Adopted for ROLL and WGL in Included Trials

Trial	ROLL group	WGL group
Mariscal Martínez and Solà [43]	A single 74-MBq dose of a ^{99m}Tc-colloid was injected in the non-palpable breast lesion using 22–25 gauge and 4–10 cm long needle If area of microcalcification was more than 3.5 cm in size, the radiotracer was distributed in various points Imaging guidance was achieved with analog mammography (MammoDiagnost UC system, Philips Healthcare) with a stereotactic system (Cytoguide, Smith-Roentgen) or with sonography (Sequoia 512 Imagegate system, Acuson) with a 13-MHz probe ROLL was performed 3–16 hr before surgery Excision biopsy was performed using a gamma-detecting probe measuring the radioactivity as a hot spot	Non-palpable lesion was targeted with needle wire insertion under imaging guidance using ultrasound or stereotaxis The repositionable localization wire (Dualok, Bard) had double helix configuration and a locking dual hook-end design. It was encased in a 20-gauge insertion needle. The lesion was crossed, and the border was exceeded by no more than 1 cm For extensive areas of microcalcification (>3.5 cm), bracketing wire was used to delimit the borders of the microcalcification Accurate localization was confirmed by craniocaudal and lateral orthogonal views of mammogram or with real-time ultrasound imaging WGL was performed 30 min before surgery
Medina-Franco et al. [44]	A single dose (0.2–0.3 ml) of ^{99m}Tc-labeled particles (10–150 μm in diameter) of human serum albumen was injected in the non-palpable breast lesion using 22–25 gauge and 4–10 cm long needle If area of microcalcification was more than 3.5 cm in size, the radiotracer was distributed in various points Imaging guidance was achieved with stereotactic mammographic guidance and ultrasonic guidance was used for solid lesions Total dose of radiotracer was 3.7 MBq (0.1 mCi) ^{99m}Tc at specific activity of 74-MBq/mg Excision biopsy was performed using a gamma-detecting probe measuring the radioactivity as a hot spot ROLL was performed 4 hr before surgery Local anesthetic was injected at marked area	Non-palpable lesion was targeted with needle wire insertion under mammographic guidance using ultrasound or stereotaxis The repositionable localization wire had double helix configuration and a locking dual hook-end design
Moreno et al. [45]	A single injection (0.2 ml saline) of ^{99m}Tc-labeled particles of macro-albumen aggregate was injected in the non-palpable breast lesion Total dose of radiotracer was 5.55 MBq (0.15 mCi) ^{99m}Tc Excision biopsy was performed using a gamma-detecting probe measuring the radioactivity as a hot spot Scintigraphy was used for radiological correlation Local anesthetic was injected at marked area	n/a
Rampaul et al. [46]	^{99m}Tc-labeled macro-albumen aggregate (CIS, High Wycombe, UK) was combined with 0.2 ml water-soluble non-ionic iodinated contrast medium. Imaging guidance was achieved with mammography	n/a

ROLL, radioguided occult lesion localization; WGL, wire guided localization.

TABLE II. Characteristics of Included Randomized Trials

	Mariscal Martínez and Solà [43]		Medina-Franco et al. [44]		Moreno et al. [45]		Rampaul et al. [46]	
Features	ROLL	WGL	ROLL	WGL	ROLL	WGL	ROLL	WGL
Publication year	2009		2008		2008		2004	
Patients number	66	68	50	50	61	59	48	47
Age in years (mean ± SD)	57.5 ± 10.5	56.4 ± 11.7	55.8 ± 9.3	55.26 ± 10.24	50.7	49.9	n/a	
Range					32–76	35–77		
Early diagnostic test			26:5	21:8	5:9	13:2	n/a	
Core biopsy	35	42						
Fine needle aspiration	31	26						
Mammographic size in mm	16.3 mm	18.2 mm	8.2 ± 3.8	7.4 ± 4.0	49 mm	40 mm	n/a	
Ethics approval	Yes		Yes		n/a		Yes	
Cases of breast cancer	66	68	9	8	10	16	39	39
Indications for procedures	Therapeutic and diagnostic		Therapeutic and diagnostic		Diagnostic		Therapeutic and diagnostic	
Localization imaging								
Stereotactic mammogram	21	31	9	11	27	31	n/a	
Ultrasonography	45	37	41	39	24	28		

ROLL, radioguided occult lesion localization; WGL, wire guided localization.

TABLE III. Outcome Variables

	Mariscal Martínez and Solà [43]		Medina-Franco et al. [44]		Moreno et al. [45]		Rampaul et al. [46]	
Variables	ROLL	WGL	ROLL	WGL	ROLL	WGL	ROLL	WGL
Localization rate	66/66	68/68	47/50	45/50	n/a	n/a	46/48	44/47
Complications	0/66	2/68	0/50	1/50	2/59	3/59	2/48	0/47
Positive margins	7/66	12/68	1/9	3/8	4/61	8/59	0/48	0/47
Reoperations	5/66	12/68	3/50	5/50	n/a	n/a	18/46	13/46
Surgery duration (min)	32.7 ± 1.7	36.5 ± 13.7	29 ± 12.8	33 ± 15.2	26.6 ± 12.7*	37.2 ± 12.7*	31 ± 13.2*	35 ± 13.2*
Localization duration (min)	14.4 ± 5.5	20.9 ± 10.2	17** (11–20)	23** (20–25)	n/a	n/a	16 ± 7.6*	23 ± 7.6*
Excised volume (mm^3)	120.7 ± 69.5	118 ± 85.5	n/a	n/a	88.70 ± 53.3*	230.15 ± 53.3*	n/a	n/a
Specimen weight (g)	68.1 ± 35.5	67.3 ± 46.7	n/a	n/a	n/a	n/a	34 ± 12.8	31 ± 12.8

*SD estimated from *P*-value.
**SD estimated from range.

Procedure Related Complications

Both localization procedures were well tolerated by patients without any major complication. However, minor complications including transient vasovagal episodes were analyzed. There was no heterogeneity [$\chi^2 = 2.49$, df = 3 ($P < 0.48$); $I^2 = 0\%$] amongst the four trials; therefore, in the fixed effects model (OR, 0.73; 95% CI, 0.24–2.22; z = 0.56; $P < 0.58$; Fig. 3) both procedures are safe and may be utilized effectively in the localization of impalpable breast tumors.

Tumor Positive Margins

There was no heterogeneity [$\chi^2 = 0.51$, df = 2 ($P < 0.78$); $I^2 = 0\%$] amongst the four trials. Therefore, in the fixed effects model (OR, 0.47; 95% CI, 0.22–0.99; z = 1.99; $P < 0.05$; Fig. 4), ROLL is superior to WGL in terms of tumor free margins following wide local excision of an impalpable breast tumor. Statistically, the risk of having positive tumor margins on wide local excision is greater after WGL than compared to ROLL.

Reoperation Rate

Three trials [43,44,46] contributed in the combined outcome of this variable. There was moderate heterogeneity [$\chi^2 = 4.42$, df = 2 ($P < 0.11$); $I^2 = 55\%$] among these trials but statistically it was not significant. Therefore, in the fixed effects model (OR, 0.84; 95% CI, 0.46–1.53; z = 0.57; $P < 0.57$; Fig. 5), the risk of reoperation following ROLL is lower as compared to WGL but statistically it is not significant.

Localization Duration

Three trials [43,44,46] contributed in the combined calculation of this variable. There was no heterogeneity [$\chi^2 = 0.48$, df = 2 ($P < 0.79$); $I^2 = 0\%$] among these trials. Therefore, in the fixed effects model (MD, −6.09; 95% CI, −6.81, −5.37; z = 16.58; $P < 0.00001$; Fig. 6), time consumed to perform ROLL is shorter than WGL.

Surgery Duration

There was moderate heterogeneity [$\chi^2 = 6.03$, df = 2 ($P < 0.11$); $I^2 = 50\%$] among these trials but it was not statistically significant. Therefore, in the random effects model (MD, −5.33; 95% CI, −7.54, −3.13; z = 4.74; $P < 0.00001$; Fig. 7), surgical excision following ROLL can be performed in a shorter duration as compared to surgery following WGL.

TABLE IV. Methodological Qualities of Included Studies Adapted From the Scottish Intercollegiate Guidelines Network [41] and Rangel et al. [42]

Quality variables	Mariscal Martínez and Solà [43]	Medina-Franco et al. [44]	Moreno et al. [45]	Rampaul et al. [46]
Inclusion criteria	1	1	1	1
Exclusion criteria	1	1	1	1
Demographics comparable?	1	1	1	0
Can the number of participating centers be determined	1	1	1	1
Can the number of surgeons who participated be determined	1	1	1	1
Can the reader determine where the authors are on the learning curve for the reported procedure	1	1	1	0
Are diagnostic criteria clearly stated for clinical outcomes if required	1	1	1	1
Is the surgical technique adequately described	1	1	0	1
Is there any way that they have tried to standardize the operative technique	1	1	0	1
Is there any way that they have tried to standardize perioperative care	1	0	0	1
Is the age mean and range given for patients in both groups	0	1	1	0
Do authors address whether there is any missing data	0	0	0	1
Were patients in each group treated along similar timelines	1	1	1	1
Did all the patients asked to enter the study take part	1	0	0	0
Dropout rates stated	0	0	0	0
Outcomes clearly defined?	1	1	1	1
Blind assessors	0	0	0	0
Standardized assessment tools?	1	1	1	1
Analysis by intention to treat	0	0	0	0
Score	14/19	13/19	11/19	12/19

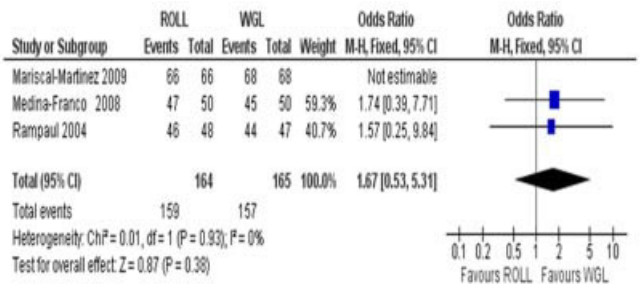

Fig. 2. Accurate localization rate.

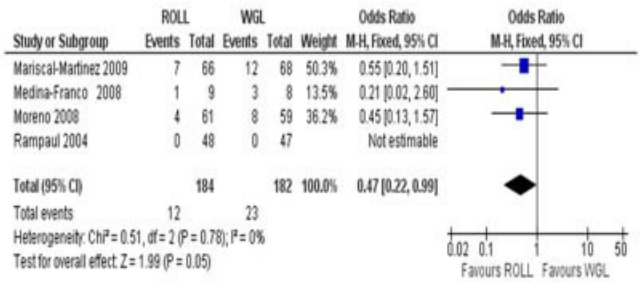

Fig. 4. Tumor positive margins.

Volume of the Excised Breast Tissue

Two trials [43,45] contributed in the calculation of this variable. There was significant heterogeneity [$\tau^2 = 10247.57$, $\chi^2 = 73.15$, df = 1 ($P < 0.00001$); $I^2 = 99\%$] between trials. Therefore, in the random effects model (MD, −69.69; 95% CI, −210.91, 71.62; z = 0.97; $P < 0.33$; Fig. 8), the excised volume of breast tissue following ROLL and WGL is statistically comparable.

Weight of the Excised Breast Tissue

Two trials [43,46] contributed in the calculation of this variable. There was no heterogeneity [$\chi^2 = 0.08$, df = 1 ($P < 0.77$); $I^2 = 0\%$] between trials. Therefore, in the random effects model (MD, 2.74; 95% CI, −2.09, 7.57; z = 1.11; $P < 0.27$; Fig. 9), the weight of the excised breast tissue following ROLL and WGL is again statistically comparable.

Other Variables

There were insufficient reported data on pathological concentricity, surgical concentricity, cost analysis, cosmetic scores, pain scores, and length of stay in hospital to allow for combined analysis of these variables.

DISCUSSION

The diagnosis of breast cancer has undergone revolutionary changes since the introduction of routine screening programs; this has directly resulted in a substantial increase in the number of diagnosed breast cancers which are clinically non-palpable. For example the incidence of ductal carcinoma in situ has increased 7.2-fold (95% CI 608–7.7) from 1980 to 2001 [44–47]. Several localization techniques [6–23] have demonstrated variable success rate but the use of WGL and ROLL is discussed more comprehensively than any other intervention. Technically high success rates can be achieved with the use of both ROLL and WGL as concluded by this review and reported by many previous studies [31–33,41,46,48–51]. Various comparative ROLL studies have indicated an operator preference towards ROLL with respect to both operating surgeon and interventional breast radiologist [31]. In addition, patients report feeling less subjective discomfort with ROLL as compared to WGL [31].

Localization times using the ROLL technique are significantly shorter; which may be considered an objective indication towards ease of the procedure. The same can be applied to the surgical resection of impalpable breast lesions following localization by ROLL. The outcome of this review is analogous to those from most other publications [31–33,43–46,52] on ROLL. We conclude that ROLL is comparable to WGL in terms of the excised volume and weight of removed breast tissue post-wide local excision. A result that concurs with other publications [43,44,46] but contrasts with a few retrospective studies [52,53]. Several published articles on ROLL have reported good resection margin clearance and thus a reduced degree of positive resection margins, with ranges from 75% to 100% [31,32,48,50,51,54]. Our results indicate that ROLL and WGL are at least comparable in terms of subsequent positive resection margins after wide local excision in breast conserving surgery. Although we did not include sentinel node localization in this review, this is yet another advantage of the ROLL technique. Radiotracer follows the route of draining lymphatic channels and accumulates in the sentinel lymph node allowing for simultaneous localization. The application of radiotracers in sentinel lymph node and impalpable lesion localization has certainly revolutionized the original two step procedure into one with very promising outcomes [49–52,55].

ROLL has several advantages but it cannot entirely replace WGL for large breast lesions. Problems have been reported with ROLL when used for stereotactic-guided procedures, errors in depth (z-axis) secondary to compressed breast tissue have resulted in inaccurate injection of the radiotracer [52]. This can cause potential problems in patients with small breast cup sizes as the release of pressure

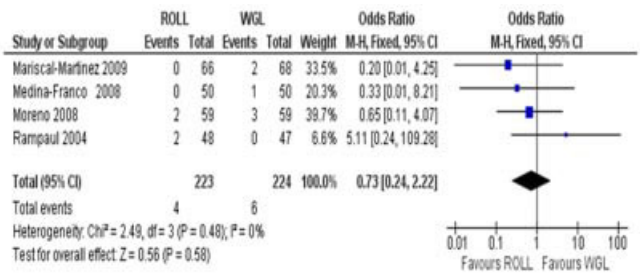

Fig. 3. Peri-procedural complications.

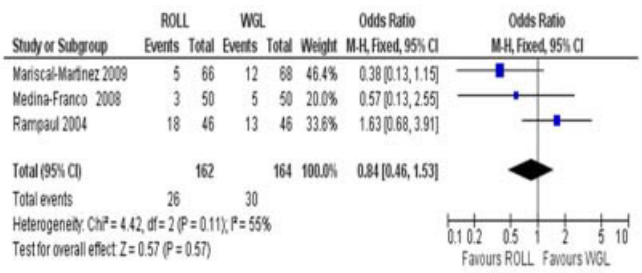

Fig. 5. Reoperation rate.

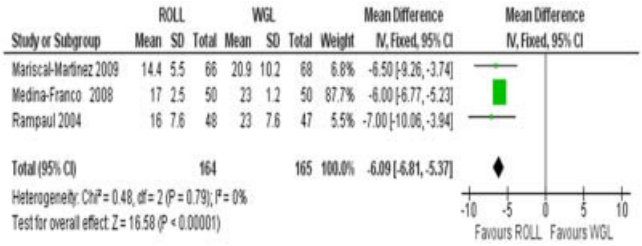

Fig. 6. Localization time.

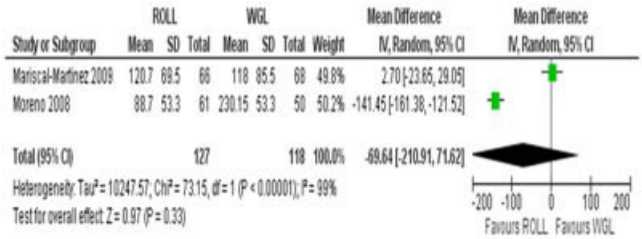

Fig. 8. Volume of excised tissue.

following stereotaxis has resulted in leakage of the radiotracer into neighboring breast quadrants [56]. Other disadvantages of ROLL include the short half-life of the radiotracer requiring surgical intervention to be performed within 4 hr of radiotracer injection, lest the radiotracer count is not strong enough to accurately guide gamma-probe localization. The radiotracer is not visible on mammograms; localization under stereotactic guidance is therefore difficult to perform and it becomes more difficult to accurately assess the boundaries of the lesion. In cases of extensive microcalcifications in the breast, the placement of several wires (brackets) may be the preferable localization technique.

Based on this systematic review of the published randomized controlled trials, ROLL is comparable to WGL in terms of localization rate, complication rate, reoperation rate, volume and weight of the excised breast lesion. However, ROLL is associated with lower risk of positive margins, shorter localization time, and shorter surgical excision time. ROLL may be considered a preferable technique for the localization of non-palpable breast cancers. These conclusions should be considered cautiously. Firstly, due to the low number of studies on this subject studying fewer patients. Secondly, there was significant clinical and methodological diversity among reported trials. Thirdly, one of the included trials [44] recruited 100 patients of occult breast lesions for ROLL versus WGL evaluation but histopathology of the excised specimens showed only 10% subjects had malignancy. Fourthly, it was not clearly reported weather same individuals (operating surgeon or radiologist) performed both the ROLL and WGL and what was their level of experience? Fifthly, routine preoperative lymphoscintigraphy was either not performed or inadequately reported. Sixthly, there was no reporting on the localization of the lesion in relevance to breast size and whether it was controlled in the sample size? Lastly, the quality of included trials is poor due to a lack of proper randomization techniques, blinding, power calculations, and intention-to-treat analysis. Therefore, authors recommend that a high quality major multicenter randomized controlled should be started in order to strengthen the existing evidence and validate these findings.

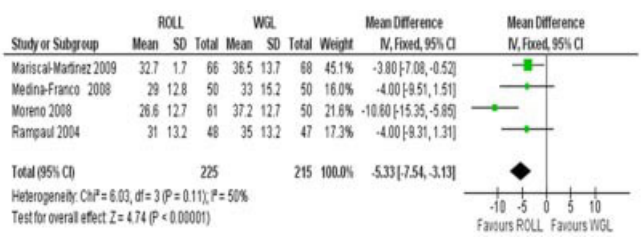

Fig. 7. Surgery time.

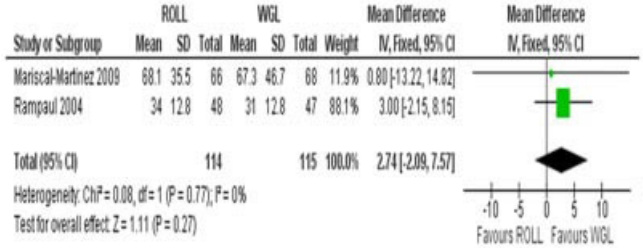

Fig. 9. Weight of the excised breast tissue.

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