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ORIGINAL ARTICLE

Radioactive seed localization and wire guided localization in breast cancer: A systematic review and meta-analysis

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Summary

Purpose: *Classically, wire-guided localization (WGL) is used for the localization of non palpable breast lesions. On the other hand, many studies report a newer technique called radioactive seed localization (RSL). The purpose of our study was a systematic review and meta analysis of the two techniques regarding the rate of positive margins and the quantity of excised tissue.*

Methods: *Our study searched publications up to March 24th 2018 in Medline, Embase and Cochrane Library regarding studies comparing the two techniques of localization of subclinical lesions with WGL or RSL using technetium 99m as radioactive agent. The primary target was the rate of positive margins and the second was the rate of second surgery for reexcision. Revman5.3 and STATE12.0 were used for the statistics.*

Results: *Five randomized controlled trials (RCTs) and 13 cohort studies comprising 3879 breast cancer patients were included. RSL was significantly superior than WGL both in better margin status(RR=0.72, 95% CI 0.56-0.92, p=0.01) and reduced reoperation rate (RR=0.68, 95% CI 0.52-0.88, p=0.004). Subgroup analysis of RCTs showed no different ability of both techniques in terms of free margin status (RR=0.85, 95% CI 0.55-1.31, p=0.46) and reoperation rate (RR=0.80, 95% CI 0.48-1.32, p=0.38). Further subgroup analysis excluding three studies with different ductal carcinoma in situ (DCIS) proportion exhibited same efficacy in margin negativity (RR=0.83, 95% CI 0.69-1.01, p=0.07) and further operation rate (RR=0.85, 95% CI 0.71-1.01, p=0.07).*

Conclusion: *In this study, we found that RSL is more efficient than RSL in keeping margin negativity and reducing reoperation rate.*

Key words: *breast neoplasms, breast conserving surgery, meta-analysis, radioactive seed localization, wire guided localization*

Introduction

The number of newly diagnosed breast cancers has been increasing in the last decades due to the promotion of breast cancer screening around the world and improved imaging technology [1]. Especially in developed countries, nearly one third of newly-diagnosed breast cancers are small, non-palpable (less than 1.5cm) and many of them are suitable for breast conserving therapy [2]. Therefore, the surgical treatment to these tiny malignant carcinomas is firstly to remove enough tumor to achieve an appropriate margin; secondly, to cut as few as we could to ensure cosmetic outcome. Wire guided localization (WGL;Photo 1) was introduced by Dodd et al. for intraoperative breast lesion localization in 1965 [3]. With its assist the surgeon can make an outline about location and size of a tumor

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during breast conserving operation. Nonetheless, it shows several drawbacks. For instance, needle displacement, inflexible scheduling, migration, diathermy burns conducted to the skin and injury by wire-tip [3-5]. Discordance between the localization pathway and incision route may lead to compromised cosmetic result. Moreover, the variable rate of positive margins range from 2.8 to 53% with WGL technique and this creates some concern to the surgeons [6,7]. An alternative technique is the radioactive seed localization (RSL;Photo 2) which was proposed by Gray et al. in 2001 [4]. The long half-life of RSL (59.6 days), this technique allows the possibility to insert the radioactive agent many days before the surgery and also in case of neoadjuvant chemotherapy [8]. A few studies showed that RSL was more efficient that WGL regarding the positive margins, the reoperation rate, the excised volume and the cosmetic result assessed by the patients. On the contrary, other studies were controversial. For this reason a synthetic analysis of the literature was performed in this paper.

Methods

Search strategy

Electronic search in Medline, Embase and Cochrane library database for potential relevant studies was performed. Search strategies for each database are listed in Appendix 1. Titles and abstracts of all papers were read in the first turn selection. Irrelevant studies, duplicated studies, review and meta-analyses were excluded. The remaining articles were examined in full-text for the second turnselection. Only randomized controlled trials or cohort studies making comparison of radioactive seed and wire guided localization were included in our systematic review and meta-analysis. The last date of the search was March 14th, 2018.

Inclusion criteria

Two reviewers (G.-L. Wang and H.-Q. Zuo) independently reviewed all the papers. Research papers with the following criteria were enrolled in our study: (i) articles written in English; (ii) assessment of efficacy of RSL and WGL containing at least the primary outcome (see below); and (iii) either RCTs or cohort studies.

The primary target for our research was the positive margin rates. The secondary target were the reoperation rates. Other parameters included the proportion of ductal carcinoma *in situ* (DCIS), size of tumor in each study and extra economic and radioactive cost.

Statistics

The relative risk (RR) was utilized to clarify, which localization method was preferable in each study. Revman 5.3 and STATA 12.0 were applied for summary statistic for efficacy of RSL vs WGL. Forest plots were created during the clarification.

x^2 and I^2 statistics were used for examination of heterogeneity between studies. A two-tailed p value of less than 0.5 was considered as statistically significant. Results were reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.

Results

Characteristics

Initially, 463 papers were picked out from Embase, 352 from Pubmed, and 224 from Cochrane Library Database. After a series of exclusion and inclusion, 18 articles including 5 RCTs and 13 cohort studies were enrolled in our final analysis [4-7, 9-22] (Figure 1). We checked the reference list of each paper and no further study was identified. These 18 trials included a total of 4664 patients. For cohort studies, Gray et al. [5] enrolled 200 patients in total with 162 breast cancer patients and Milligan et al. [14] included 200 invasive breast cancer patients. These two cohort studies were contained in the studies Hughes et al. [10] and Pieri et al. [17] respectively. While Milligan et al. found no difference between RSL and WGL, Pieri et al. concluded that RSL was better. One study described by Parvez et al. [16] was a subanalysis of the RCT reported by Lovrics et al. [12] comparing the cosmetic

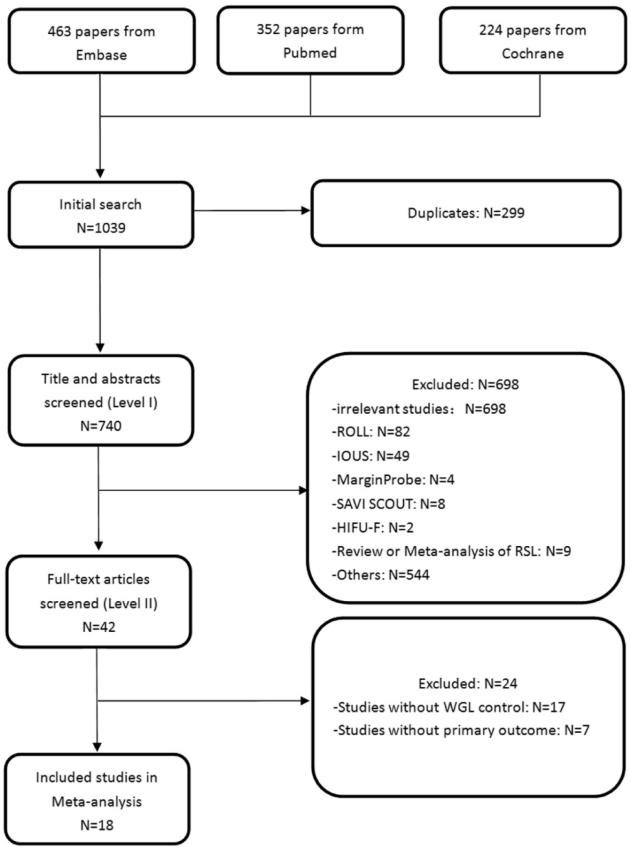

Figure 1. Flow chart.

Table 1. Characteristics of included studies

First author [REF]	*Country*	*Study period*	*Purpose of localization**	*Design*	*Patients*		*Definition of positive margin*
					RSL	*WGL*	
Bloomquist [9]	USA	2011-2014	1	RCT	72	59	ink on tumor
Gray [4]	USA	November 1999 -February 2001	1 or 2	RCT	51 (35)†	46 (26)	>1mm
Gray [5]	USA	NG	1 or 2	cohort study	100 (83)	100 (79)	≥2 mm
Hughes [10]	USA	NG	1 or 2	cohort study	383 (306)	99 (79)	≥2 mm
Langhans [11]	Denmark	January 2014 - February 2016	1	RCT	195	195	ink on tumor for invasive lesions
Lovrics [12]	Canada	June 2004- January 2010	1	RCT	152	153	ink on tumor (stratified by positive margin, i.e. tumor on the ink, close margin, i.e. malignant lesion within 1 mm, negative margin, i.e. no ink on the margin)
Luiten [13]	Netherlands	March 2006 - June 2013	1	cohort study	91	78	Focally involved margins: tumors extending to the inked resection margin over a distance of 4mm or less. Extensively involved margins: tumor involvement of the inked margins extends beyond 4 mm.
Milligan [14]	UK	NG	1	cohort study	100	100	more than 1mm radial margin for invasive carcinoma and 2mm for pre-invasive carcinoma
Murphy [15]	USA	RSL: January 2012-June 2012 WGL: July 2011 -December 2011	1	cohort study	431	256	ink on the margin
Parvez [16]	Canada	June 2007 -January 2010	1	RCT	35	38	malignant lesion over 1mm
Pieri [17]	UK	RSL: September 2014-May 2016 WGL: January 2014-September 2014	1	cohort study	233	100	within 1 mm of an inked radial margin
Rao [18]	USA	2005 -2010	1 or 2	cohort study	50 (33)	33	ink on the margin
Sharek [19]	USA	April 2011- March 2012	1	cohort study	114	118	ink on the margin
Silva [7]	USA	January 2004 -September 2014	1	cohort study	98	74	<2mm as close margin and as an indicator for reoperation
Stelle [20]	USA	November 2013 – November 2015	1 or 2	cohort study	187 (94)	109 (60)	>2 mm for DCIS, ink on tumor for invasive lesions
Theunissen [21]	Netherlands	January 2011 - December 2013	1	cohort study	69	76	ink on tumor
Tran [6]	Canada	December 2012 - March 2015	1 or 2	cohort study	247 (161)	244 (141)	ink on tumor (stratified by positive margin, i.e. tumor on the ink, close margin, i.e. malignant lesion within 1 mm, negative margin, i.e. no ink on the margin)
Zhang [22]	Canada	RSL: April 2015 - March 2016 WGL: April 2014 - March 2015	1	cohort study	194	153	presence of tumor on ink for invasive carcinoma and >2 mm for DCIS

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Researched outcomes	*Significant findings in researched outcomes*	*NOS*
positive margin rate, volume of the main specimen, volume of the first surgery, pain and convenience during localization	less severe pain and higher convenience in RSL group	
positive margin rate, mean times for operative excision, subjective ease of the procedures as rated by surgeons, radiologists and patients	better margin status in favor of RSL	
positive margin rate, reoperation rate, sentinel lymph node (SLN) identification rate	better margin status and lower reoperation rate in favor of RSL	8
positive margin rate, reoperation rate, pain and convenience rated by patients	better margin status, lower reoperation rate and higher convenience in favor of RSL	7
positive margin rate, duration of the surgery, weight of surgical specimen and pain rated by patients	no significant findings	
positive margin rate, reoperation rate, mean operative duration, specimen volume, ease of the procedures as rated by surgeons, radiologists and pain rated by patients	shorter operative time and easier of procedure rated by surgeon in RSL group	
positive margin rate, reoperation rate	reduced risk of extensively involved resection margins in RSL group	8
positive margin rate, reoperation rate and mean total excision weight of specimen	lower mean total specimen excision weight in RSL group	9
positive margin rate, reoperation rate, median operative time and volume of excision specimen	no significant findings	8
positive margin rate, reoperation rate and cosmetic outcomes rated by patient and panel	no significant findings	
positive margin rate, mean specimen weights	better margin status and lower median specimen weights in favor of RSL	8
positive margin rate, reoperation rate	no significant findings	8
positive margin rate, reoperation rate, ratio of the tumor volume to initial surgical specimen volume, ratio of the tumor volume to total volume resected and cosmesis scores	no significant findings	9
positive margin rate, reoperation rate, Initial and total specimen volumes	better margin status, lower reoperation rate and higher convenience in favor of RSL	8
positive margin rate, mean specimen size and mean operating room time	longer operative times with RSL	7
positive margin rate, reoperation rate and mean resection volumes	better margin status, lower reoperation rate and higher convenience in favor of RSL	7
positive margin rate, reoperation rate, specimen mean weight, largest diameter, and volume excised.	no significant findings	8
positive margin rate, reoperation rate, surgical time, specimen volume and average cost	lower average cost using RSL	9

Abbreviation: RSL: radioactive seed localization, WGL: wire guided localization, RCT: randomized controlled trial, NOS: Newcastle-Ottawa Scale
*1: therapeutic resection, 2: excision biopsy
† actual number of breast cancer patient was written in the bracket

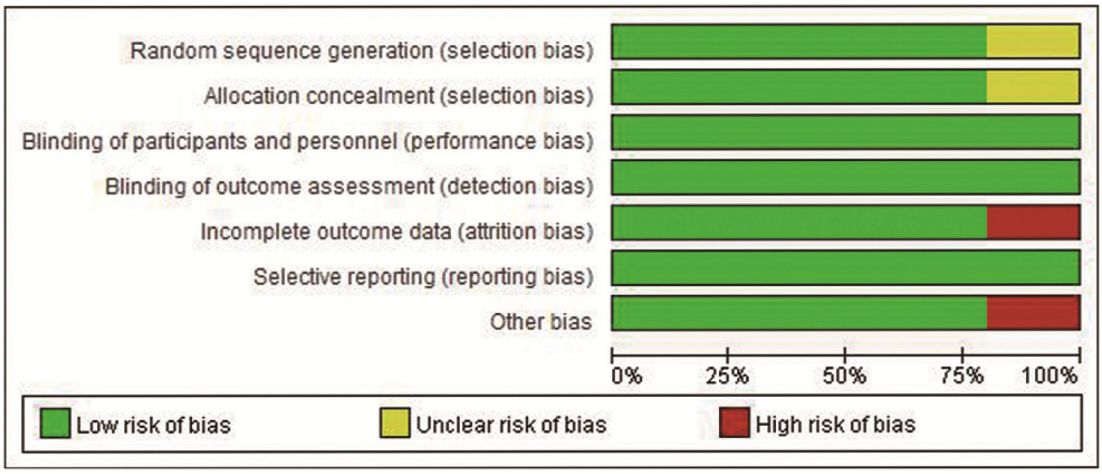

Figure 2. Risk of bias graph for randomized controlled studies.

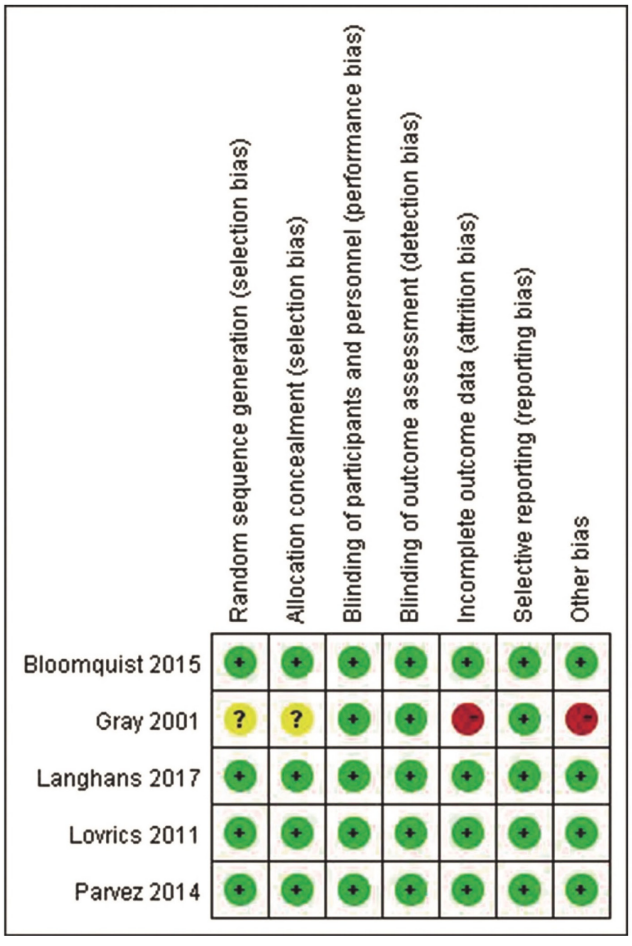

Figure 3. Risk of bias summary for randomized controlled studies.

outcome generated from RSL and WGL intervention. The experimental method of this subanalysis was randomized, centrally concealed. These 3 overlapped and smaller trials were not considered when comparing the efficacy of RSL and WGL unless they had unique information. After exclusion of benign lesions,the actual breast cancer patients were 3879. All the studies presented the positive margin rate, 13 studies reported the reoperation rate, some of them defined the excision volume (or weight), margin definition, operation duration and subjective assessment by surgeons and patients (Table 1). Risk of bias of RCTs enrolled was low in general (Figures 2 and 3).

Margin status

A total of 15 studies with available, non-overlapped margin status data were pooled for relative risk (RR) assessment [4,6-7,9-13,15,17-22]. Analysis of 15 trials were in favor of RSL in achieving better margin status (RR=0.72, 95% CI 0.55-0.92, Z=2.57, p=0.01) (Figure 4). According to analysis of the RCTs subgroup we found no preference of either modality (RR=0.85, 95% CI 0.55-1.31, Z=0.74, p=0.46) (Figure 4). Three studies had different proportion of DCIS, 2 of them were statistically significant [7,10,21] (Table 2). After exclusion of DCIS, we defined another subgroup (named adjusted subgroup) which revealed a same conclusion to the RCTs subgroup analysis (RR=0.83, 95% CI 0.69-1.01, Z=1.84, p=0.07) (Figure 5). Heterogeneity was significantly high in the entire study group (I^2=62%, p=0.001), it was insignificant and moderate in RCTs subgroup (I^2=45%, p=0.14) and fell to insignificant and mild in the adjusted subgroup (I^2=19%, p=0.26).Reporting bias was low for the whole group and subgroups (Figure 6).

The effect of reoperation rate

Eleven non-overlapped studies reported the reoperation rate [6,7,10,12-15,18,19,21,22]. RSL was more efficient than WGL in terms of lower reoperation rate (RR=0.68, 95% CI 0.52-0.88, Z=2.88, p=0.004) (Figure 7). No difference was found in the RCTs subgroup (RR=0.80, 95% CI 0.48-1.32,

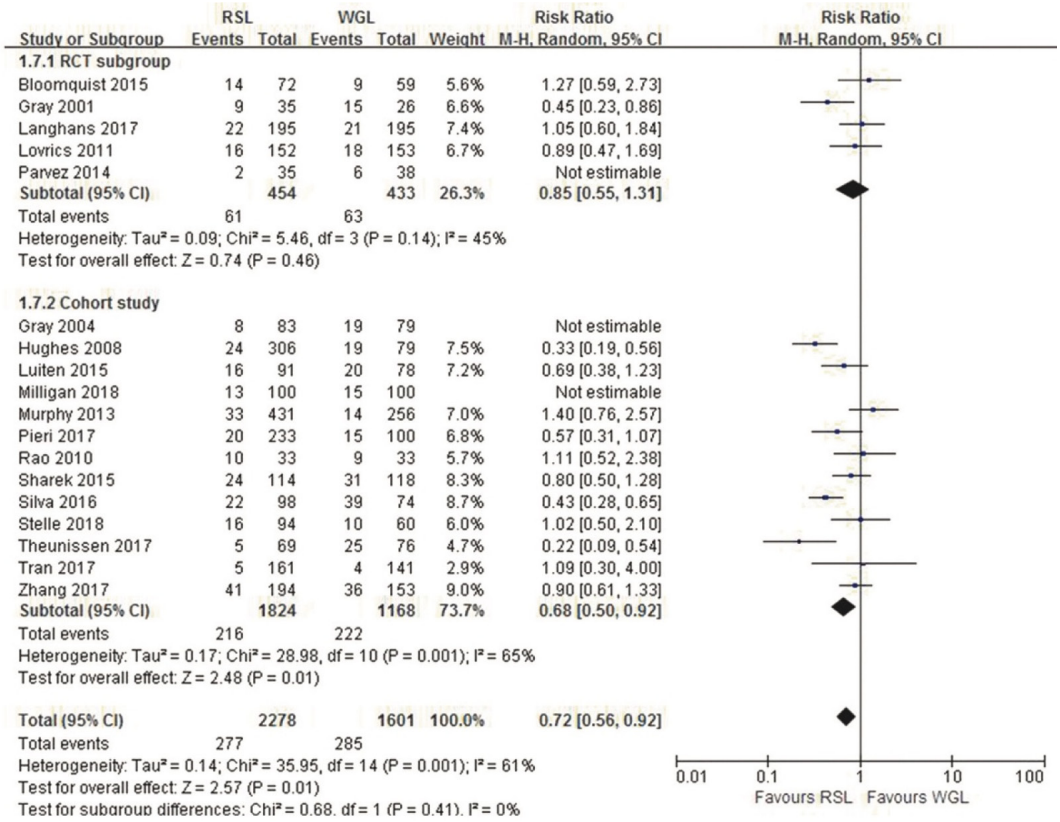

Figure 4. Combined relative risks (RRs) of positive margin status: RSL versus WGL. CI:confidence interval, RSL: radioactive seed localization, WGL: wire guided localization.

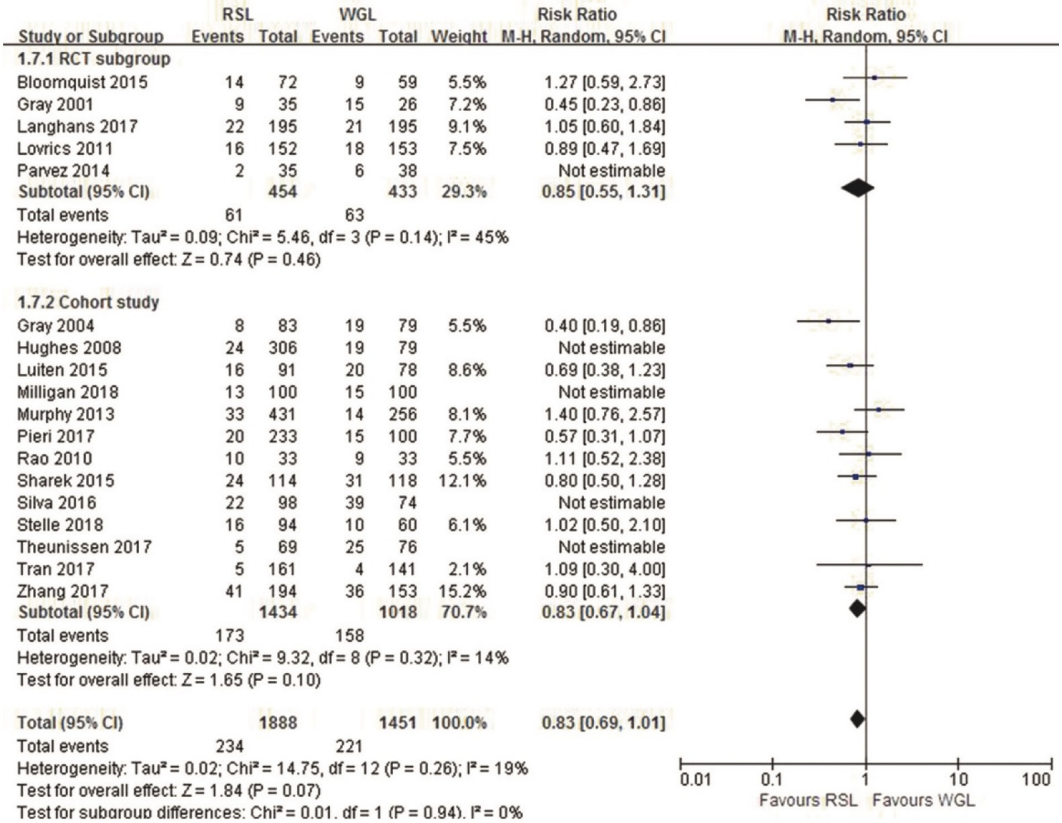

Figure 5. Combined relative risks (RRs) of positive margin status: RSL versus WGL (subgroup analysis of studies without significant different proportion of ductal carcinoma in situ). CI:confidence interval, RSL: radioactive seed localization, WGL: wire guided localization.

Table 2. Proportion of DCIS in each study

First author [Ref]	*Year*	*Number of DCIS*		*p*
		RSL group	*WGL group*	
Bloomquist [9]	2015	24	16	0.44224
Gray [4]	2001	4	5	0.39548
Gray [5]	2004	16	9	0.21291
Hughes [10]	2008	77	9	0.00880
Langhans [11]	2017	0	0	
Lovrics [12]	2011	29	22	0.27143
Luiten [13]	2015	91	78	
Milligan [14]	2018	0	0	
Murphy [15]	2013	103	58	0.71028
Parvez [16]	2014	7	3	0.13290
Pieri [17]	2017	0	0	
Rao [18]	2010	12	12	
Sharek [19]	2015	22	23	0.97031
Silva [7]	2016	32	35	0.05118
Stelle [20]	2018	15	16	0.10603
Theunissen [21]	2017	12	40	<0.00001
Tran [6]	2017	34	27	0.67068
Zhang [22]	2017	35	30	0.71037

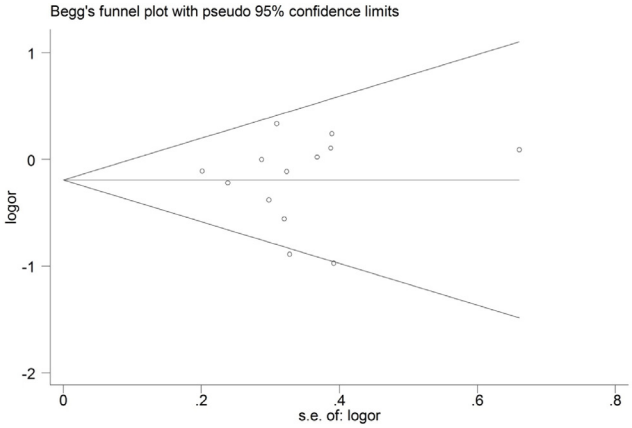

Figure 6. Begg's test of positive margin status. RCT: randomized controlled trial.

Z=0.88, p=0.38) (Figure 7) and the adjusted subgroup (RR=0.85, 95% CI 0.71-1.01, Z=1.81, p=0.07) (Figure 8). There was statistically significant heterogeneity (p=0.01, I^2=57%) amongst these 11 trials. No heterogeneity was found in the adjusted subgroup (I^2=0%, p=0.51). Reporting bias was low for the whole group and subgroups (Figure 9).

Discussion

In the last 18 years, a series of studies have been carried out to verify which of the 2 methods (RSL and WGL) is more efficient in gaining negative margin, low rate of reoperation and so on. As we can see, RSL has drawn much attention with the passing of time, and especially in the recent few years. We registered all the available RCTs or cohort studies comparing RSL with WGL from 2001 to 2017 (since the first comparison made by Gray et al. in 2001) in our meta-analysis and observed that 7 studies were published after 2016, which makes a thorough analysis necessary.

Positive margin rate

After quantitative synthesis of all 15 trials (irrespective of three smaller overlapped trials), we revealed the superiority of RSL over WGL in achieving better margin status. In the studies examined there was a high and significant heterogeneity (p=0.001). We noticed a different distribution of DCIS in some studies. The presence of DCIS was an independent factor of involved margin status [23]. It is hard to intraoperatively clarify the range and margin of DCIS regardless of localization techniques. Inconsistent allocation of DCIS in different study groups could make the interpretation of results more complicated and a major source of heterogeneity in our synthesis analysis. Hence, we calculated the proportion of DCIS in each study using x^2 test (Table 2). We extracted studies with obvious different proportion of DCIS in case of DCIS interference like Hughes et al.; p<0.01, Theunissen

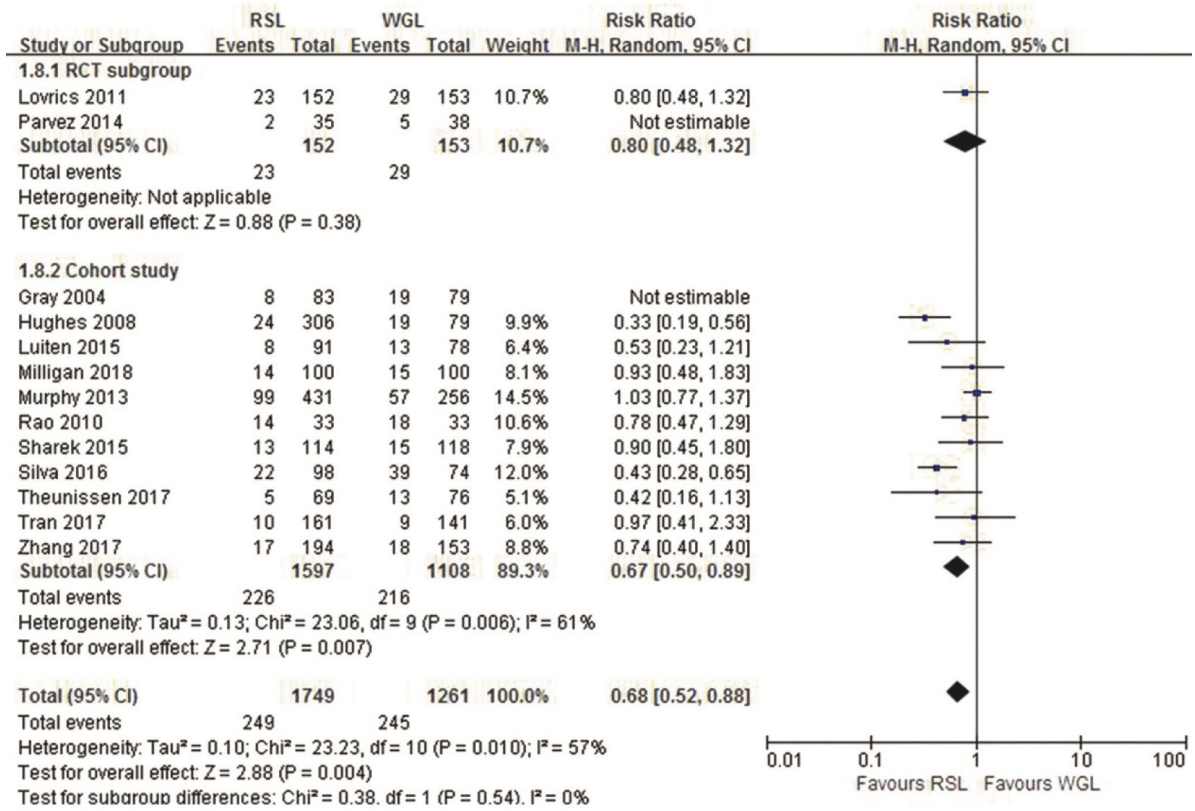

Figure 7. Combined relative risks (RRs) of re-operation rate: RSL versus WGL. CI:confidence interval, RSL: radioactive seed localization, WGL: wire guided localization.

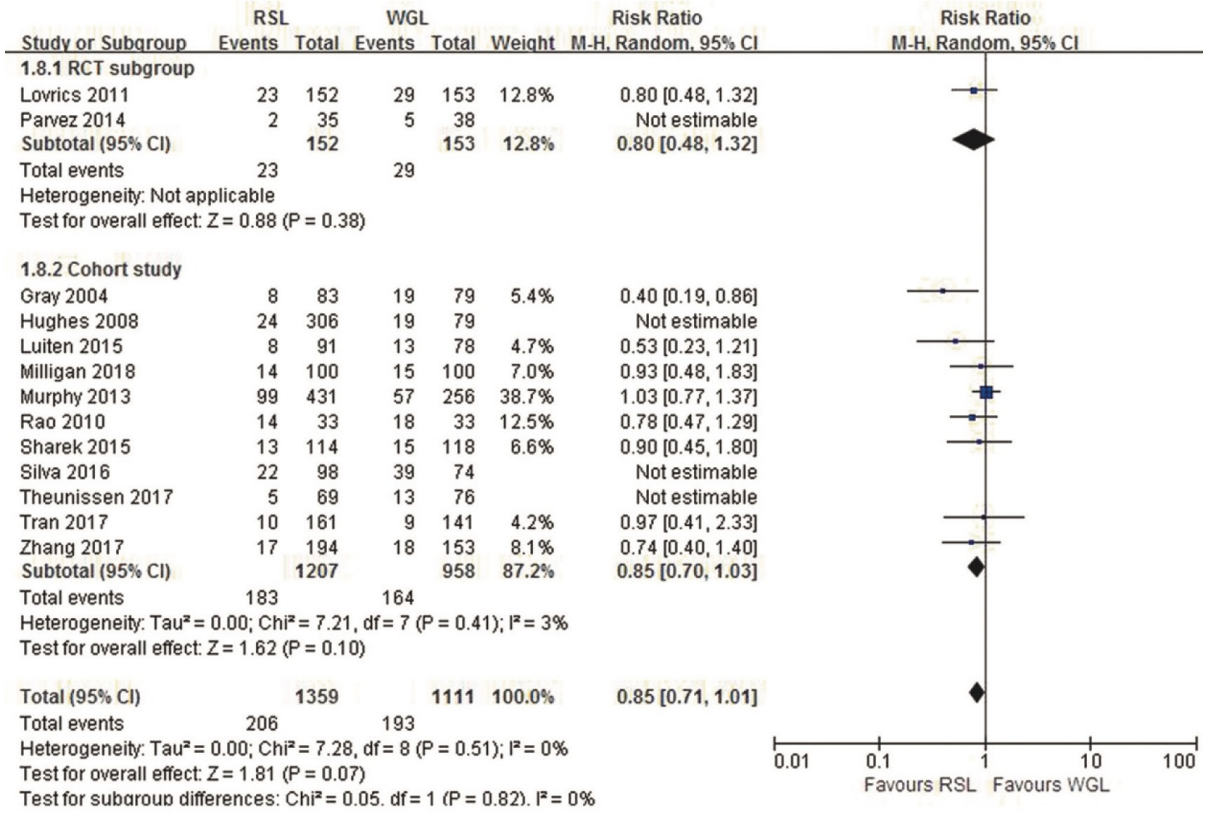

Figure 8. Combined relative risks (RRs) of re-operation rate: RSL versus WGL (subgroup analysis of studies without significant different proportion of ductal carcinoma in situ). RSL: radioactive seed localization, WGL: wire guided localization, CI=confidence interval.

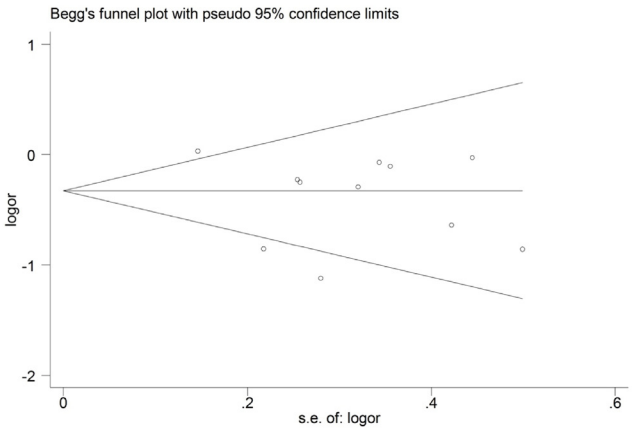

Figure 9. Begg's test of re-operation rate. RCT: randomized controlled trial.

et al.; p<0.00001 and Silva et al.; p=0.051 [7,10,21]. Hughes et al. compared the efficiency of both localization techniques partially in excisional biopsy. The RSL group contained more DCIS tumors than WGL group (31 vs 11%). Twenty-one percent and 25% of tumors were preoperatively benign in the RSL intervention group and WGL group respectively. Hughes et al. collected data from three Mayo Clinic centers. While participants receiving RSL were from three different centers, patients treated with WGL originated from only one center. Intraoperative procedure for each center was inconsistent. At Mayo Clinic Arizona, where data of WGL accumulated, frozen section was selectively performed, meanwhile comprehensive frozen section analysis was performed for all excisional tissue at Rochester center and not carried out in Florida center. Silva et al. searched the bracketed seed localization and bracketed wire localization instead of single localization during excision of radiographically extensive breast lesions which was different from the rest of literature. Thirty-eight percent of lesions were multifocal in breast RSL and 45% in breast WGL respectively. And there were significantly more multicentric lesions in breast WGL group (p<0.05). Silva et al. defined close margin as malignant lesion within 2 mm and as an indication for re-operation. Besides, Luiten et al. [13] reported the only study comparing the efficacy of both modalities in pure DCIS patients. The structure of disease was quite different from the rest of researches. Although in Luiten' s work we observed no significant difference between these two modalities in terms of focally involved margins which were defined by tumors extending to the inked resection margin for 4 mm or less, we noticed a significant lower risk of extensively involved margins characterized as more than 4 mm involved margins in the RSL subgroup. The results of the remaining 13 studies (Gray et al. 2004 was included again due to exclusion of Hughes et al.) showed no superiority for RSL anymore, while heterogeneity decreased to mild and insignificant (p=0.26).

RCTs subgroup analysis revealed similar quality of both modalities in terms of margin negativity. The heterogeneity of RCTs subgroup derived from Gray et al. in 2001, in which the patients were randomized in RSL and WGL groups according to imaging discovered lesions instead of pathologically confirmed malignant tumor. These authors reported 31% of benign tumor in RSL and 43% in WGL respectively, thereby implementing the localization techniques for excision biopsy instead of therapeutic excision, while their patient group was smallest among all the trials in our analysis. The extraction of Gray et al. study resulted in decrease of the data heterogeneity (x^2=0.49, I^2=0%). Another study proved that DCIS can lead to worse margin status using WGL , pointing out the impact of the proportion of DCIS in the lesion [24]. In a retrospective study including 725 DCIS patients and 3393 invasive breast cancer (IBC) patients the authors assessed the efficiency of WGL in both DCIS and IBC subgroup and they found a worse margin status (unadjusted odds ratio, 2.21; 95%CI, 1.42-3.43; p<0.001) and increased reoperation rate (adjusted odds ratio, 3.82; 95% CI, 3.19-4.58; p<0.001) in patients in the DCIS subgroup. A worth thinking question is whether it is the localization techniques that achieve a better margin status or the global management of the patient including the therapeutic procedures. To localize in a bracketing way may result in improved clinical outcome. Breast cancer lesions, especially diffuse lesions such as DCIS, could not be completely removed with a point placed in the center of the lesion and by far most of the studies focused on single localization. The accomplishment of a successful breast conserving operation needs experienced surgeons, precise localization, appropriate intraoperative detection mechanism (such as intraoperative ultrasound/IOUS), accurate intraoperative frozen section, good collaboration with other departments, deep understanding of each case, such as grade of calcification, and magnetic resonance imaging when necessary to discover potential multicentric or multifocal lesions. All these factors could make an influence on margin status. But by far, all the presented studies failed to either report or eliminate these elements.

Reoperation rate

We observed a superiority of RSL with decreased rate of reoperation. Heterogeneity was

significant and high in the total of pooled studies RCTs(p=0.01, I^2=57%) and cohort studies subgroup (p=0.006, I^2=61%). But when we ignored the three studies with significantly different proportion of DCIS (i.e. Hughes et al, Theunissen et al and Silva et al), heterogeneity became insignificant and low in the remainingRCTs (p=0.51, I^2=0%) and cohort studies subgroup (p=0.41, I^2=3%) and the preference for RSL disappeared. This identical trend could be explained in the same way as what happened in margin status. Reoperation derived from a bad surgical outcome, deficient radiation therapy and different frozen section techniques.

To our knowledge, our meta-analysis contains by far the largest patient population and numbers of trials comparing these two modalities. The latest similar meta-analysis was from the Cochrane Collaboration, concluding no superiority of either techniques [25], but there were only two studies with 366 participants [4,12]. We also recommended further larger RCTs for more accurate evaluation of the efficiency. The largest study enrolled 3168 patients which was nearly compatible to our patients' pool [26], but it contained too much non-controlled trials, and the goal of this study was not to evaluate the superiority of different techniques in achieving better margin status but to judge the rationality of the no radicality of resection margins in each case. Twelve trials enrolled in our research were conducted after that systematic review. Since the first comparison made in 2001, a series of trials were carried out to test the efficiency of RSL. However, no consensus was reached to conclude a better efficacy. Moreover, another important point to assess the efficacy of the techniques is the definition of the free margins. Actually, many changes have occurred in the last decades. At present, the definition is "no ink on the margin" for IBC and negative margin >2 mm for DCIS. Only 2 RCTs and 7 controlled trials included in our analysis met this standard regarding the margins [27,28]. Thus, an integrated analysis becomes difficult due to inconsistent criteria. As far as we know, the radiation issue is still an obstacle for the practical use of RSL in many countries, for example in China. Due to the characteristic of localization techniques, researchers could not achieve blinding of either participants or personnel.

In the 3 studies with significant discordance of DCIS, we found the DCIS rates for RSL group and WGL group in Hughes et al., Theunissen et al. and Silva et al. studies were 31 versus 11%, 17 versus 53% and 33 versus 47%, respectively. RR for positive margin rate was 0.34 (95% CI 0.24-0.47, p<0.01), and 0.39 for reoperation rate (95% CI 0.28-0.53, p<0.01).

Localization techniques alone could not obviously decrease either the positive margin rate or the reoperation rate, and they were not initially recommended to achieve it. When wire was first introduced by Dodd et al. in 1965, it was set for precise localization and excisional biopsy. This function faded away after the wide use of core-needle biopsy. Besides, Fung et al. conducted a 5-year follow-up of the RCT by Lovrics et al., and they found no significant difference of breast cancer recurrence between these two groups [29]. When weighing and judging a use of localization method, maybe we should not be restricted on margin status and reoperation rate. Different kinds of localization tools could be utilized in different treatment plans. As discussed before, RSL offers many advantages in contrast to WGL: it can be used in cases when long-time localization is necessary, for example for patients prepared for neoadjuvant chemotherapy. As discussed before RSL presents many advantages in contrast with WGL: the procedure is less painful and because the particles remain long time *in situ* and are detectable many days after the injection, it allows a delay for the surgery if it is necessary . On the contrary, WGL should proceed a few minutes before surgery to avoid moving of the hook and wrong surgical excision.

RSL could also be performed in large breast tumors or in metastatic axillary lymph nodes. Sentinel lymph node biopsy in patients after neoadjuvant chemotherapy was biased because of axillary fibrosis and obstruction of lymphatic vessels and its false negative rate increased to 20% [30,31]. Donker et al. [8] studied 100 patients with proved lymph nodes metastasis who underwent seed localization of metastatic lymph nodes before neoadjuvant chemotherapy. Ninety-five patients underwent axillary lymph node dissection for further analysis and the authors found the response of localized lymph nodes reflected the response of the remained lymph nodes, thus making an axillary conserving operation possible (identification rate: 97%, false negative rate: 7%). Furthermore, Caudle et al. [31] selectively excised axillary lymph nodes using combination of sentinel lymph node biopsy and radioactive seed following neoadjuvant chemotherapy and they reported a false negative rate of 2 %. Meanwhile, radio-guide occult lesion localization (ROLL) uses the same isotope which is used in sentinel lymph node biopsy (SNOLL) [32].

Conclusion

In our meta-analysis, RSL was superior over WGL to gain negative margin as well as to reduce reoperation rate. Finally the use of RSL could not

obtain significantly better clinical outcomes in all cases. However, it is still recommended for practical use because of its more comprehensive and flexible application before and after neoadjuvant chemotherapy.

Authors' contributions

Dr. Gui-lin Wang contributed to study design, data collection, statistical analysis, data interpretation, manuscript preparation and literature search. Drs. Panagiotis Tsikouras, Anastasia Bothou and Stefanos Zervoudis corrected the paper. Dr. Huaiquan Zuo contributed to data collection, statistical analysis and data interpretation. Dr. Ming-quan Huang contributed to statistical analysis, data interpretation and literature search. Dr. Lin Peng contributed to statistical analysis and literature search. Dr. Alexander Tobias Teichmann has the supervision of the study.

Conflict of interests

The authors declare no conflict of interests.

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Appendix 1

Search strategy

Pubmed

(randomised controlled trial*) OR randomized controlled trial*) OR controlled clinical trial*) OR random allocation) OR double-blind method) OR single-blind method) OR clinical trial*) OR randomised) OR randomized) OR placebo) OR randomly) OR crossover) OR cross-over) AND (lesion*) OR cancer*) OR neoplasm*) OR carcinoma*) AND breast) AND (nonpalpable) OR non-palpable) OR non palpable) OR occult) AND (localization) OR localization) OR wire guided localization) OR WGL) OR needle wire localization) OR NWL) OR radioactive seed localization) OR RSL) OR (retrospective*) OR registry) OR consecutive*) OR prospective*) OR cohort) OR double blind) OR randomized) OR placebo controlled) OR parallel-group) OR single-center) OR multi-center) OR case-control) OR controlled trial) OR multi-site) NOT Meta analysis[Title]) AND (lesion*) OR cancer*) OR neoplasm*) OR carcinoma*) AND breast)) AND (nonpalpable) OR non-palpable) OR non palpable) OR occult)) AND (localization) OR localization) OR wire guided localization) OR WGL) OR needle wire localization) OR NWL) OR radioactive seed localization) OR RSL)

Embase

#1. 'breast cancer'/exp
#2. 'breast neoplasm' OR 'neoplasm, breast' OR 'breast tumors'/exp OR 'breast tumors' OR 'breast tumor'/exp OR 'breast tumor' OR 'tumor, breast' OR 'tumors, breast' OR 'neoplasms, breast' OR 'breast carcinoma'/exp OR 'breast carcinoma' OR 'breast carcinomas' OR 'carcinoma, breast' OR 'car-

cinomas, breast' OR 'mammary neoplasms, human' OR 'human mammary neoplasm' OR 'human mammary neoplasms' OR 'neoplasm, human mammary' OR 'neoplasms, human mammary' OR 'mammary neoplasm, human' OR 'breast cancer'/exp OR 'breast cancer' OR 'cancer, breast'/exp OR 'cancer, breast' OR 'mammary cancer'/exp OR 'mammary cancer' OR 'cancer, mammary' OR 'cancers, mammary' OR 'mammary cancers' OR 'malignant neoplasm of breast' OR 'breast malignant neoplasm' OR 'breast malignant neoplasms' OR 'malignant tumor of breast' OR 'breast malignant tumor' OR 'breast malignant tumors' OR 'cancer of breast' OR 'cancer of the breast'
#3. #1 OR #2
#4. 'nonpalpable' OR 'non-palpable' OR 'non palpable' OR 'occult'
#5. 'localization'/exp OR 'localization' OR 'wire guided localization'/exp OR 'wire guided localization' OR 'wgl' OR 'needle wire localization' OR 'nwl' OR 'radioactive seed localization'/exp OR 'radioactive seed localization' OR 'rsl'
#6. 'randomised controlled trial'/exp OR 'randomised controlled trial' OR 'randomised controlled trials' OR 'randomized controlled trial'/exp OR 'randomized controlled trial' OR 'randomized controlled trials'/exp OR 'randomized controlled trials' OR 'controlled clinical trial'/exp OR 'controlled clinical trial' OR 'controlled clinical trials'/exp OR 'controlled clinical trials' OR 'random allocation'/exp OR 'random allocation' OR 'double-blind method'/exp OR 'double-blind method' OR 'single-blind method'/exp OR 'single-blind method' OR 'clinical trial'/exp OR 'clinical trial' OR 'clinical trials'/exp OR 'clinical trials' OR 'randomised' OR 'randomized' OR 'placebo'/exp OR 'placebo' OR 'randomly' OR 'crossover' OR 'cross-over'
#7. 'retrospective*' OR 'registry' OR 'consecutive*' OR 'prospective*' OR 'cohort' OR 'double blind' OR 'randomized' OR 'placebo controlled' OR 'parallel-group' OR 'single-center' OR 'multi-center' OR 'case-control' OR 'controlled
trial' OR 'multi-site'
#8. #3 AND #4 AND #5
#9. #6 OR #7
#10.#8 AND #9

Cochrane

#1 Breast
#2 Breast lesion
#3 Breast lesions
#4 Breast cancer
#5 Breast cancers
#6 Breast neoplasm
#7 Breast neoplasms
#8 Breast carcinoma
#9 Breast carcinomas
#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
#11 Nonpalpable
#12 Non-palpable
#13 Non palpable
#14 Occult 2015
#15 #11 or #12 or #13 or #14
#16 #10 and #15