European Review for Medical and Pharmacological Sciences 2021; 25: 1387-1398

Effectiveness of intra-operative ultrasonography, compared to conventional techniques, in attaining tumour free lumpectomy margins in breast cancer: a meta-analysis

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Abstract. – OBJECTIVE: The aim of the study was to summarize and update evidence on whether intra-operative ultrasonography (IOUS) guided breast conserving surgery (BCS) can be more effective than wire-guided or palpation-guided excision for both nonpalpable, as well as palpable breast cancers in achieving tumor free negative margins after lumpectomy for breast cancer.

MATERIALS AND METHODS: Comprehensive searches were done systematically through PubMed, Scopus, CENTRAL (Cochrane Central Register of Controlled Trials) and Google scholar databases. Statistical analysis was done using STATA version 13.0. The primary outcome was proportion of patients that achieved tumor free resection margins after lumpectomy. Effect sizes were reported as pooled relative risks (RR). All estimates were reported with 95% confidence intervals (CI).

RESULTS: A total of 20 RCTs with 2519 participants were included in the meta-analysis. Use of intra-operative ultrasonography was associated with 1.18 times higher chances [RR 1.18; 95% CI, 1.10-1.27] of attaining a tumor free margin for all breast cancers, 1.16 times higher chances [RR 1.16; 95% CI, 1.10-1.23] of attaining a tumor free margin for all palpable breast cancers and 1.20 times higher chances [RR 1.20; 95% CI, 1.05-1.38] of attaining a tumor free margin for all non-palpable breast, compared to wire-guided or palpation guided localization. There was no evidence of publication bias.

CONCLUSIONS: The findings support that intra-operative ultrasonography increases the chances of obtaining negative margins for tissue resected in breast conserving surgeries. The findings support the observations of previous reviews published in this aspect nearly half a decade back.

Key Words:
Intra-operative ultrasonography, Breast cancer, Tumour free lumpectomy, Meta-analysis.

Introduction

Around a half million deaths annually are caused by breast cancer, with about 1.7 million new cases occur every year[1]. Breast-conserving surgery (BCS) is a widely performed surgery used for treating breast cancer and includes the complete removal of the cancerous tissue[2]. Estimates[3] suggest that almost 20-30% of patients operated using BCS require multiple surgeries. It will be mainly due to cancer recurrence near the (margin) boundary of the excised tissue. The intraoperative detection of the margins involved could significantly decrease the proportion of patients requiring repeat surgeries.

The precision of surgical margins is enhanced by ensuring the margin of malignant tissue completely free by limiting the excision volume[4-7]. A number of methods are used to assist during the BCS. The standard practice is the process of breast conservation guided-wire localization[8]. However, there are several hazards in using the wire-guided localization which include missing or dislocation of wire or migration[9,10]. On the other hand, preoperative diagnostic images and surgeon's expertise in palpation are usually the guiding principles of tumour excision. Palpation-led surgery is shown to lead to a high incidence of malignant margins between 20 or 60%[11,12]. These problems with traditional tools, such as palpation and wire-guided BCS, indicate that surgical procedures should aim to achieve a higher rate of negative margins and less discomfort. Intraoperative ultrasound guidance (IOUS) was introduced in clinical practice in contrast to Wire-guided location as a visualizing method for non-palpable tumours[13,14]. In IOUS, an ultrasound probe is used to identify the breast tumour in the surgical process to increase the clinical preci-

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sion of breast cancer excision. Multiple studies on the IOUS for nonpalpable and palpable breast cancers have been performed since it was introduced.

Intra-operative ultrasound guidance (IOUS) may boost the precision of the BCS. However, IOUS is a rather new concept for protecting the tissue and non-infiltrated areas. Improving the targeted and appropriate excision of breast cancer tissue is necessary if real-time visibility of tumor and surrounding tissue are available. Absence of conclusive evidence supporting higher rates of tumour free margins of excised mass, compared to the current standard practice, limits use of newer technologies such as IOUS. One review was published in 2013 by Pan et al[15]. The authors included 13 studies and found that use of intra-operative ultrasonography was associated with higher chances of achieving negative margins for resected breast mass (in both palpable and non-palpable breast cancer) compared to control group with either wire-guided or palpation guided localization. Similar findings were reported by Ahmed et al[16] in their published review in 2013 in which they assessed the efficacy of IOUS, compared to guided wire localization, in surgical management of non-palpable breast cancer. Both these systematic reviews and meta-analysis were done nearly half a decade back and there is a need to update this evidence, as more studies on this aspect have been conducted. Therefore, we aim to conduct a systematic review of whether IOUS guided BCS can be more effective than wire-guided or palpation-guided excision for both nonpalpable, as well as palpable breast cancers in achieving tumor free or negative margins after lumpectomy for breast cancer.

Materials and Methods

Search Strategy

A comprehensive search was done systematically through PubMed, Scopus, CENTRAL (Cochrane Central Register of Controlled Trials) and Google scholar databases for English language papers published up to 15th November 2019. Free text words and medical subject heading (MeSH) terms were used. Details of the search strategy have been provided in supplementary documents (*Supplementary Table I*). The aim of the research was to identify studies, either observational or randomized controlled trials, that assessed the efficacy of intra-operative ultrasonography in achieving tumor free or negative margins after lumpectomy for breast cancer, in comparison to either wire-guided or palpation guided localization. A negative margin was operationally defined as a margin of at least 1 mm that was tumor free when examined microscopically.

Selection Criteria and Methods

Two authors reviewed citations and selected studies. After removing the duplicates, screening of titles and abstracts was performed as an initial step. Subsequently, review of the full text of potential studies was done. Any discrepancies related to the inclusion of studies were resolved through discussion among the study authors. Studies that adequately suited the inclusion criteria were selected for the meta-analysis. The bibliographic list of the identified studies and relevant reviews on the subject were examined for additional possible studies.

Inclusion Criteria

We included either an observational (cross-sectional or cohort) or randomized controlled trial conducted in breast cancer patients with either a palpable or a non-palpable lesion. Both prospectively and retrospectively conducted studies were eligible for inclusion. Further, the study should have compared intra-operative ultrasonography, against use of wire-guided or palpation-guided localization of tumor. The study should also have provided outcome measure of interest, i.e., proportion of patients that achieved tumor free resection margins after lumpectomy in both intervention and control groups.

Exclusion Criteria

We excluded any non-English language publications, conference abstracts, case reports, editorials, commentaries, review articles, incomplete original data, and studies where ultrasound or other tools were performed for diagnostic purposes, surgical staging or recurrence of the disease. Also, those studies that did not furnish extractable and meaningful data on effect sizes were excluded.

Data Extraction and Quality Assessment

Extraction of relevant data from included studies was done by two authors independently, using a data extraction sheet. Following data from eligible studies were extracted: surname of first author, year in which the study was published, geographical location where the study was done, presentation of breast cancer (palpable or non-palpable), design of the study (prospective or retrospective) and key findings of the study. The meth-

odological assessment was done independently by two authors using the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement[17].

Statistical Analysis

Statistical analysis was done using STATA version 13.0 (Software for Statistics and Data Science). Effect sizes were reported as pooled relative risks (RR). Analysis was done among women who were diagnosed with either palpable or nonpalpable breast cancer separately. All estimates were reported with 95% confidence intervals (CI). Heterogeneity of effects was assessed and quantified by the I^2. I^2 value >50% was considered to represent substantial heterogeneity[18]. In cases with substantial heterogeneity, random effects model was used[18]. A *p*-value of <0.05 was considered statistically significant. Publication bias was assessed using Egger's test and visually inspected using funnel plots[18].

Results

Selection of Articles, Study Characteristics and Quality of Included Studies

A total of 487 unique citations were obtained upon executing the search strategy in the PubMed, Scopus, CENTRAL (Cochrane Central Register of Controlled Trials) and Google scholar databases (Figure 1). Out of these, 439 were excluded based on title screening. Further, 20 citations were excluded after reading the abstract. Full text of the remaining 28 articles were reviewed. Out of these, 8 articles were excluded upon full text review. The final number of included articles in this meta-analysis was 20 with a total of 2519 participants[19-37]. Table I presents the key characteristics of the included studies along with the key findings. Seven studies were done in United States and Netherlands each.

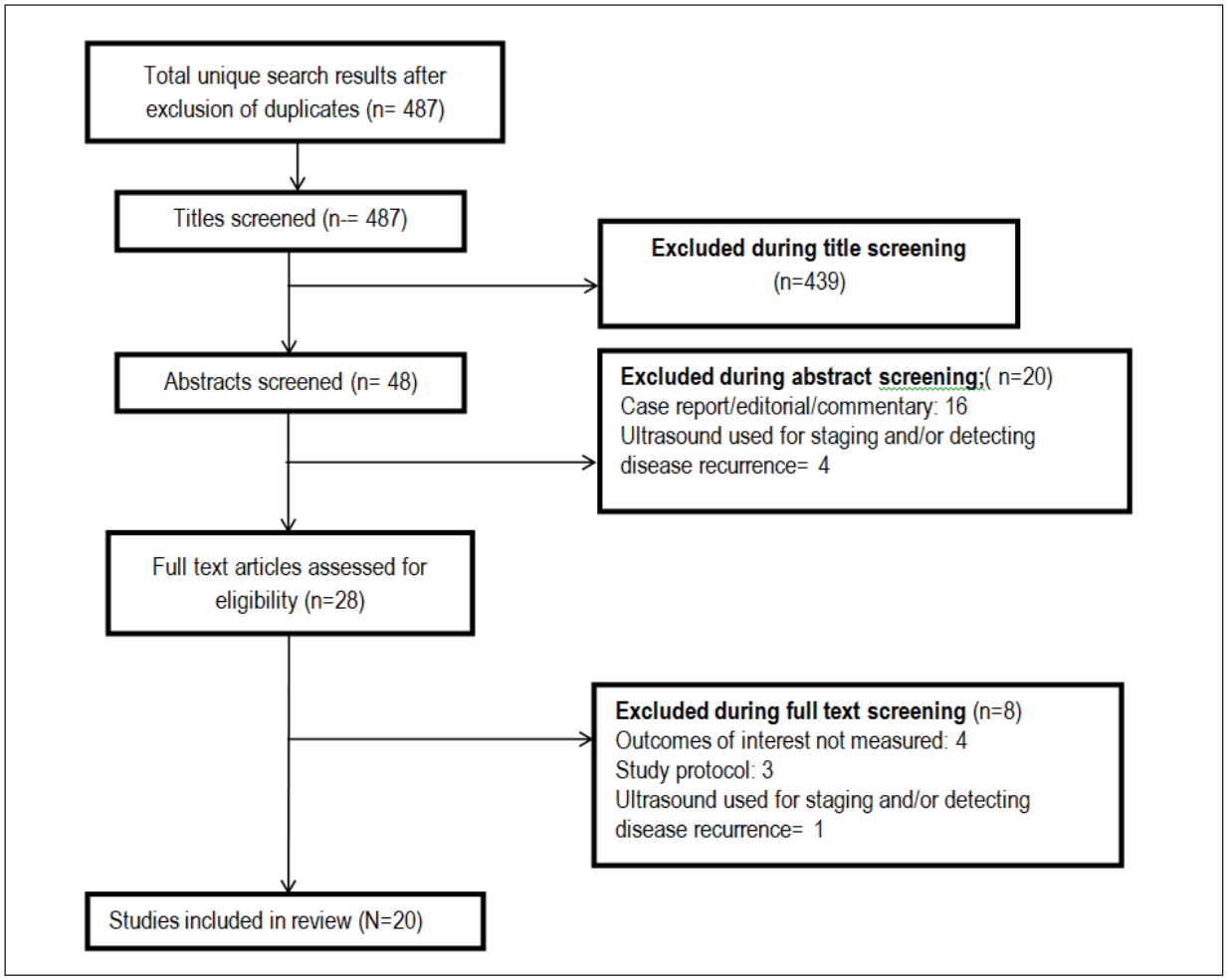

Figure 1. Selection process of the studies included in the review.

Table I. Key details of the studies included in the meta-analysis.

Author (year of publication)	Study design	Country	Presentation of breast cancer	Study groups	Key outcome *(Proportion; Resection with negative margins)*
Rahusen FD et al[19] (1999)	Prospective	Netherlands	Non-palpable	Intervention: Ultrasound guided lumpectomy Control: excision after guidewire localization	Intervention: 17/19 (89.4%) Control: 17/43 (39.5%)
Snider HC et al[20] (1999)	Prospective	United States	Non-palpable	Intervention: Ultrasound guided lumpectomy Control: excision after guidewire localization	Intervention: 18/22 (81.8%) Control: 18/22 (81.8%)
Rahusen FD et al[21] (2002)	Prospective	Netherlands	Non-palpable	Intervention: Ultrasound guided lumpectomy Control: excision after guidewire localization	Intervention: 24/27 (88.9%) Control: 12/22 (54.5%)
Bennet IC et al[22] (2005)	Prospective	Australia	Non-palpable	Intervention: Ultrasound guided lumpectomy Control: excision after guidewire localization	Intervention: 39/42 (92.8%) Control: 19/24 (79.2%)
Haid A et al[23] (2007)	Prospective	Austria	Non-palpable	Intervention: Ultrasound guided lumpectomy Control: excision after guidewire localization	Intervention: 242/299 (80.9%) Control: 38/61 (62.3%)
James TA et al[24] (2009)	Retrospective; data were collected from Breast Cancer Surgery Database	United States	Non-palpable	Intervention: Ultrasound guided lumpectomy Control: excision after guidewire localization	Intervention: 64/96 (66.7%) Control: 36/59 (61.0%)
Krekel NMA et al[25] (2011)	Retrospective	Netherlands	Non-palpable	Intervention: Ultrasound guided lumpectomy Control: excision after guidewire localization	Intervention: 43/52 (82.7%) Control: 86/117 (73.5%)
Barentsz MW[26] (2012)	Prospective	Netherlands	Non-palpable	Intervention: Ultrasound guided lumpectomy Control: excision after guidewire localization	Intervention: 112/120 (93.3%) Control: 129/138 (93.5%)
Moore MM et al[27] (2001)	Prospective	United States	Palpable	Intervention: Ultrasound guided lumpectomy Control: Standard excision of mass with no sham ultrasound	Intervention: 26/27 (96.3%) Control: 17/24 (70.8%)
Davis KM et al[28] (2011)	Retrospective chart review	United States	Palpable	Intervention: Ultrasound guided lumpectomy Control: Palpation guided with no intra-operative ultrasound	Intervention: 20/22 (90.9%) Control: 26/44 (59.1%)
Fisher CS et al29 (2011)	Retrospective	United States	Palpable	Intervention: Ultrasound guided lumpectomy Control: Palpation guided with no intra-operative ultrasound	Intervention: 66/73 (90.4%) Control: 104/124 (83.8%)
Krekel NMA et al[30] (2013)	Prospective	Netherlands	Palpable	Intervention: Ultrasound guided lumpectomy Control: Palpation guided with no intra-operative ultrasound	Intervention: 58/65 (89.2%) Control: 50/69 (72.5%)

Continued

Table I (continued). Key details of the studies included in the meta-analysis.

Author (year of publication)	Study design	Country	Presentation of breast cancer	Study groups	Key outcome *(Proportion; Resection with negative margins)*
Eichler C et al[31] (2012)	Retrospective	Germany	Both palpable and non-palpable	Intervention: Ultrasound guided lumpectomy Control: Palpation guided with no intra-operative ultrasound	Intervention: 81/84 (96.4%) Control: 137/166 (82.5%)
Karanlik H et al[32] (2015)	Prospective	Turkey	Palpable	Intervention: Ultrasound guided lumpectomy Control: Palpation guided with no intra-operative ultrasound	Intervention: 79/84 (94.0%) Control: 66/80 (82.5%)
Vispute T et al[33] (2018)	Prospective	India	Palpable	Intervention: Ultrasound guided lumpectomy Control: Palpation guided with no intra-operative ultrasound	Intervention: 31/32 (96.8%) Control: 24/28 (85.7%)
Eggermann H et al[34] (2014)	Retrospective	Germany	Palpable	Intervention: Ultrasound guided lumpectomy Control: Palpation guided with no intra-operative ultrasound	Intervention: 174/198 (87.9%) Control: 99/137 (72.3%)
Slijkhuis WA et al[35] (2016) (A)	Prospective	Netherlands	Palpable	Intervention: Ultrasound guided lumpectomy Control: Palpation guided with no intra-operative ultrasound	Intervention: 19/21 (90.4%) Control: 20/24 (83.3%)
Slijkhuis WA et al[35] (2016) (B)	Prospective	Netherlands	Non-palpable	Intervention: Ultrasound guided lumpectomy Control: Palpation guided with no intra-operative ultrasound	Intervention: 39/45 (86.7%) Control: 38/44 (86.4%)
Arentz C et al[36] (2010)	Retrospective	United States	Non-palpable	Intervention: Ultrasound guided Control: guidewire localization	Intervention: 135/177 (76.3%) Control: 20/38 (52.6%)
Paramos JC et al[37] (1999)	Prospective	United States	Non-palpable	Intervention: Ultrasound guided Control: guidewire localization	Intervention: 15/15 (100.0%) Control: 15/15 (100.0%)

One study each was conducted in India, Turkey, Australia and Austria whereas 2 studies were conducted in Germany. ***Supplementary Table II*** presents the findings of the quality assessed of studies using STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement. All the studies had clear study objectives. A total of 16 studies, out of 20, had clear inclusion criteria. All the studies had used standard tumor localization technique. In all the studies, standard histopathology was used to identify negative tumor margins. The overall quality of included studies was good.

Effect of Intra-Operative Ultrasonography on Rates of Negative Margins of all Breast Cancers

Use of intra-operative ultrasonography (USG) was associated with 1.18 times higher chances [RR 1.18; 95% CI, 1.10-1.27] of attaining a tumor free margin for all breast cancers, compared with control group with guide wire localization or palpation guidance (Figure 2). Further, for both prospective [RR 1.18; 95% CI, 1.07-1.31] and retrospective studies [RR 1.19; 95% CI, 1.08-1.31], USG was associated with higher chances of attaining negative margins (Figure 2). There was

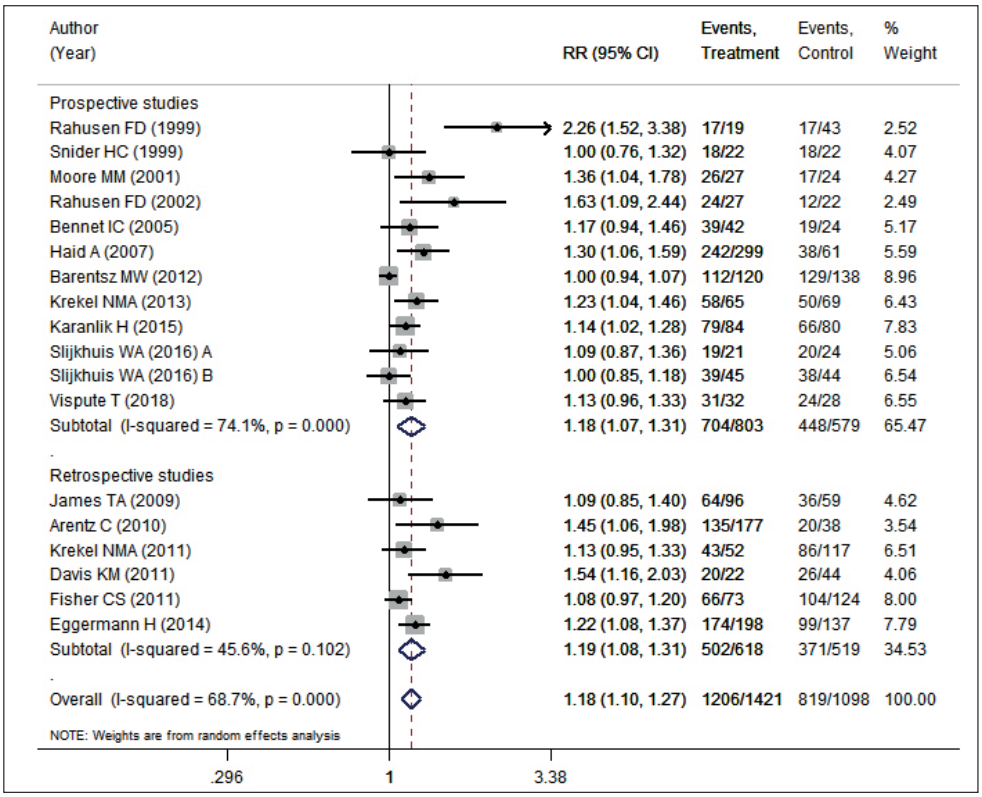

Figure 2. Effect of intra-operative ultrasonography on rates of negative margins of all breast cancers.

no evidence of publication bias (p=0.182). Funnel plot is presented as ***Supplementary Figure 1***.

Effect Of Intra-Operative Ultrasonography on Rates of Negative Margins of Palpable Breast Cancers

Use of intra-operative ultrasonography (USG) was associated with 1.16 times higher chances [RR 1.16; 95% CI, 1.10-1.23] of attaining a tumor free margin for all palpable breast cancers, compared with control group with guide wire localization or palpation guidance (Figure 3). Further, the pooled chances of attaining a tumor free margin was higher with use of intra-operative USG both among prospectively done studies [RR 1.16; 95% CI, 1.08-1.25] and among retrospectively done studies [RR 1.21; 95% CI, 1.04-1.42] (Figures 4 and 5). There was no evidence of publication bias (p=0.101). Funnel plot is presented as ***Supplementary Figure 2***.

Effect of Intra-Operative Ultrasonography on Rates of Negative Margins of Non-Palpable Breast Cancers

Use of intra-operative ultrasonography (USG) was associated with 1.20 times higher chances [RR 1.20; 95% CI, 1.05-1.38] of attaining a tumor free margin for all non-palpable breast cancers, compared with control group with guide wire localization or palpation guidance (Figure 6). Further, the pooled chances of attaining a tumor free margin was higher with use of intra-operative USG both among prospectively done studies [RR 1.22; 95% CI, 1.01-1.47] and among retrospectively done studies [RR 1.16; 95% CI, 1.03-1.32] (Figures 7 and 8). There was no evidence of publication bias (p=0.119). Funnel plot is presented as ***Supplementary Figure 3***.

Discussion

In females suffering from early-stage breast cancer, breast conserving surgery is usually done. Surgeons have used different techniques to ensure that a negative margin is obtained during the surgery[2,7]. This is important as a lack of a negative margin would lead to recurrence of the disease and the patient may have to undergo a repeat surgery. For breast cancers that are non-palpable, guided wire localization is commonly used[5,7,12]. On the other hand, for palpable breast cancers, the surgeons use their clinical skills augmented by their tactile skills to ensure tumor free margins during lumpectomy[2,5,7].

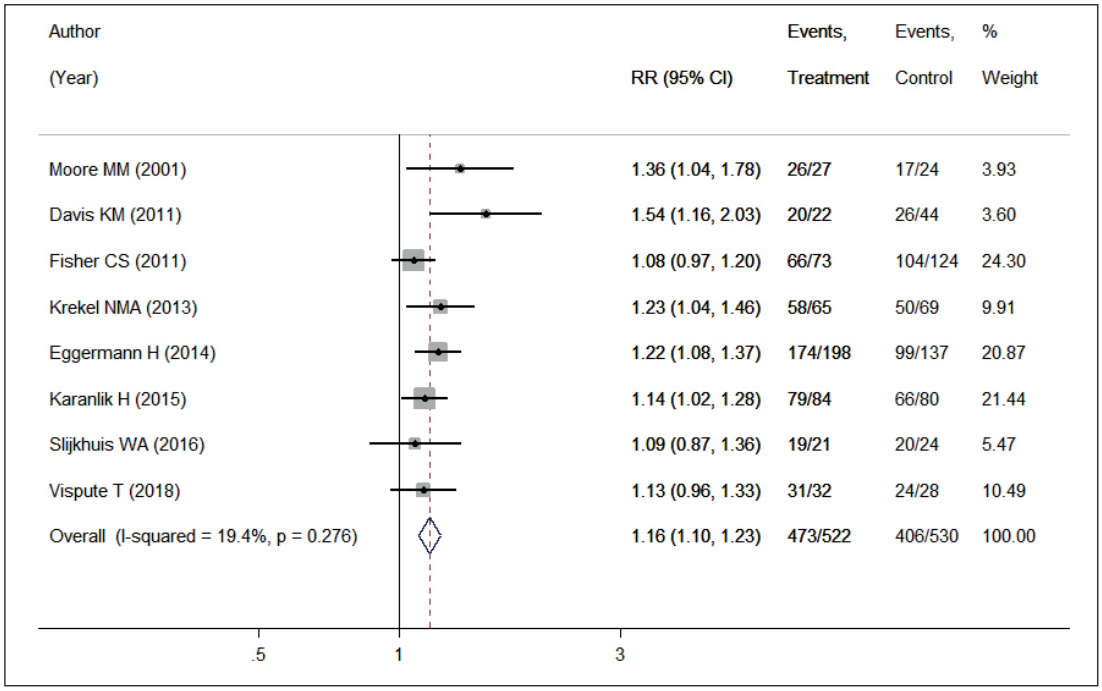

Figure 3. Effect of intra-operative ultrasonography on rates of negative margins of overall palpable breast cancers.

Intra-operative ultrasonography (IOUS) is a relatively new concept aimed to guide the breast conserving surgery in a way that the non-infiltrated areas are protected, and negative margins are achieved with high precision. The current meta-analyses show that the use of intra-operative ultrasonography was associated with around 20% higher chances of attaining a tumor free margin

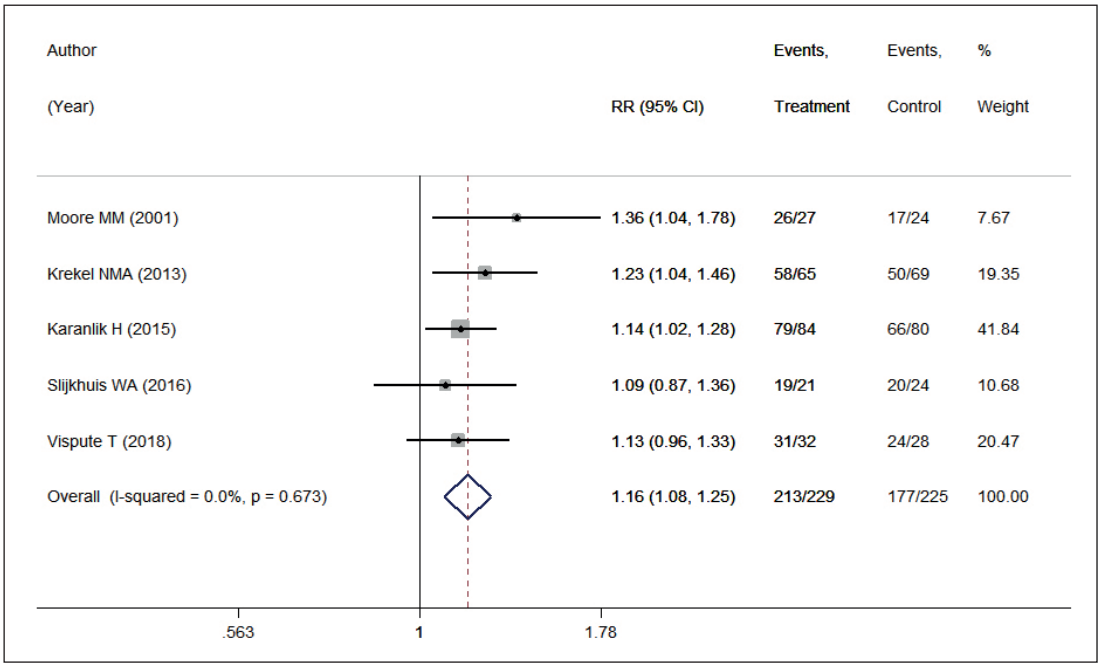

Figure 4. Effect of intra-operative ultrasonography, using prospectively conducted studies, on rates of negative margins of palpable breast cancers.

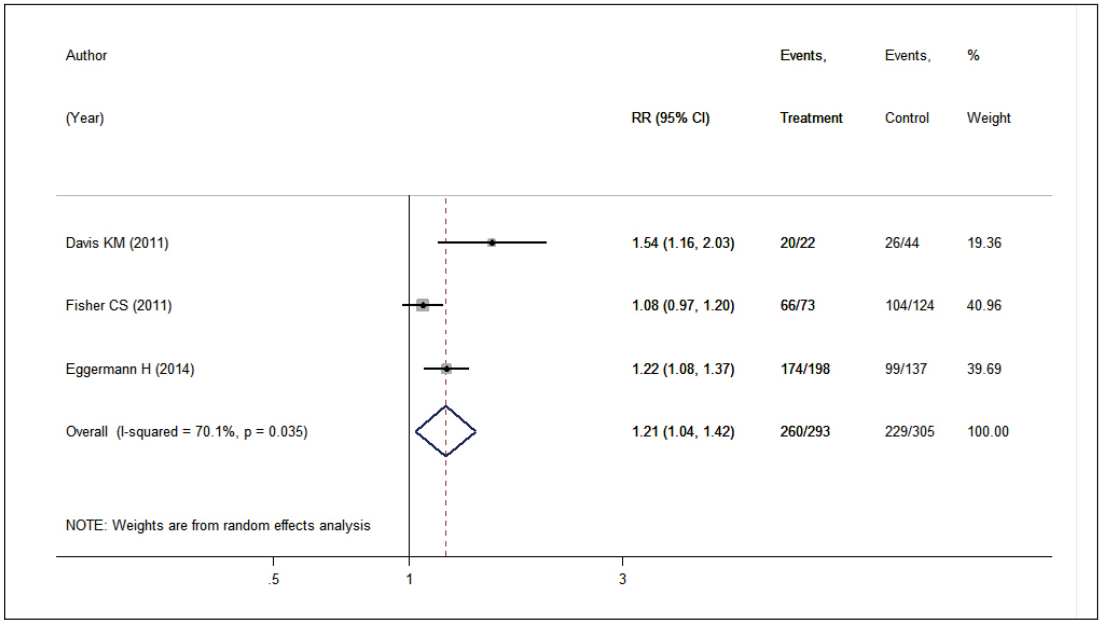

Figure 5. Effect of intra-operative ultrasonography, using retrospectively conducted studies, on rates of negative margins of palpable breast cancers.

for all breast cancers, compared with control group with guide wire localization or palpation guidance. Furthermore, the use of intra-operative ultrasonography was associated with 16% higher chances and 20% higher chances of attaining a tumor free margin for all palpable and non-palpable breast cancers, respectively. These findings are somewhat different from previous meta-analyses on this issue, published around half decade earlier[15,16]. The meta-analysis by Pan et al[15] documented a much higher chance of obtaining negative margins with use of IOUS. According to this meta-analysis, the use of intra-operative ultrasonography was associated with around 37%

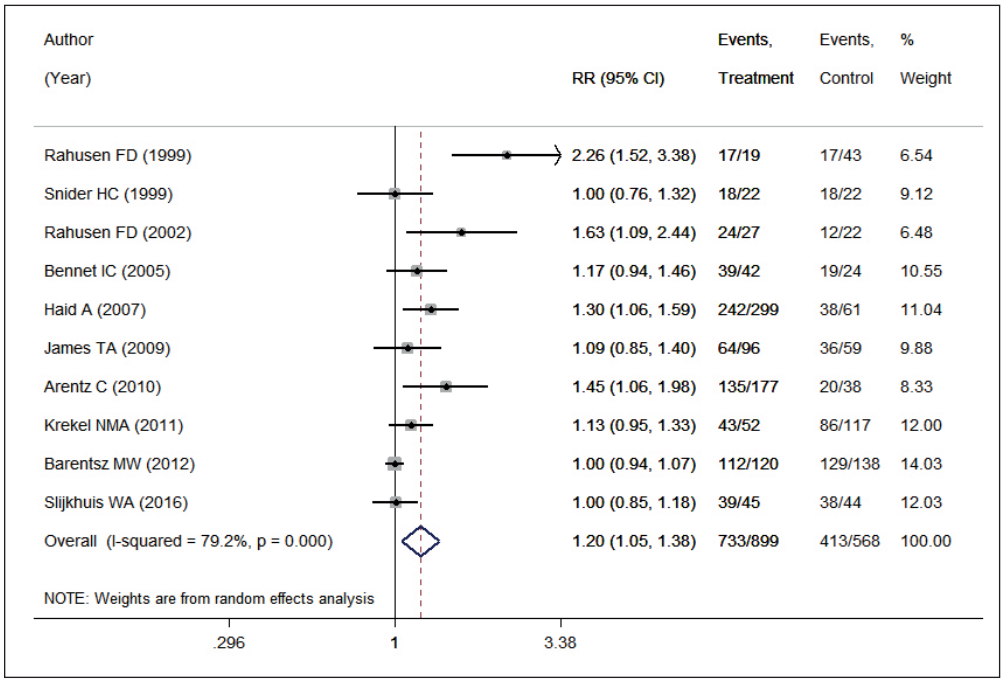

Figure 6. Effect of intra-operative ultrasonography on rates of negative margins of overall non-palpable breast cancers.

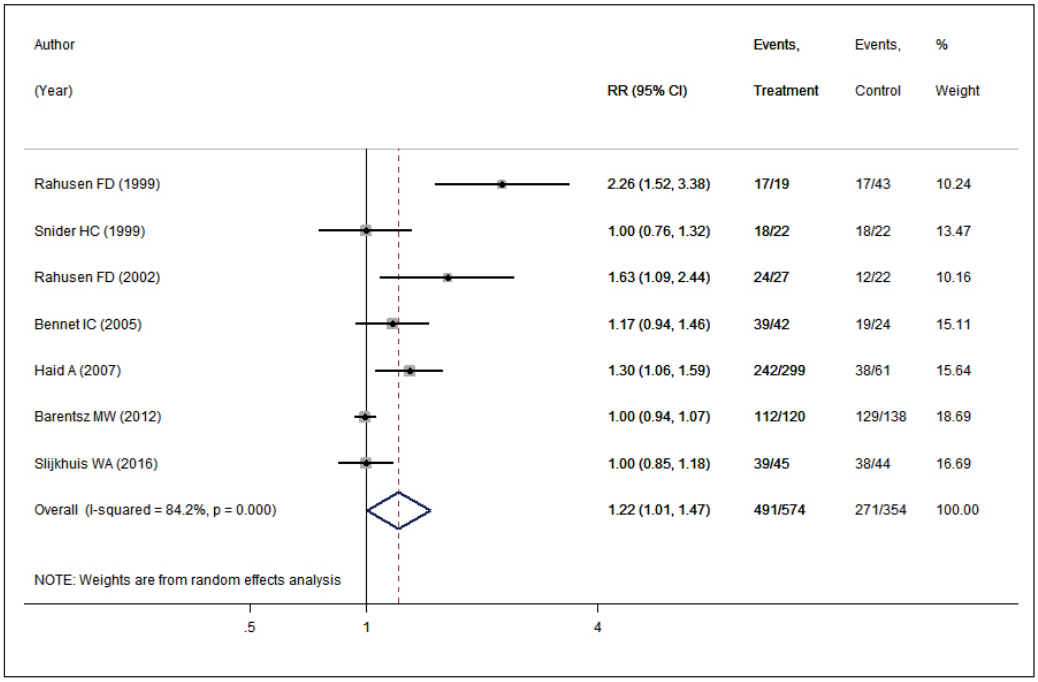

Figure 7. Effect of intra-operative ultrasonography, using prospectively conducted studies, on rates of negative margins of non-palpable breast cancers.

higher chances of attaining a tumor free margin for all breast cancers and 26% higher chances of attaining a tumor free margin for palpable breast cancers, when prospective studies were pooled. Ahmed et al[16] documented 48% less chance of having an involved surgical margin with use of IOUS, compared to wire-guided localization. It should be worth mentioning that our meta-analysis builds upon the existing meta-analyses that were published in 2013 and, since then, 6 more studies on this issue have been published. The inclusion of these new studies would probably

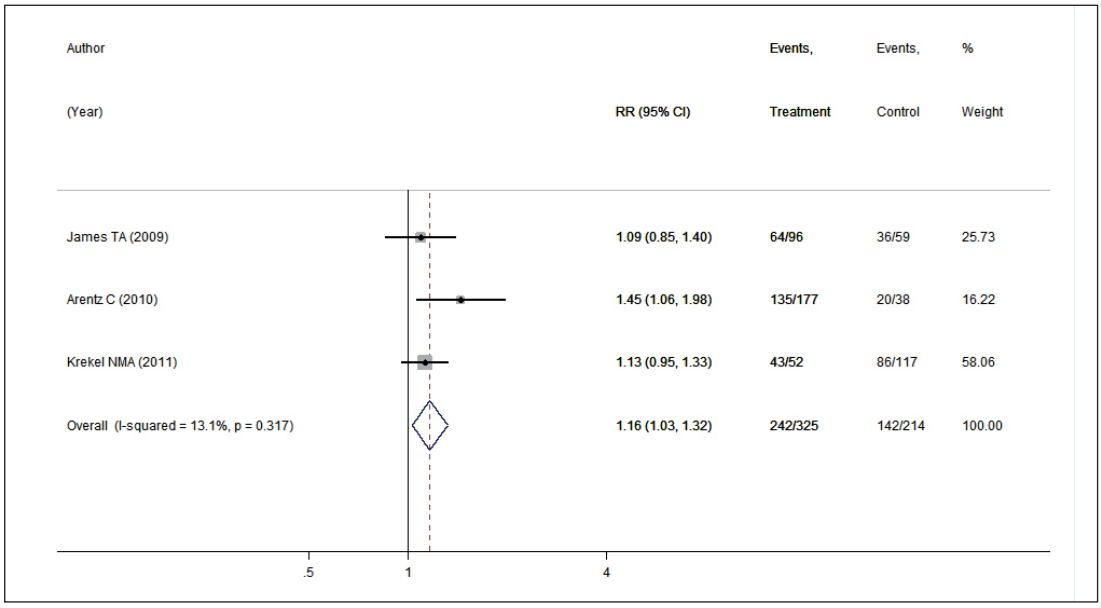

Figure 8. Effect of intra-operative ultrasonography, using retrospectively conducted studies, on rates of negative margins of non-palpable breast cancers.

change our estimates resulting from the earlier published ones. The findings of our meta-analysis support that IOUS is beneficial in achieving negative margins in breast conserving surgery, compared to wire-guided or palpation guided localization. However, the magnitude of benefits is lower compared to earlier published estimates by Pan et al[15] and Ahmed et al[16].

It is important to use a technique that, not only provides benefits in terms of attaining high rates of negative tumor margins in lumpectomy, but also preserves the cosmetic appearance of breast. In this regard, previous studies[26,30,38] have stated that IOUS is better than the conventional techniques as the volume of breast mass excised to achieve a tumor free margin is lesser. However, in this meta-analysis, we could not compare pooled estimates for volume of mass excised as most of the included studies did not provide data regarding this aspect. This could be one of the limitations of this review. Cost of any treatment modality is an essential aspect to consider when making recommendations for its wide use. Cost effectiveness was not considered in the present meta-analysis as an outcome. However, previous literature has indicated IOUS to be cost-effective compared to wire-guided technique[23]. This further supports the recommendation to scale up use of IOUS in breast conservative surgeries. It cannot be overlooked, however, that the use of IOUS to identify breast cancer needs to be adapted to each individual case, as there are still cases where GWL is more suitable. For instance, many mammographically observed lesions are not evident by ultrasound, such as microcalcifications and it may be appropriate to combine IOUS with guide wire localization.

There are few limitations of this meta-analysis. First, for some of the studies, the sample size was small and could have affected the overall pooled estimates. Second, the findings present the unadjusted pooled effect size (i.e., pooled relative risk). These are prone to change if adjustments are made for potential covariates, such as age and racial distribution. Third, we were unable to provide comparative pooled estimates for volume of resected breast mass to achieve tumor free margins for IOUS and wire-guided/palpation guided procedures. Fourth, we were unable to provide findings related to cost-effectiveness of the compared procedures. Finally, for assessing the publication bias, Egger's test was used over Begg's test. There are limitations with both these tests; however, the reason for using Egger's test was that Begg's bias indicator is insensitive to many types of bias to which the Egger test is sensitive. Consequently, Begg's test has a lower power than the Egger's test.

Conclusions

This meta-analysis reviewed the previously published reviews, which date back around half a decade. The aim was to provide updated evidence on the effect of intra-operative ultrasonography, compared to wire-guided or palpation guided localization, in attaining tumor free margins in patients that undergo breast conserving surgery. The findings support that intra-operative ultrasonography substantially increases the chances of obtaining negative margins for tissue resected. This positive effect was seen in both palpable and non-palpable breast cancers, as well as in studies done prospectively or retrospectively.

Author Contribution Statement

QZ conceived and designed the study; QZ and FW were involved in literature search and data collection; FW analyzed the data; QZ wrote the paper; and XW reviewed and edited the manuscript. All authors read and approved the final manuscript.

Conflict of Interests

The authors declare that they have no conflict of interest.

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