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Title Page

A systematic review and meta-analysis on the role of repeat breast conserving surgery for the management of ipsilateral breast cancer recurrence

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Synopsis

Repeat breast conserving surgery (BCS) for the management of ipsilateral breast cancer recurrence, in patients previously treated with BCS and radiotherapy, may be associated with increased risk of local recurrence but may not have an adverse effect on overall survival.

Abstract

Introduction: The standard surgical management of ipsilateral breast cancer recurrence (IBCR) in patients previously treated with breast conserving surgery (BCS) and radiotherapy is mastectomy. Recent international guidelines provide conflicting recommendations. The aim of this study was to perform a systematic literature review and meta-analysis of the oncological outcomes in patients with IBCR treated with repeat BCS (rBCS).

Methods: Medline and EMBASE databases were searched for relevant publications in English language with no date restrictions. All relevant studies providing sufficient data to assess oncological outcomes [second local recurrence (LR) and overall survival (OS)] of rBCS for the management of IBCR after previous BCS and radiotherapy were included (PROSPERO registration CRD42021286123).

Results: 42 observational studies met the criteria and were included in the analysis. The pooled second LR rate after rBCS was 15.7% (95%CI:12.1-19.7) and after salvage mastectomy was 10.3% (95%CI:6.9-14.3). On meta-analysis of comparative studies (n=17), the Risk Ratio (RR) for second LR following rBCS compared to mastectomy was 2.103 (95%CI:1.535-2.883, p<0.001, I^2=55.1%). Repeat radiotherapy had a protective effect (coefficient:-0.317;95%CI:-0.596,-0.038, p=0.026, I^2=40.4%) for second LR. Pooled 5-year OS was 86.8% (95%CI:83.4-90.0) vs 79.8%

(95%CI:74.7-84.5) for rBCS and salvage mastectomy respectively. Meta-analysis of comparative studies (n=20) showed a small OS benefit in favour of rBCS (RR:1.040;95%CI:1.003-1.079, p=0.032, I^2=70.8%). Overall evidence certainty was very low.

Conclusions: This meta-analysis suggests rBCS could be considered as an option for the management of IBCR in patients previously treated with BCS and radiotherapy. Shared-decision making, appropriate patient selection and individualized approach are important for optimal outcomes.

Introduction

Management of breast cancer has evolved significantly over the past decades, moving away from radical procedures towards less aggressive surgery. Breast conserving surgery (BCS), when combined with radiotherapy (RT), has been shown to confer equivalent oncological outcomes compared to mastectomy (1-3) and has been established as standard of care, when technically feasible, especially for patients with early-stage disease.

Advances in the multimodality management of breast cancer have led to improved oncological outcomes and reduced local recurrence rates (4). However, despite these advances 5-15% (5-7) of patients treated with BCS and RT may still experience ipsilateral breast cancer recurrence (IBCR). The surgical management of IBCR has traditionally been mastectomy. This has been supported by international recommendations including the National Comprehensive Cancer Network (NCCN) Guidelines (8). However, a number of studies have suggested that repeat BCS (rBCS) with or without repeat RT (rRT) may be an alternative (9-12). In one of the first reports, Kurtz et al. (9) showed that rBCS without rRT in a selected cohort of patients, was associated with acceptable oncological outcomes as demonstrated by overall survival (OS). Similar results in terms of OS and breast cancer specific survival (BCSS) have also been shown in more recent studies (13-16), although there are also publications reporting opposite results (17, 18). In addition, the reported local recurrence rates after rBCS have been variable (11, 15, 18-20). However, despite the conflicting data, there has been a trend towards increasing utilization of rBCS (15, 21) and recently the St. Gallen International Consensus guidelines also supported rBCS as an option, no longer considering mastectomy as absolutely obligatory for the management of IBCR (22) .

The aim of this study was to perform a systematic review of the literature and meta-analysis of the oncological outcomes in patients treated with rBCS with or without rRT for the management of IBCR following previous BCS and radiotherapy.

Methods

Search strategy and Inclusion criteria

A systematic review of the literature was conducted in Medline and EMBASE databases, using the search terms “ipsilateral breast tumour recurrence”,” ipsilateral breast cancer recurrence”, ”ipsilateral breast tumor recurrence”, “ipsilateral recurrent breast cancer”, “IBTR”, “local recurrence + breast cancer + breast conserving surgery + mastectomy”. No chronological limitations were stipulated. In the absence of dedicated randomized controlled trials, prospective and retrospective comparative and non-comparative cohort studies, cross-sectional studies reporting on second local recurrence (LR) and / or survival after rBCS for IBCR following previous BCS and RT were considered eligible. Studies that did not clearly specify whether the reference population had initially been treated for only DCIS, or both DCIS and invasive breast cancer (IBC), were included in the primary analysis. Respectively, we registered whether data regarding the type of in-breast recurrence (IBC or DCIS) was reported separately or cumulatively. If more than one reports on the same patients were available, only the most recent was included.

Data extraction

Data extraction was performed independently by two authors (CJT and EP) in a preformed Microsoft Excel© working sheet. The data extraction procedure for the whole dataset (including all eligible studies) was standardised during two training sessions with the senior authors (AK and MKT) using a random sample of five studies. Disagreement was resolved by group consensus. The study methodology was registered with PROSPERO International prospective register of systematic reviews (CRD42021286123, https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021286123).

Quality assessment

The Newcastle-Ottawa-Scale (NOS) (23) for observational studies, as assessed by two authors (EP, AK) was used to evaluate the quality of the included studies. Publication bias was assessed with funnel plots and the Egger's test for small studies. Following analyses and critical appraisal, the GRADE approach (24) was used to assess the strength of evidence and recommendations by two authors (AV and AK). Subsequently, knowledge gaps and research priorities were defined.

Statistical analyses and reporting

Rates of a second LR and OS at 5 years for rBCS and salvage mastectomy were calculated separately, by pooling the outcomes from single-arm and comparative studies. Subgroup analyses were performed depending on whether the reference population had initially been treated for only DCIS, both DCIS and IBC or IBC only. Subgroup analyses were also undertaken to define the effect of study design (comparative or single-arm), propensity score matching and the effect of radiotherapy, regardless of the technique that was utilized. The median follow-up was also extracted. Meta-analyses of comparative studies were also performed. Additionally, leave-one-out meta-analyses of comparative studies were performed, to allow for the identification of studies with exaggerated effect sizes and guide further subgroup and meta-regression analyses. As literature search was expected to retrieve observational studies, the use of a random-effects model using the DerSimonian Laird method was decided *a priori*. For source studies directly reporting odds ratio (OR), risk ratio (RR) or hazard ratio (HR), the adjusted analyses and Kaplan-Meier curves were considered for data extraction and calculation of 5-year second LR and OS (25, 26). Effect sizes were reported with 95% confidence intervals (95% CI). Study heterogeneity was assessed with the I^2 statistic.

The manuscript was prepared according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines (27). Stata v17 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC.) was used for all statistical analyses.

Results

Study selection and characteristics

The literature search, after the removal of duplicates, retrieved 42 studies, with 24 examining outcomes after a primary IBC, 17 reporting on both IBC and DCIS and 1 on DCIS only (MOOSE flowchart presented in Figure 1). Twenty-eight studies examined outcomes on both LR and OS, 9 on OS only and 5 on LR only. Study characteristics and NOS scores are shown in Table 1. On two occasions, it was not explicitly reported by the authors if the study population was the same as in another publication by the same group (28, 29). Therefore, all the studies were included in Table 1, but only the most recent studies providing data following propensity score matching were included in the meta-analysis (19, 30).

Second Local Recurrence

Source studies reporting on a second LR had a median follow-up ranging from 24.5 to 165.6 months [median of medians 70 months, interquartile range (IQR): 52-73]. The overall pooled incidence of a second LR after rBCS was 15.7% (95% CI: 12.1-19.7) and after salvage mastectomy was 10.3% (95% CI: 6.9-14.3). Despite the fact these were separately pooled outcomes without comparison, the confidence intervals were numerically overlapping, suggesting that the difference may not be significant, but study heterogeneity was high. The results of the subgroup analyses across all included studies are summarized in Table 2. Overall, among patients treated with rBCS, those who received rRT had the lowest pooled second LR rate compared to the other subgroups (9.6%, 95% CI: 5.0-15.3).

A total of 17 studies provided comparative data on second LR after rBCS and salvage mastectomy. The median follow-up ranged from 30 to 165.5 months (median of medians 72

months, IQR: 52-79). In comparative studies, the pooled second LR rate was higher after rBCS (19.6%, 95% CI: 15.5-24.0) versus after salvage mastectomy (9.6%, 95% CI: 6.3-13.5) (Table 2). On meta-analysis, rBCS was associated with a significantly increased risk of second LR [Risk Ratio (RR) = 2.103; 95% CI: 1.535 - 2.883, p < 0.001, I^2= 55.1%), as shown in Figure 2. Leave-one-out meta-analysis (Supplement, Figure S1) did not demonstrate any differences. Only concomitant radiotherapy retained a protective effect in meta-regression analysis (coefficient: -0.317; 95% CI: -0.596, -0.038, p= 0.026, I^2= 40.4%). No publication bias or small-studies effect was detected (Egger's test beta1: 1.540, p= 0.103).

Overall Survival

Pooled OS rates and subgroup analyses for patients treated with rBCS or salvage mastectomy are presented in Table 3. Overall, at a median follow-up ranging from 30 to 168 months (median of medians 66 months, IQR: 55 - 79), the pooled 5-year OS rate was 86.8% (95% CI: 83.4 - 90.0) after rBCS and 79.8% (95% CI: 74.7 - 84.5) after salvage mastectomy. Subgroup analyses (Table 3) did not demonstrate any factor that correlated with difference in outcomes for each group (rBCS or salvage mastectomy). Meta-analysis of comparative studies (n=20) showed a small OS benefit in favour of rBCS (RR: 1.040, 95% CI: 1.003 - 1.079, p = 0.032, I^2= 70.8%) (Figure 3). The median follow-up in these studies ranged from 42 to 168 months (median of medians 72 months, IQR: 59 – 126.6). Leave-one-out meta-analysis (Supplement, Figure S2) showed that the omission of four studies (one at a time) would result in a difference, despite that the numeric value of the RR was not significantly affected. Subsequent subgroup

and meta-regression analysis was performed (Supplement, Table S1). Radiotherapy did not affect the outcome on meta-regression analysis (coefficient: 0.0019; 95% CI: -0.0274, 0.0312, p= 0.898, I^2= 70.8%). With regards to primary tumor, studies reporting on both DCIS and IBC reported survival benefit for rBCS (RR: 1.119; 95% CI: 1.019 – 1.230, p=0.019), but this effect was not retained on meta-regression analysis (coefficient: 0.0721; 95% CI: -0.0017, 0.1458, p=0.056). When looking into publication bias, the Egger's test detected small-studies effect (Egger's test beta1: 0.93, p= 0.041).

Study quality and strength of recommendations

The median NOS score was 8.5 (IQR: 7-9). No correlation was identified between the timing of the study publication and the median NOS, suggesting that study quality has not improved over the years.

The GRADE recommendations from the meta-analysis are summarized in Table 4. The certainty of evidence was very low, due to serious risk of bias (mainly selection), inconsistency and imprecision. The main reasons for that were deemed to be the design of available studies (retrospective single-arm and comparative, mostly without matching or consecutive patients), the fact that most studies reported outcomes in form of rates, rather than effect sizes such as hazard ratios that are much more appropriate for time-to-event outcomes and, finally, that most source studies did not accurately report on primary and recurrent tumour biology as well as adjuvant therapy, for example use of radiotherapy after BCS for the management of the initial cancer or radiotherapy for the management of the recurrence, which may play pivotal

role in oncological outcomes. These factors constituted the main knowledge gaps and, thus, research priorities for future studies.

Discussion

Mastectomy has traditionally been considered as the standard of care for the management of IBCR. This has been recommended by national and international guidelines, including the NCCN guidelines (8). Reasons for this practice include the concerns about rRT and also the fact that IBCR has been associated with poor prognosis (31, 32), potentially supporting the argument for more aggressive local treatment. However, salvage mastectomy does not eliminate the risk of local or distant recurrence (33, 34) and there is increasing data supporting the feasibility of rRT (16, 35). In addition, advances in multidisciplinary management of breast cancer, including systemic therapy and radiotherapy options, and a general trend towards surgical de-escalation have likely contributed to the increasing use of rBCS as part of an individualized, tailored approach (15, 21). This is also now supported by the St. Gallen International Consensus Guidelines (22). Avoidance of mastectomy, if oncologically safe, could be associated with improved patient satisfaction in terms of cosmetic outcome and quality of life (36, 37) apart from cost and resource implications for healthcare providers. However, the existing data do not conclusively support rBCS or salvage mastectomy in terms of oncological outcomes, with a number of studies reporting opposite results (9-13, 17-20, 29, 38, 39).

The present systematic literature review showed variable second LR rates after rBCS. The overall pooled second LR rate was found to be 15.7% after rBCS compared to 10.3% after

salvage mastectomy. However, it should be noted that the included studies are markedly heterogeneous, and there was not a standardized multidisciplinary treatment protocol for the management of IBCR. In addition, it is important to highlight that in a number of studies, a proportion of patients did not receive RT for the management of the primary cancer, with not enough data provided to allow stratification for this in the analysis. On meta-analysis, rBCS was associated with a significantly higher RR for second LR (RR= 2.103), albeit with moderate study heterogeneity. This RR is similar to that reported in a recent meta-analysis (RR = 1.87) (40). The small observed difference may be explained by the fact that the present meta-analysis included 17 studies providing data on second LR compared to 13 studies in the meta-analysis by Mo et al (40).

On sub-group analysis, the lowest second LR rate among patients treated with rBCS was observed in those receiving rRT (9.6%). The protective effect of rRT was also demonstrated in meta-regression analysis. This finding is in line with previous reports highlighting the potentially important role of rRT in improving local control after rBCS for IBCR (35, 40). This is an important consideration when individualizing the management plan especially as a number of rRT options, for example brachytherapy (41-43), intraoperative radiotherapy (44, 45) and external beam radiotherapy (16) have been shown to be associated with acceptable toxicity profile. In the RTOG 1014 prospective Phase 2 clinical trial, 3-dimensional conformal external beam partial breast rRT after rBCS for IBCR in patients previously treated with BCS and RT was associated with low risk of second LR (5%) and late Grade 3 adverse events in only 7% of the cases while there were no Grade 4 or higher reported adverse events (16). Tolerability of rRT has also been supported by the results from a recent meta-analysis (35).

Despite the finding that rBCS may be associated with a higher risk of second LR, which was two-fold higher based on the results of the present meta-analysis, it may not have a negative impact on survival. A number of retrospective studies have shown that OS was not inferior or was even improved in patients treated with rBCS with or without rRT compared to those treated with salvage mastectomy (13, 15, 19, 29, 30, 43, 46). An analysis of the Surveillance, Epidemiology, and End Results (SEER) database including data from 1998 to 2013 showed no significant difference in terms of OS and BCSS in patients treated with rBCS or salvage mastectomy (14). However, another analysis of the SEER database looking into data from 1973 to 2003 showed different results (17). In this study the authors found that rBCS was associated with worse OS and BCSS and that rRT had a protective effect in terms of OS. Although, there is no clear explanation for the discordant findings, a potential reason may be the different time periods, as multidisciplinary breast cancer management has significantly evolved over the past decades. A recent meta-analysis by Mo et al also supports the findings that rBCS may not be associated with worse OS (40). The results of the present meta-analysis showed a marginal benefit in OS in favour of rBCS (RR: 1.040). The difference between the two meta-analyses may be explained by the different number of included studies (8 versus 20 in the present analysis). The median NOS of the studies (10-12, 34, 38, 43, 46, 47) included in the meta-analysis by Mo et al (40) is 9 (IQR: 7-9), and the median NOS of the studies in the present meta-analysis is also 9 (IQR: 8-9), with the additional 12 studies having a median NOS of 9 (IQR: 9-9). It has to be noted though that a small-study effect was found, underlining potential publication bias. While such an effect was not detected in the meta-analysis by Mo et al (40) cautiousness is required due the small number of included studies.

Although rRT was found to have a protective effect in terms of local control and has previously been shown to have a role in improving OS (17, 46), in the present meta-analysis, OS was not affected by rRT on meta-regression analysis. However, these results should be interpreted with caution as the included studies were substantially heterogeneous, and the effect size had marginal significance.

The findings of this meta-analysis suggest that although rBCS may be associated with higher risk of subsequent LR, this may not have a negative impact on OS. This suggests that rBCS may be an alternative option in the context of individualized management of IBCR in line with the St. Gallen International Consensus Guidelines (22), especially for women who want to preserve their breast, following careful consultation about the currently accepted standard recommendation of salvage mastectomy as per NCCN (8) guidelines. However, appropriate patient selection for such an approach would be of paramount importance. In the first report of rBCS for IBCR, Kurtz et al suggested an algorithm for patient selection including tumour size < 2 cm, no fixation of the cancer on the skin or chest wall, clinically node negative status and no significant RT changes (9). Other important parameters include disease free interval, and the size and histopathology of the recurrence as these have been shown to be independent prognostic factors of OS (46). Gentilini et al have suggested that patients with small (≤ 2 cm) late (> 48 months) IBCR would be the ideal candidates for rBCS (48). Similar selection criteria have been proposed by the German Society of Radiation Oncology (DEGRO) expert panel suggesting that rBCS can be considered in patients ≥ 50 years with unifocal, small (< 2 – 3 cm) IBCR, ≥ 48 months after primary treatment who are willing to undergo rBCS and this is technically feasible (49). The St. Gallen International Panel suggests that rBCS can be considered

for low-risk recurrent cancers with favourable tumour biology (small, Luminal A) for which rRT may not be required or for IBCR > 5 years after primary treatment (22). The common denominator of these suggested algorithms for patient selection is an individualized approach mainly based on tumour biology and anatomical stage. The role of multidisciplinary management of IBCR, with systemic therapy (endocrine therapy, chemotherapy or targeted therapy for example anti-HER2) with or without rRT cannot be overemphasized. The potential effect of such recommendations could not be assessed in this meta-analysis due to lack of studies providing data that would allow such an analysis.

Although, rBCS is increasingly being used for the management of IBCR (15, 21), and de-escalated tailored therapeutic approaches are favoured within modern multidisciplinary working, the quality of the studies providing data on oncological outcomes of rBCS does not appear to improve over time as demonstrated by the NOS assessment of the studies included in this meta-analysis. The low quality of available source studies constitutes the limitation of this meta-analysis, as potentially uncontrolled biases, lack of standardized reports of treatment modalities and outcomes of interest increase heterogeneity and mandate a careful interpretation of the results. This fact was illustrated in the outcomes of the GRADE approach and highlights the importance of collaboration across different specialties to set up prospective research studies, designed to address the knowledge gaps highlighted.

Conclusions

Repeat BCS may have a role in the management of IBCR in patients previously treated with BCS and RT. This should be based on individualized assessment of tumour and patient factors, and multidisciplinary working to develop a tailored management plan. Further research in this field is warranted to allow optimal patient selection and address existing knowledge gaps.

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Figure legends

Figure 1. Flowchart of systematic review and meta-analysis of observational studies in epidemiology. *2 studies were not explicitly described by the authors if they represented same population as other publications

Figure 2. Forest plot of studies comparing repeat breast conserving surgery versus salvage mastectomy for second local recurrence. * Study by Kurtz et al *International journal of radiation oncology, biology, physics 1990*

Figure 3. Forest plot of studies comparing repeat breast conserving surgery versus salvage mastectomy for overall survival.

Supplemental Figure 1. Leave-one-out meta-analysis forest plot of studies comparing repeat breast conserving surgery versus salvage mastectomy for second local recurrence

Supplemental Figure 2. Leave-one-out meta-analysis forest plot of studies comparing repeat breast conserving surgery versus salvage mastectomy for overall survival.

Tables

Table 1. Characteristics of Included Studies.

													Newcastle-Ottawa Scale			
Reference Number	**Author**	**Year**	**Primary diagnosis**	**IBCR diagnosis**	**Study Outcome**	**Total number of patients**	**Previous breast RT after BCS**	**Previous RT Axilla / Regional nodes after BCS**	**Number of patients rBCS**	**rRT breast after rBCS**	**rRT axilla / Regional nodes after rBCS**		**Selection**	**Comparability**	**Outcomes**	**Total**
(9)	Kurtz et al	1988	IBC	NS	OS	118	Yes	Yes	52	No	No		3	1	3	**7**
(50)	Kurtz et al	1990	IBC	NS	LR	50	Yes	Yes	50	Yes* (n=11) EBR (n=7) and BT (n=4)	NS		4	0	3	**7**
(51)	Abner et al	1993	IBC	IBC and DCIS	LR, OS	139	Yes	Yes*	16	No	No		3	1	3	**7**
(52)	Voogd et al	1998	IBC	IBC and DCIS	LR	266	Yes	NS	20	Yes*	NS		4	0	2	**6**
(18)	Dalberg et al	1998	IBC	IBC and DCIS	LR	85	Yes* (n=67)	NS	14	Yes* (n=2)	NS		4	0	3	**7**
(10)	Salvadori	1999	IBC	NS	LR, OS	197	Yes	NS	57	NS	NS		4	0	3	**7**

	et al															
(53)	Deutsch et al	2002	IBC and DCIS	IBC and DCIS	LR, OS	39	Yes	Yes* (n=3)	39	Yes EBR	NS		3	0	3	**6**
(11)	Alpert et al	2004	IBC and DCIS	IBC and DCIS	LR, OS	146	Yes	Yes*	30	Yes* BT (n=1)	NS		4	1	3	**8**
(54)	Hannoun-Levi et al	2004	IBC and DCIS	IBC and DCIS	LR, OS	69	Yes	NS	69	Yes BT	Yes* (n=49)		4	0	3	**7**
(12)	Komoike et al	2005	IBC	NS	LR, OS	136	Yes*	NS	55	NS	NS		4	1	3	**7**
(34)	Fodor et al	2007	IBC	IBC and DCIS	LR, OS	124	Yes* (n=60)	NS	32	Yes* (n=4)	NS		4	2	3	**9**
(42)	Chadha et al	2008	IBC and DCIS	IBC and DCIS	LR, OS	15	Yes	NS	15	Yes LDR BT	NS		4	0	3	**7**
(38)	Chen et al	2008	IBC	IBC and DCIS	OS	747	Yes	NS	180	Yes* (n=38)	NS		4	2	3	**9**
(55)	Botteri et al	2009	IBC	IBC	LR, OS	282	Yes	Yes*		No	No		4	1	3	**8**
(39)	Panet-Raymond et al	2011	IBC	IBC and DCIS	OS	269	Yes	NS	48	Yes* (n=33)	NS		4	2	3	**9**

(56)	Kauer-Dorner et al	2012	IBC	IBC and DCIS	LR, OS	39	Yes	No	39	Yes PDR brachy-therapy	No		4	1	3	**8**
(48)	Gentilini et al	2012	IBC	IBC	LR, OS	161	Yes	Yes*	161	No	No		4	2	3	**9**
(57)	Shah et al	2012	IBC and DCIS	IBC and DCIS	OS	18	Yes	NS	4	Yes APBI	NS		4	0	3	**7**
(58)	Demicheli et al	2013	IBC	NS	LR	338	Yes*	NS	148	Yes* (n=43)	NS		4	1	3	**8**
(41)	Hannoun-Levi et al	2013	IBC	NS	LR, OS	217	Yes	Yes*	217	Yes LDR (n=27), PDR (n=88), HDR (n=102), BT	NS		4	2	3	**9**
(28)	Ishitobi et al†	2013	IBC	NS	LR, OS	271	Yes* (n=69)	NS	143	Yes* (n=1)	NS		4	2	3	**9**
(20)	Kolben et al	2015	IBC	IBC and DCIS	LR, OS	170	Yes	NS	58	Yes* (n=11)	NS		4	2	3	**9**
(46)	Lee et al	2015	IBC and DCIS	IBC and DCIS	OS	157	Yes* (n=135)	NS	23	Yes* (n=13)	NS		4	2	3	**9**

(30)	Yoshida et al	2016	IBC	NS	OS	271	Yes* (n=133)	NS	149	NS	NS		4	2	3	**9**
(59)	Wapnir et al	2017	IBC	IBC	LR, OS	162	Yes* (n=92)	NS	16	Yes* (n=2)	NS		4	2	3	**9**
(60)	Ishitobi et al	2017	IBC and DCIS	IBC and DCIS	LR, OS	65	Yes	NS	65	No	No		4	2	3	**9**
(47)	Sellam et al	2018	IBC and DCIS	IBC and DCIS	LR, OS	121	Yes	NS	47	Yes* (n=16) EBR-PB (n=15), EBR-WB (n=1)	Yes* (n=1)		4	2	3	**9**
(61)	Houvenaeghel et al	2018	IBC	NS	LR, OS	348	Yes	NS	116	Yes* (n=62) BT (n=62)	NS		4	2	3	**9**
(43)	Smanyko et al	2019	IBC and DCIS	IBC and DCIS	LR, OS	195	Yes	NS	39	Yes HDR BT	NS		4	2	3	**9**
(62)	Montagne et al	2019	IBC and DCIS	IBC and DCIS	LR, OS	143	Yes	NS	143	Yes LDR BT (n=26), HDR BT (n=117)	NS		4	2	3	**9**
(63)	Forster et al	2019	IBC and DCIS	IBC and DCIS	LR, OS	19	Yes	Yes*	19	Yes HDR BT	NS		4	1	3	**8**

										(n=11), PDR BT (n=8)						
(64)	Cozzi et al	2019	IBC and DCIS	IBC and DCIS	LR, OS	40	Yes	NS	40	Yes HDR BT	NS		4	0	3	**7**
(17)	Su et al	2019	IBC	NS	OS	5098	Yes* (n=3687)	NS	1050	Yes* (n=259)	NS		4	2	3	**9**
(29)	Sagona et al†	2020	IBC and DCIS	IBC and DCIS	LR, OS	309	Yes* (n=300)	NS	143	Yes* (n=50)	NS		4	1	3	**8**
(65)	Boehm et al	2020	IBC and DCIS	IBC and DCIS	LR, OS	57	Yes* (n=55)	NS	57	Yes IORT	NS		4	0	3	**7**
(16)	Arthur et al	2020	IBC and DCIS	IBC and DCIS	LR, OS	58	Yes	NS	58	Yes 3D-CRT PBI	NS		4	0	3	**7**
(15)	Van den Bruele et al	2021	IBC	IBC and DCIS	LR	322	Yes* (n=258)	NS	130	Yes* (n=41)	NS		4	2	3	**9**
(14)	Wu et al	2020	IBC	NS	OS	2075	Yes	NS	475	Yes* (n=255)	NS		4	2	3	**9**
(19)	Gentile et al	2021	IBC	IBC and DCIS	LR, OS	309	Yes* (n=300)	NS	143	Yes* (n=50)	NS		4	2	3	**9**
(66)	Li et al	2021	DCIS	IBC and DCIS	LR, OS	5344	Yes* (n=2625)	NS	1812	Yes* (n=735)	NS		4	1	3	**9**

(21)	El Sherif et al	2021	IBC and DCIS	IBC and DCIS	LR, OS	113	Yes* (n=86)	NS	32	Yes* APBI (n=10), IORT (n=1), WBRT (n=2)	NS		4	1	3	**8**
(67)	Wang et al	2021	IBC	NS	LR, OS	5413	Yes	NS	773	Yes* (n=124)	NS		4	2	3	**9**
(68)	Chatzikonstantinou et al	2021	IBC and DCIS	IBC and DCIS	LR, OS	20	Yes	Yes*	20	Yes HDR BT	NS		4	0	3	**7**
(13)	Baek et al	2021	IBC and DCIS	NS	OS	335	Yes* (n=303)	NS	155	Yes* (n=24)	NS		4	3	2	**9**

IBCR: ipsilateral breast cancer recurrence, rBCS: repeat breast conserving surgery, RT: radiotherapy, rRT: repeat radiotherapy, IBC: Invasive breast cancer, DCIS: ductal carcinoma in situ, NS: Not specified, OS: overall survival, LR: local recurrence, EBR: external beam radiotherapy, BT: brachytherapy, LDR: low dose rate, PDR: pulse dose rate, HDR: high dose rate, APBI: Accelerated partial breast irradiation, IORT: intra-operative radiotherapy, 3D-CRT: 3D conformal radiotherapy, PBI: partial breast irradiation, WBRT: whole breast radiotherapy. * Proportion of patients did not receive the respective treatment modality, †Study included in the table but not in the final analysis as it was not explicit if it was duplicate patient population.

Table 2. Pooled rates of second local recurrence with separate subgroup analyses across all studies (single-arm and comparative).

	rBCS				Salvage mastectomy		
Subgroup	2nd LR %	95% CI	Weight (%)		2nd LR %	95% CI	Weight (%)
Primary diagnosis							
IBC	15.5	9.9 – 22.0	44.34		8.7	4.6 – 13.8	44.62
IBC and DCIS	15.7	11.2 – 20.8	55.66		11.7	6.5 – 18.2	55.38
Propensity analysis performed							
Yes	16.0	11.4 – 21.1	7.82		5.0	2.8 - 7.6	11.80
No	15.7	11.8 – 20.8	92.18		11.1	7.3 - 15.6	88.20
Study design							
Comparative	19.6	15.5 - 24.0	53.16		9.6	6.3 – 13.5	94.25
Single-arm	11.37	6.5 – 17.2	46.84		23.1	16.0 – 31.7	5.75
Concomitant radiotherapy*							
Yes	9.6	5.0 – 15.3	43.38		17.9	12.3 - 24.9	5.92
No	25.5	16.3 - 35.9	5.57		13.1	9.1 – 17.7	11.52
In selected patients	16.1	13.2 - 19.3	24.28		5.61	3.0 - 8.8	33.92
Not reported	23.9	17.4 – 31.1	26.77		12.4	7.3 - 18.5	48.64
Overall	**15.7**	**12.1 - 19.7**	**100.0**		**10.3**	**6.9 - 14.3**	**100.0**

rBCS: repeat breast conserving surgery, LR: local recurrence, 95% CI: 95% Confidence Intervals, IBC: invasive breast cancer, DCIS: ductal carcinoma in situ**, ***Use and type of repeat radiotherapy for the management of IBCR was not consistently reported and therefore analysis could not be stratified based on specific details.

Table 3. Pooled overall 5-year survival rates with separate subgroup analyses across all studies (single-arm and comparative).

	rBCS			Salvage mastectomy		
Subgroup	%	95% CI	Weight (%)	%	95% CI	Weight (%)
Primary diagnosis						
IBC	80.73	76.0 - 85.4	56.32	75.5	70.0 - 81.0	62.55
IBC and DCIS	91.2	88.6 - 93.7	38.72	81.8	71.8 – 91.8	32.20
DCIS	86.5	84.4 - 88.4	4.96	87.0	85.0 – 88.9	5.25
Propensity analysis performed						
Yes	87.1	81.3 - 92.9	26.63	77.6	74.0 - 90.5	28.42
No	84.0	80.4 - 87.6	73.37	76.5	71.1 - 81.9	71.58
Study design						
Comparative	82.3	78.4 - 86.2	63.64	77.6	73.3 - 81.9	86.11
Single-arm	89.7	86.6 - 92.8	36.36	82.8	68.7 - 96.9	13.89
Concomitant radiotherapy*						
Yes	90.2	87.2 - 93.2	36.81	87.3	83.4 - 91.1	9.45
No	82.8	77.8 - 94.2	8.10	75.7	69.7 - 81.8	8.26
In selected patients	81.9	77.1 - 86.7	35.49	78.4	73.3 - 83.5	55.34
Not reported	84.2	74.2 - 94.2	19.60	78.8	73.1 - 84.6	26.95
Overall	**86.8**	**83.4 - 90**	**100.0**	**79.8**	**74.7 - 84.5**	**100.0**

rBCS: repeat breast conserving surgery, OS: overall survival, 95% CI: 95% Confidence Intervals, IBC: invasive breast cancer, DCIS: ductal carcinoma in situ, *****Use and type of repeat radiotherapy for the management of IBCR was not consistently reported and therefore analysis could not be stratified based on specific details.

Table 4. GRADE assessment and recommendations

Question: Repeat breast conserving surgery compared to salvage mastectomy for management of local breast cancer recurrence in patients previously treated with breast conserving surgery and radiotherapy

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	repeat breast conserving surgery	salvage mastectomy	Relative (95% CI)	Absolute (95% CI)		
Second local recurrence after surgical treatment for recurrent breast cancer previously treated with breast conserving surgery and radiotherapy (follow-up: median 72 months)												
17	observational studies	serious[a]	serious[b,c]	not serious	serious[b]	all plausible residual confounding would suggest spurious effect, while no effect was observed	186/941 (19.8%)	218/2024 (10.8%)	**RR 2.103** (1.535 to 2.883)	**119 more per 1 000** (from 58 more to 203 more)	⨁◯◯◯ Very low	IMPORTANT
Overall survival after surgical treatment for recurrent breast cancer previously treated with breast conserving surgery and radiotherapy (follow-up: median 72 months)												
20	observational studies	serious[a,b,c]	serious[b,c]	not serious	serious[b]	all plausible residual confounding would suggest spurious effect, while no effect was observed	3368/3932 (85.7%)	7605/8968 (84.8%)	**RR 1.040** (1.003 to 1.079)	**34 more per 1.000** (from 3 more to 67 more)	⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval; **RR:** risk ratio

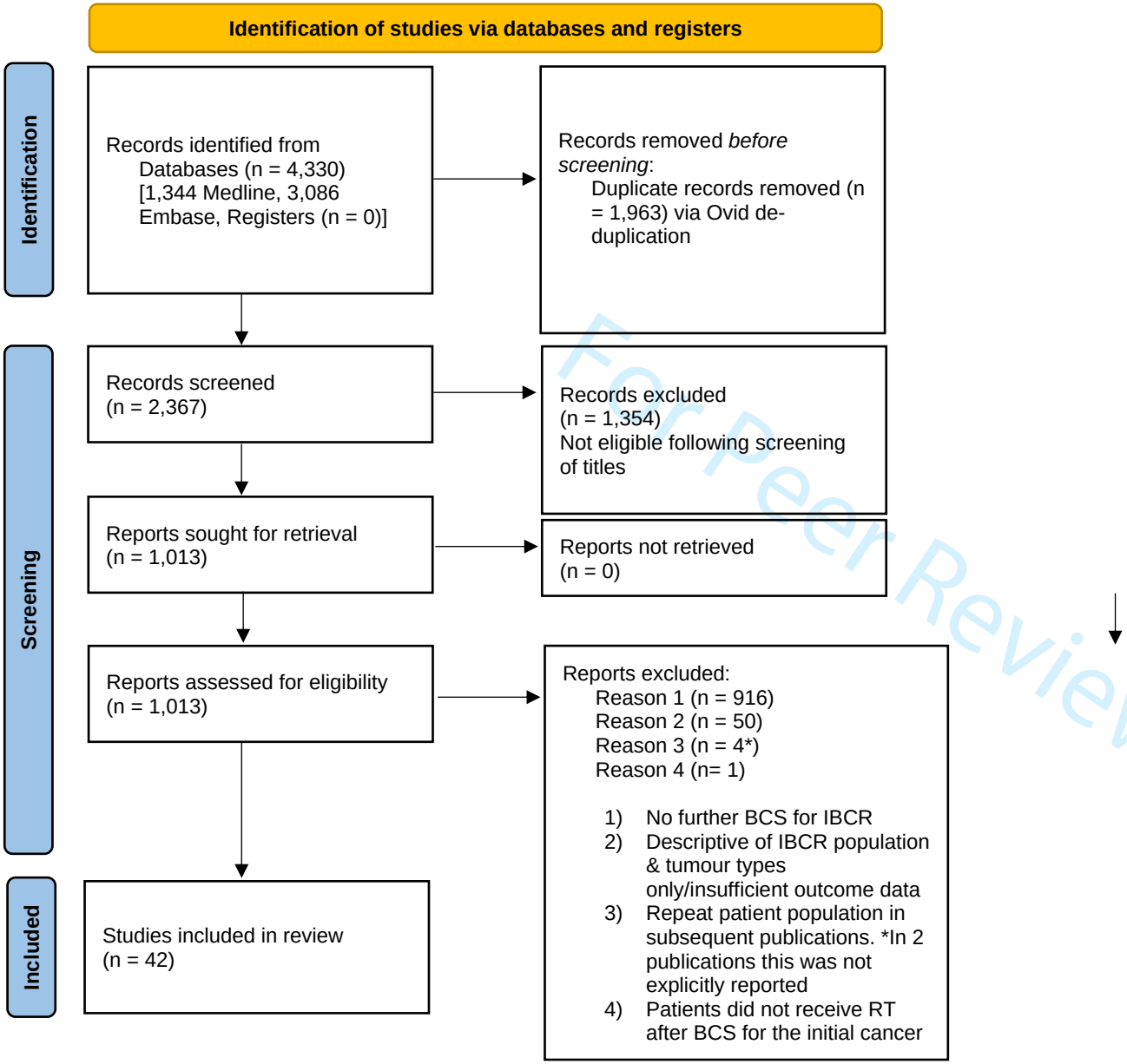
Explanations

a. Retrospective single-arm and comparative studies, mostly without matching.

b. Source studies do not accurately report on primary and recurrent tumor biology

c. Outcomes in available studies are often expressed as rates and not Hazard Ratios

Meta-analysis of Observational Studies in Epidemiology



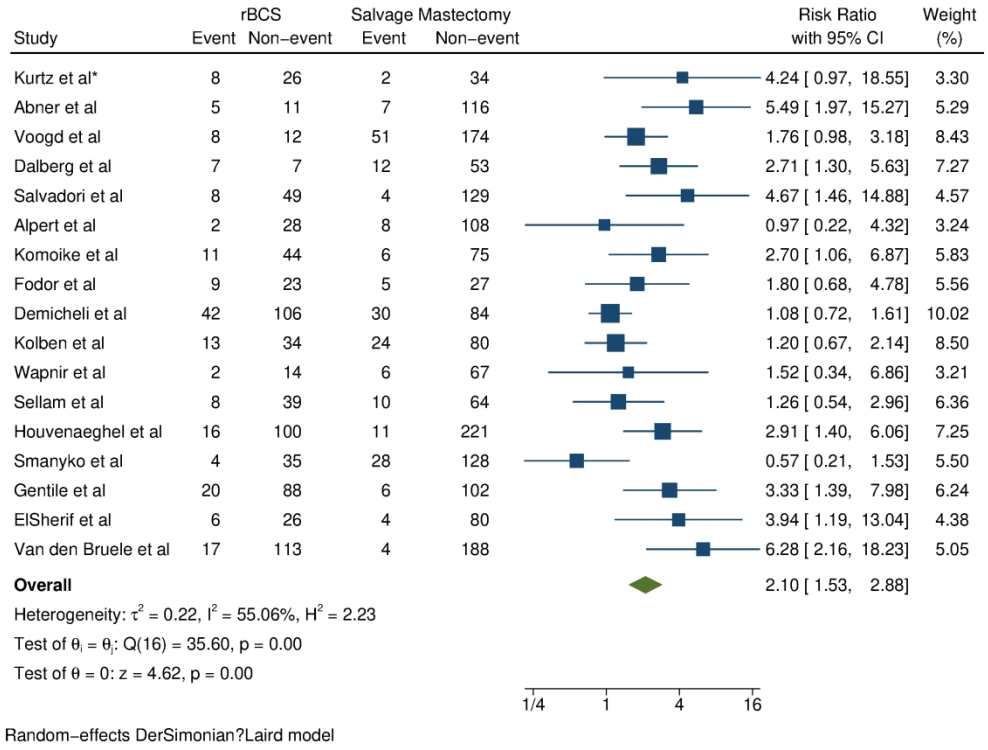


Figure 2. Forest plot of studies comparing repeat breast conserving surgery versus salvage mastectomy for second local recurrence. * Study by Kurtz et al International journal of radiation oncology, biology, physics 1990

571x433mm (118 x 118 DPI)

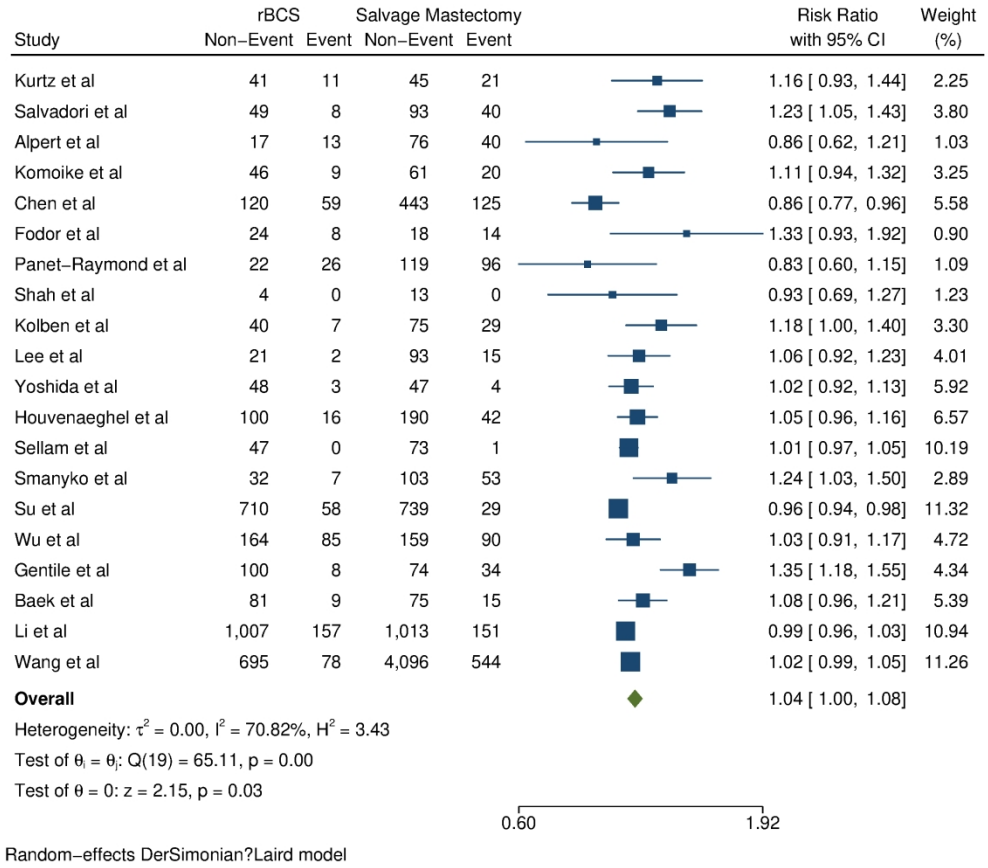


Figure 3. Forest plot of studies comparing repeat breast conserving surgery versus salvage mastectomy for overall survival.

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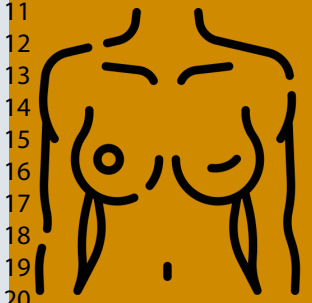
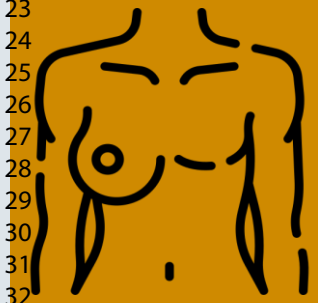
A Systematic Review and Meta-analysis on the role of Repeat Breast Conserving Surgery for the Management of Ipsilateral Breast Cancer Recurrence

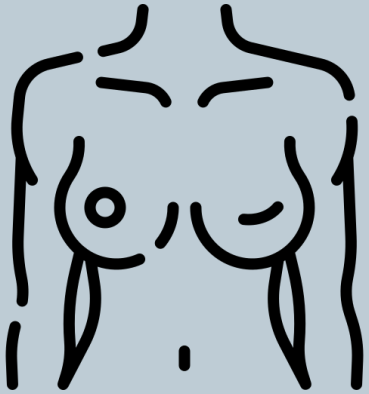
Breast conserving surgery standard of care for early-stage breast cancer



5-15% ipsilateral breast cancer recurrence (IBCR)



Mastectomy standard surgical treatment for local recurrence (LR)



Systematic Review & Meta-analysis of oncological outcomes of repeat breast conserving surgery (rBCS) for IBCR

42 observational studies

17 studies rBCS vs Mastectomy 2nd LR

20 studies rBCS vs Mastectomy Overall Survival (OS)

(PROSPERO #CRD42021286123)

Studies' quality: moderate to low

RR for 2nd LR 2.103 (95% CI: 1.535-2.883) after rBCS

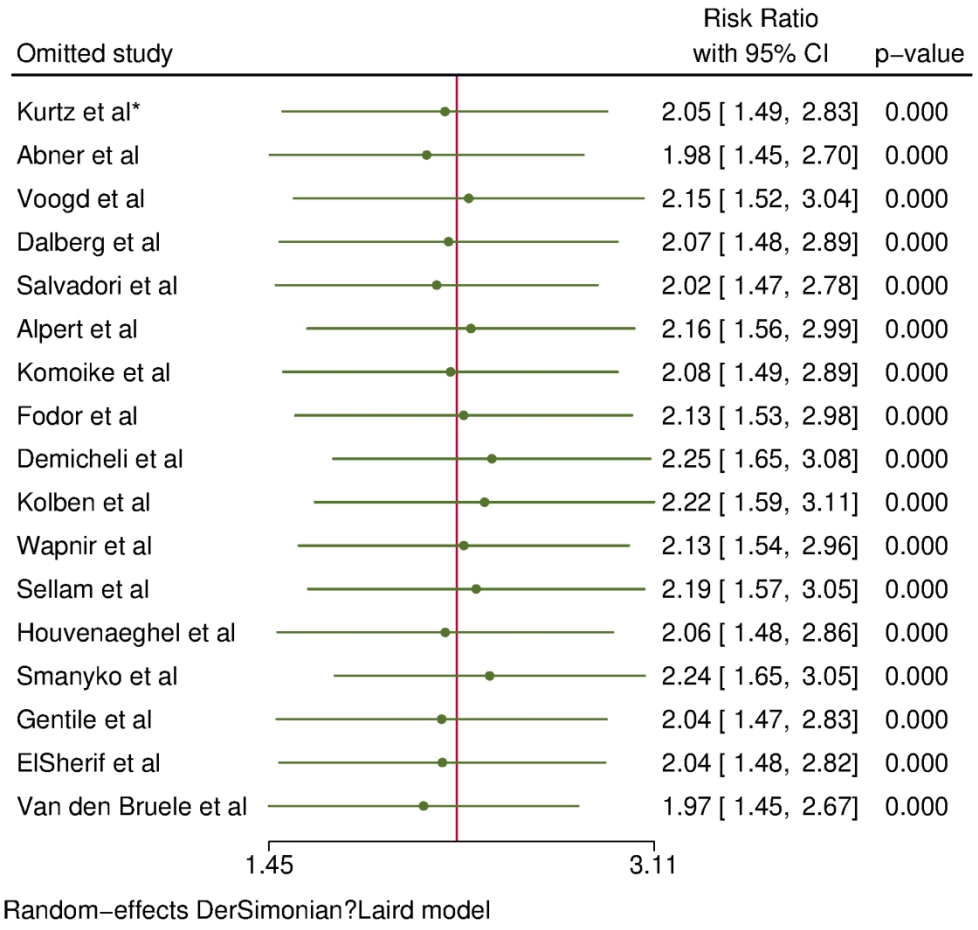
Repeat radiotherapy protective effect on 2nd LR

RR for OS 1.04 (95% CI: 1.003-1.079) after rBCS

GRADE: very low certainty of evidence

Tollan et al. *Ann Surg Oncol*.
Visual Abstract @CjSivarajan for @AnnSurgOncol

ANNALS OF SURGICAL ONCOLOGY



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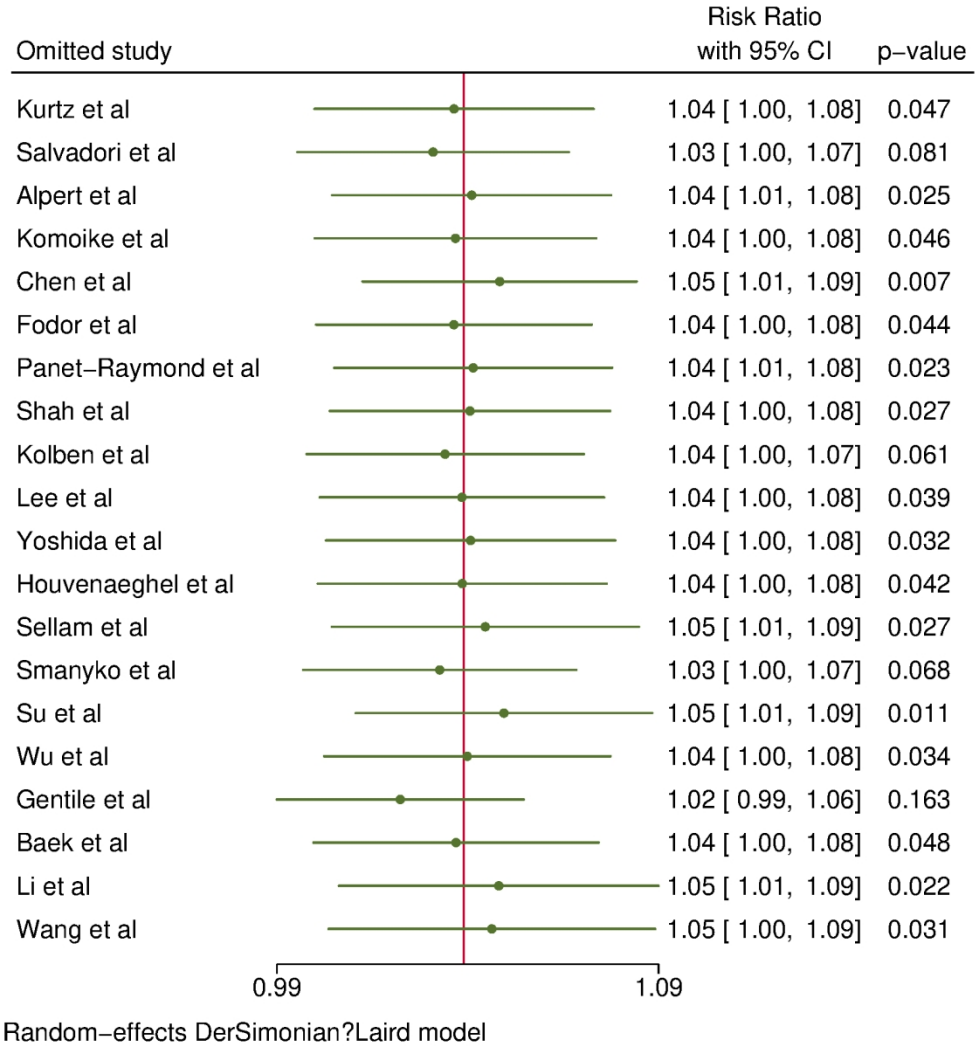

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Supplement, Table S1. Subgroup and meta-regression analyses of comparative studies on five-year overall survival rates.

Subgroup analysis					Meta-regression analysis		
	Risk Ratio	95% CI	p-value		coefficient b	95% CI	p-value
Primary							
DCIS	0.994	0.963 - 1.026	0.714		0.0721	-0.0017 - 0.1458	0.056
IBC	1.015	0.968 - 1.064	0.536				
IBC and DCIS	1.119	1.019 -1.230	0.019				
Propensity score matching							
No	1.045	0.995 - 1.097	0.077		0.0098	-0.0696 - 0.1107	0.655
Yes	1.039	0.979 - 1.103	0.210				
Concomitant radiotherapy							
Yes	1.107	0.841 - 1.458	0.467		0.0019	-0.0274 - 0.0312	0.898
No	1.156	0.931 - 1.436	0.189				
In selected patients	1.029	0.990 - 1.069	0.152				
Not reported	1.045	0.930 - 1.174	0.458				
Overall	1.040	1.003 - 1.079	0.032				

Title Page

A systematic review and meta-analysis on the role of repeat breast conserving surgery for the management of ipsilateral breast cancer recurrence

Running head: Redo breast conserving surgery for recurrence

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Synopsis

Repeat breast conserving surgery (BCS) for the management of ipsilateral breast cancer recurrence, in patients previously treated with BCS and radiotherapy, may be associated with increased risk of local recurrence but may not have an adverse effect on overall survival.

Abstract

Introduction: The standard surgical management of ipsilateral breast cancer recurrence (IBCR) in patients previously treated with breast conserving surgery (BCS) and radiotherapy is mastectomy. Recent international guidelines provide conflicting recommendations. The aim of this study was to perform a systematic literature review and meta-analysis of the oncological outcomes in patients with IBCR treated with repeat BCS (rBCS).

Methods: Medline and EMBASE databases were searched for relevant publications in English language with no date restrictions. All relevant studies providing sufficient data to assess oncological outcomes [second local recurrence (LR) and overall survival (OS)] of rBCS for the management of IBCR after previous BCS and radiotherapy were included (PROSPERO registration CRD42021286123).

Results: 425 observational studies met the criteria and were included in the analysis. The pooled second LR rate after rBCS was 15.78% (95%CI:12.13-19.76) and after salvage mastectomy was 10.3% (95%CI:6.9-14.3)~~10.8% (95%CI:7.4-14.8)~~. On meta-analysis of comparative studies (n=178), the Risk Ratio (RR) for second LR following rBCS compared to mastectomy was 2.103 (95%CI:1.535-2.883, p<0.001, I^2=55.1%)~~1.950 (95%CI:1.411-2.695, p<0.001, I^2=60.1%)~~. Repeat radiotherapy had a protective effect (coefficient:-0.317;95%CI:-

0.596,-0.038, p=0.026, I^2=40.4%~~coefficient: -0.333;95%CI:-0.617,-0.049, p= 0.022, I^2=46.6%~~) for second LR. Pooled 5-year OS was 86.~~7~~8% (95%CI:83.4-~~89.6~~90.0) vs 79.~~3~~8% (95%CI:74.~~2~~7-8~~3~~4.~~95~~) for rBCS and salvage mastectomy respectively. Meta-analysis of comparative studies (n=20~~21~~) showed a small OS benefit in favour of rBCS (RR:1.~~060~~040;95%CI:1.~~018~~003-1.~~10~~079, p~~<~~=0.~~001~~032, I^2=~~77~~70.~~51~~8%). Overall evidence certainty~~quality ranged from moderate to~~ was very low.

Conclusions: This ~~systematic review and~~ meta-analysis ~~further~~ suggests~~supports~~ rBCS could be~~as~~ considered as an option for the management of IBCR in patients previously treated with BCS and radiotherapy. Shared-decision making, appropriate patient selection and individualized approach are important for optimal outcomes.

Introduction

Management of breast cancer has evolved significantly over the past decades, moving away from radical procedures towards less aggressive surgery. Breast conserving surgery (BCS), when combined with radiotherapy (RT), has been shown to confer equivalent oncological outcomes compared to mastectomy (1-3) and has been established as standard of care, when technically feasible, especially for patients with early-stage disease.

Advances in the multimodality management of breast cancer have led to improved oncological outcomes and reduced local recurrence rates (4). However, despite these advances 5-15% (5-7) of patients treated with BCS and RT may still experience ipsilateral breast cancer recurrence (IBCR). The surgical management of IBCR has traditionally been mastectomy. This has been supported by international recommendations including the National Comprehensive Cancer Network (NCCN) Guidelines (8). However, a number of studies have suggested that repeat BCS (rBCS) with or without repeat RT (rRT) may be an alternative (9-12). In one of the first reports, Kurtz et al. (9) showed that rBCS without rRT in a selected cohort of patients, was associated with acceptable oncological outcomes as demonstrated by overall survival (OS). Similar results in terms of OS and breast cancer specific survival (BCSS) have also been shown in more recent studies (13-16), although there are also publications reporting opposite results (17, 18). In addition, the reported local recurrence rates after rBCS have been variable (11, 15, 18-20). However, despite the conflicting data, there has been a trend towards increasing utilization of rBCS (15, 21) and recently the St. Gallen International Consensus guidelines also supported rBCS as an option, no longer considering mastectomy as absolutely obligatory for the management of IBCR (22) .

The aim of this study was to perform a systematic review of the literature and meta-analysis of the oncological outcomes in patients treated with rBCS with or without rRT for the management of IBCR following previous BCS and radiotherapy.

Methods

Search strategy and Inclusion criteria

A systematic review of the literature was conducted in Medline and EMBASE databases, using the search terms “ipsilateral breast tumour recurrence”,” ipsilateral breast cancer recurrence”, ”ipsilateral breast tumor recurrence”, “ipsilateral recurrent breast cancer”, “IBTR”, “local recurrence + breast cancer + breast conserving surgery + mastectomy”. No chronological limitations were stipulated. In the absence of dedicated randomized controlled trials, prospective and retrospective comparative and non-comparative cohort studies, cross-sectional studies reporting on second local recurrence (LR) and / or survival after rBCS for IBCR following previous BCS and RT were considered eligible. Studies that did not clearly specify whether the reference population had initially been treated for only DCIS, or both DCIS and invasive breast cancer (IBC), were included in the primary analysis. Respectively, we registered whether data regarding the type of in-breast recurrence (IBC or DCIS) was reported separately or cumulatively. If more than one reports on the same patients were available, only the most recent was included.

Data extraction

Data extraction was performed independently by two authors (CJT and EP) in a preformed Microsoft Excel© working sheet.~~, after two training sessions with the senior authors (AK and MKT) in a random sample of five studies, to standardize the extraction procedure.~~ The data extraction procedure for the whole dataset (including all eligible studies) was standardised during two training sessions with the senior authors (AK and MKT) using a random sample of five studies. Disagreement was resolved by group consensus. The study methodology was registered with PROSPERO International prospective register of systematic reviews (CRD42021286123, https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021286123).

Quality assessment

The Newcastle-Ottawa-Scale (NOS) (23) for observational studies, as assessed by two authors (EP, AK) was used to evaluate the quality of the included studies. Publication bias was assessed with funnel plots and the Egger's test for small studies. Following analyses and critical appraisal, the GRADE approach (24) was used to assess the strength of evidence and recommendations by two authors (AV and AK). Subsequently, knowledge gaps and research priorities were defined.

Statistical analyses and reporting

Rates of a second LR and OS at 5 years for rBCS and salvage mastectomy were calculated separately, by pooling the outcomes from single-arm and comparative studies. Subgroup analyses were performed depending on whether the reference population had initially been treated for only DCIS, both DCIS and IBC or IBC only. Subgroup analyses were also undertaken to define the effect of study design (comparative or single-arm), propensity score matching and the effect of radiotherapy, regardless of the technique that was utilized. The median follow-up was also extracted. Meta-analyses of comparative studies were also performed. ~~If preliminary subgroup analyses had denoted any difference, meta-regression for the respective factor was undertaken.~~ Additionally, leave-one-out meta-analyses of comparative studies were performed, to allow for the identification of studies with exaggerated effect sizes and guide further subgroup and meta-regression analyses. As literature search was expected to retrieve observational studies, the use of a random-effects model using the DerSimonian Laird method was decided *a priori*. For source studies directly reporting odds ratio (OR), risk ratio (RR) or hazard ratio (HR), the adjusted analyses and Kaplan-Meier curves were considered for data extraction and calculation of 5-year second LR and OS (25, 26). Effect sizes were reported with 95% confidence intervals (95% CI). Study heterogeneity was assessed with the I^2 statistic.

The manuscript was prepared according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines (27). Stata v17 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC.) was used for all statistical analyses.

Results

Study selection and characteristics

The literature search, after the removal of duplicates, retrieved 425 studies, with 42 24 examining outcomes after a primary IBC, 2 17 reporting on both IBC and DCIS and 1 on DCIS only (MOOSE flowchart presented in Figure 1). Twenty-eightnine studies examined outcomes on both LR and OS, 9 on OS only and 75 on LR only. Study characteristics and NOS scores are shown in Table 1. On two occasions, it was not explicitly reported by the authors if the study population was the same as in another publication by the same group (28, 29). Therefore, all the studies were included in Table 1, but only the most recent studies providing data following propensity score matching were included in the meta-analysis (19, 30).

Second Local Recurrence

Source studies reporting on a second LR had a median follow-up ranging from 24.5 to 165.6 months [median of medians 7062 months, interquartile range (IQR): 52-732.5]. The overall pooled incidence of a second LR after rBCS was 15.78% (95% CI: 12.13-19.76) and after salvage mastectomy was 10.38% (95% CI: 76.49-14.38). Despite the fact these were separately pooled outcomes without comparison, the confidence intervals were numerically overlapping, suggesting that the difference may not be significant, but study heterogeneity was high. The results of the subgroup analyses across all included studies are summarized in Table 2. Overall, among patients treated with rBCS, those who received rRT had the lowest pooled second LR rate compared to the other subgroups (9.68%, 95% CI: 5.08-153.38).

A total of 178 studies provided comparative data on second LR after rBCS and salvage mastectomy. The median follow-up ranged from 30 to 165.5 months (median of medians 72 0.5 months, IQR: 525.5-796). In comparative studies, the pooled second LR rate was higher after rBCS (19.63%, 95% CI: 15.5--243.02) versus after salvage mastectomy (9.610.9%, 95% CI: 67.38 --13.59) (Table 2). On meta-analysis, rBCS was associated with a significantly increased risk of second LR [Risk Ratio (RR) = 21.103950; 95% CI: 1.535411 - 2.883695, p < 0.001, I^2= 5560.1%), as shown in Figure 2. Leave-one-out meta-analysis (Supplement, Figure S1) did not demonstrate any differences. Only concomitant radiotherapy retained a protective effect in meta-regression analysis (coefficient: -0.31733; 95% CI: -0.596617, -0.03849, p= 0.0262, I^2= 406.46%). No publication bias or small-studies effect was detected (Egger's test beta1: 1.5400.11, p= 0.103917).

Overall Survival

Pooled OS rates and subgroup analyses for patients treated with rBCS or salvage mastectomy are presented in Table 3. Overall, in at a median follow-up ranging from 30 to 168 months (median of medians 656 months, IQR: 575 - 739), the pooled 5-year OS rate was 86.78% (95% CI: 83.4 - 89.690.0) after rBCS and 79.38% (95% CI: 74.2 7 - 8384.95) after salvage mastectomy. Subgroup analyses (Table 3) did not demonstrate any factor that correlated with difference in outcomes for each group (rBCS or salvage mastectomy). Meta-analysis of comparative studies (n=2021) showed a small OS benefit in favour of rBCS (RR: 1.060040, 95% CI: 1.018 003 - 1.104079, p <= 0.001032, I^2= 7770.518%) (Figure 3). The median follow-up in these studies

ranged from 42 to 168 months (median of medians 7~~1.5~~2 months, IQR: 59 ~~–~~ – ~~130~~126.6). Leave-one-out meta-analysis (Supplement, Figure S2) showed that the omission of four studies (one at a time) would result in a difference, despite that the numeric value of the RR was not significantly affected. Subsequent subgroup and meta-regression analysis was performed (Supplement, Table S1). Radiotherapy did not affect the outcome on meta-regression analysis (coefficient: 0.~~026~~0019; 95% CI: -0.~~011~~0274, 0.~~064~~0312, p= 0.~~170~~898, I^2= ~~78~~70.~~5~~8%). With regards to primary tumor, studies reporting on both DCIS and IBC reported survival benefit for rBCS (RR: 1.119; 95% CI: 1.019 – 1.230, p=0.019), but this effect was not retained on meta-regression analysis (coefficient: 0.0721; 95% CI: -0.0017, 0.1458, p=0.056). When looking into publication bias, the Egger's test detected small-studies effect (Egger's test beta1: 0.93, p= 0.041).~~No publication bias or small-studies effect was detected (Egger's test beta1: 0.94, p= 0.062).~~

Study quality and strength of recommendations

The median NOS score was 8.5 (IQR: 7-9). No correlation was identified between the timing of the study publication and the median NOS, suggesting that study quality has not improved over the years.

The GRADE recommendations from the meta-analysis are summarized in Table 4. The certainty of evidence was very low, due to serious risk of bias (mainly selection), inconsistency and imprecision. The main reasons for that were deemed to be the design of available studies (retrospective single-arm and comparative, mostly without matching or consecutive patients),

the fact that most studies reported outcomes in form of rates, rather than effect sizes such as hazard ratios that are much more appropriate for time-to-event outcomes and, finally, that most source studies did not accurately report on primary and recurrent tumour biology as well as adjuvant ~~systemic~~ therapy, for example use of radiotherapy after BCS for the management of the initial cancer or radiotherapy for the management of the recurrence, which may play pivotal role in oncological outcomes. These factors constituted the main knowledge gaps and, thus, research priorities for future studies.

Discussion

Mastectomy has traditionally been considered as the standard of care for the management of IBCR. This has been recommended by national and international guidelines, including the NCCN guidelines (8). Reasons for this practice include the concerns about rRT and also the fact that IBCR has been associated with poor prognosis (31, 32), potentially supporting the argument for more aggressive local treatment. However, salvage mastectomy does not eliminate the risk of local or distant recurrence (33, 34) and there is increasing data supporting the feasibility of rRT (16, 35). In addition, advances in multidisciplinary management of breast cancer, including systemic therapy and radiotherapy options, and a general trend towards surgical de-escalation have likely contributed to the increasing use of rBCS as part of an individualized, tailored approach (15, 21). This is also now supported by the St. Gallen International Consensus Guidelines (22). Avoidance of mastectomy, if oncologically safe, could be associated with improved patient satisfaction in terms of cosmetic outcome and quality of life (36, 37) apart

from cost and resource implications for healthcare providers. However, the existing data do not conclusively support rBCS or salvage mastectomy in terms of oncological outcomes, with a number of studies reporting opposite results (9-13, 17-20, 29, 38, 39).

The present systematic literature review showed variable second LR rates after rBCS. The overall pooled second LR rate was found to be 15.~~8~~7% after rBCS compared to 10.~~8~~3% after salvage mastectomy. However, it should be noted that the included studies are markedly heterogeneous, and there was not a standardized multidisciplinary treatment protocol for the management of IBCR. In addition, it is important to highlight that in a number of studies, a proportion of patients did not receive RT for the management of the primary cancer, with not enough data provided to allow stratification for this in the analysis. On meta-analysis, rBCS was associated with a significantly higher RR for second LR (RR= 2.103~~1.950~~), albeit with moderate study heterogeneity. This RR is similar to that reported in a recent meta-analysis (RR = 1.87) (40). The small observed difference may be explained by the fact that the present meta-analysis included 1~~8~~7 studies providing data on second LR compared to 13 studies in the meta-analysis by Mo et al (40).

On sub-group analysis, the lowest second LR rate among patients treated with rBCS was observed in those receiving rRT (9.6~~8~~%). The protective effect of rRT was also demonstrated in meta-regression analysis. This finding is in line with previous reports highlighting the potentially important role of rRT in improving local control after rBCS for IBCR (35, 40). This is an important consideration when individualizing the management plan especially as a number of rRT options, for example brachytherapy (41-43), intraoperative radiotherapy (44, 45) and external beam radiotherapy (16) have been shown to be associated with acceptable toxicity profile. In the

RTOG 1014 prospective Phase 2 clinical trial, 3-dimensional conformal external beam partial breast rRT after rBCS for IBCR in patients previously treated with BCS and RT was associated with low risk of second LR (5%) and late Grade 3 adverse events in only 7% of the cases while there were no Grade 4 or higher reported adverse events (16). Tolerability of rRT has also been supported by the ~~including~~ results from a recent meta-analysis (35).

Despite the finding that rBCS may be associated with a higher risk of second LR, which was ~~almost~~ two-fold higher based on the results of the present meta-analysis, it may not have a negative impact on survival. A number of retrospective studies have shown that OS was not inferior or was even improved in patients treated with rBCS with or without rRT compared to those treated with salvage mastectomy (13, 15, 19, 29, 30, 43, 46). An analysis of the Surveillance, Epidemiology, and End Results (SEER) database including data from 1998 to 2013 showed no significant difference in terms of OS and BCSS in patients treated with rBCS or salvage mastectomy (14). However, another analysis of the SEER database looking into data from 1973 to 2003 showed different results (17). In this study the authors found that rBCS was associated with worse OS and BCSS and that rRT had a protective effect in terms of OS. Although, there is no clear explanation for the discordant findings, a potential reason may be the different time periods, as multidisciplinary breast cancer management has significantly evolved over the past decades. A recent meta-analysis by Mo et al also supports the findings that rBCS may not be associated with worse OS (40). The results of the present meta-analysis showed a ~~small~~ marginal benefit in OS in favour of rBCS (RR: 1.0~~6~~40). The difference between the two meta-analyses may be explained by the different number of included studies (8 versus 20~~21~~ in the present analysis). The median NOS of the studies (10-12, 34, 38, 43, 46, 47) included

in the meta-analysis by Mo et al (40) is 9 (IQR: 7-9), and the median NOS of the studies in the present meta-analysis is also 9 (IQR: 8-9), with the additional ~~13~~ 12 studies having a median NOS of 9 (IQR: ~~8.5~~9-9). It has to be noted though that a small-study effect was found, underlining potential publication bias. While such an effect was not detected in the meta-analysis by Mo et al (40) cautiousness is required due the small number of included studies.

Although rRT was found to have a protective effect in terms of local control and has previously been shown to have a role in improving OS (17, 46), in the present meta-analysis, OS was not affected by rRT on meta-regression analysis. However, these results should be interpreted with caution as the included studies were substantially heterogeneous, and the effect size had marginal significance.

The findings of this meta-analysis suggest that although rBCS may be associated with higher risk of subsequent LR, this may not have a negative impact on OS. This ~~further supports~~suggests that rBCS may be an alternative option in the context of individualized management of IBCR in line with the St. Gallen International Consensus Guidelines (22), especially for women who want to preserve their breast, following careful consultation about the currently accepted standard recommendation of salvage mastectomy as per NCCN (8) guidelines. However, appropriate patient selection for such an approach would be of paramount importance. In the first report of rBCS for IBCR, Kurtz et al suggested an algorithm for patient selection including tumour size < 2 cm, no fixation of the cancer on the skin or chest wall, clinically node negative status and no significant RT changes (9). Other important parameters include disease free interval, and the size and histopathology of the recurrence as these have been shown to be independent prognostic factors of OS (46). Gentilini et al have suggested that patients with small (≤ 2 cm)

late (> 48 months) IBCR would be the ideal candidates for rBCS (48). Similar selection criteria have been proposed by the German Society of Radiation Oncology (DEGRO) expert panel suggesting that rBCS can be considered in patients ≥ 50 years with unifocal, small (< 2 – 3 cm) IBCR, ≥ 48 months after primary treatment who are willing to undergo rBCS and this is technically feasible (49). The St. Gallen International Panel suggests that rBCS can be considered for low-risk recurrent cancers with favourable tumour biology (small, Luminal A) for which rRT may not be required or for IBCR > 5 years after primary treatment (22). The common denominator of these suggested algorithms for patient selection is an individualized approach mainly based on tumour biology and anatomical stage. The role of multidisciplinary management of IBCR, with systemic therapy (endocrine therapy, chemotherapy or targeted therapy for example anti-HER2) with or without rRT cannot be overemphasized ~~for the success of this approach~~. The potential effect of such recommendations could not be assessed in this meta-analysis due to lack of studies providing data that would allow such an analysis.

Although, rBCS is increasingly being used for the management of IBCR (15, 21), and de-escalated tailored therapeutic approaches are favoured within modern multidisciplinary working, the quality of the studies providing data on oncological outcomes of rBCS does not appear to improve over time as demonstrated by the NOS assessment of the studies included in this meta-analysis. The low quality of available source studies constitutes the limitation of this meta-analysis, as potentially uncontrolled biases, lack of standardized reports of treatment modalities and outcomes of interest increase heterogeneity and mandate a careful interpretation of the results. This fact was illustrated in the outcomes of the GRADE approach

and highlights the importance of collaboration across different specialties to set up prospective research studies, designed to address the knowledge gaps highlighted.

Conclusions

Repeat BCS may ~~be considered an option for~~have a role in the management of IBCR in patients previously treated with BCS and RT. This should be based on individualized assessment of tumour and patient factors, and multidisciplinary working to develop a tailored management plan. Further research in this field is warranted to allow optimal patient selection and address existing knowledge gaps.

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Figure legends

Figure 1. Flowchart of systematic review and meta-analysis of observational studies in epidemiology. *2 studies were not explicitly described by the authors if they represented same population as other publications

Figure 2. Forest plot of studies comparing repeat breast conserving surgery versus salvage mastectomy for second local recurrence. * Study by Kurtz et al *International journal of radiation oncology, biology, physics 1990*

Figure 3. Forest plot of studies comparing repeat breast conserving surgery versus salvage mastectomy for overall survival.

Supplemental Figure 1. Leave-one-out meta-analysis forest plot of studies comparing repeat breast conserving surgery versus salvage mastectomy for second local recurrence

Supplemental Figure 2. Leave-one-out meta-analysis forest plot of studies comparing repeat breast conserving surgery versus salvage mastectomy for overall survival.

Tables

Table 1. Characteristics of Included Studies.

													Newcastle-Ottawa Scale			
Reference Number	**Author**	**Year**	**Primary diagnosis**	**IBCR diagnosis**	**Study Outcome**	**Total number of patients**	**Previous breast RT after BCS**	**Previous RT Axilla / Regional nodes after BCS**	**Number of patients rBCS**	**rRT breast after rBCS**	**rRT axilla / Regional nodes after rBCS**		**Selection**	**Comparability**	**Outcomes**	**Total**
(9)	Kurtz et al	1988	IBC	NS	OS	118	Yes	Yes	52	No	No		3	1	3	**7**
(50)	Kurtz et al	1990	IBC	NS	LR	50	Yes	Yes	50	Yes* (n=11) EBR (n=7) and BT (n=4)	NS		4	0	3	**7**
(51)	Abner et al	1993	IBC	IBC and DCIS	LR, OS	139	Yes	Yes*	16	No	No		3	1	3	**7**
(52)	Voogd et al	1998	IBC	IBC and DCIS	LR	266	Yes	NS	20	Yes*	NS		4	0	2	**6**
(18)	Dalberg et al	1998	IBC	IBC and DCIS	LR	85	Yes* (n=67)	NS	14	Yes* (n=2)	NS		4	0	3	**7**
(10)	Salvadori	1999	IBC	NS	LR, OS	197	Yes	NS	57	NS	NS		4	0	3	**7**

	et al															
(53)	Deutsch et al	2002	IBC and DCIS	IBC and DCIS	LR, OS	39	Yes	Yes* (n=3)	39	Yes EBR	NS		3	0	3	**6**
(11)	Alpert et al	2004	IBC and DCIS	IBC and DCIS	LR, OS	146	Yes	Yes*	30	Yes* BT (n=1)	NS		4	1	3	**8**
(54)	Hannoun-Levi et al	2004	IBC and DCIS	IBC and DCIS	LR, OS	69	Yes	NS	69	Yes BT	Yes* (n=49)		4	0	3	**7**
(12)	Komoike et al	2005	IBC	NS	LR, OS	136	Yes*	NS	55	NS	NS		4	1	3	**7**
(34)	Fodor et al	2007	IBC	IBC and DCIS	LR, OS	124	Yes* (n=60)	NS	32	Yes* (n=4)	NS		4	2	3	**9**
(42)	Chadha et al	2008	IBC and DCIS	IBC and DCIS	LR, OS	15	Yes	NS	15	Yes LDR BT	NS		4	0	3	**7**
(38)	Chen et al	2008	IBC	IBC and DCIS	OS	747	Yes	NS	180	Yes* (n=38)	NS		4	2	3	**9**
(55)	Botteri et al	2009	IBC	IBC	LR, OS	282	Yes	Yes*		No	No		4	1	3	**8**
(39)	Panet-Raymond et al	2011	IBC	IBC and DCIS	OS	269	Yes	NS	48	Yes* (n=33)	NS		4	2	3	**9**

(56)	Kauer-Dorner et al	2012	IBC	IBC and DCIS	LR, OS	39	Yes	No	39	Yes PDR brachy-therapy	No		4	1	3	**8**
(48)	Gentilini et al	2012	IBC	IBC	LR, OS	161	Yes	Yes*	161	No	No		4	2	3	**9**
(57)	Shah et al	2012	IBC and DCIS	IBC and DCIS	OS	18	Yes	NS	4	Yes APBI	NS		4	0	3	**7**
(58)	Demicheli et al	2013	IBC	NS	LR	338	Yes*	NS	148	Yes* (n=43)	NS		4	1	3	**8**
(41)	Hannoun-Levi et al	2013	IBC	NS	LR, OS	217	Yes	Yes*	217	Yes LDR (n=27), PDR (n=88), HDR (n=102), BT	NS		4	2	3	**9**
(28)	Ishitobi et al†	2013	IBC	NS	LR, OS	271	Yes* (n=69)	NS	143	Yes* (n=1)	NS		4	2	3	**9**
(20)	Kolben et al	2015	IBC	IBC and DCIS	LR, OS	170	Yes	NS	58	Yes* (n=11)	NS		4	2	3	**9**
(46)	Lee et al	2015	IBC and DCIS	IBC and DCIS	OS	157	Yes* (n=135)	NS	23	Yes* (n=13)	NS		4	2	3	**9**

(30)	Yoshida et al	2016	IBC	NS	OS	271	Yes* (n=133)	NS	149	NS	NS		4	2	3	**9**
(59)	Wapnir et al	2017	IBC	IBC	LR, OS	162	Yes* (n=92)	NS	16	Yes* (n=2)	NS		4	2	3	**9**
(60)	Ishitobi et al	2017	IBC and DCIS	IBC and DCIS	LR, OS	65	Yes	NS	65	No	No		4	2	3	**9**
(47)	Sellam et al	2018	IBC and DCIS	IBC and DCIS	LR, OS	121	Yes	NS	47	Yes* (n=16) EBR-PB (n=15), EBR-WB (n=1)	Yes* (n=1)		4	2	3	**9**
(61)	Houvenaeghel et al	2018	IBC	NS	LR, OS	348	Yes	NS	116	Yes* (n=62) BT (n=62)	NS		4	2	3	**9**
(43)	Smanyko et al	2019	IBC ~~and DCIS~~ and DCIS	IBC and DCIS	LR, OS	195	Yes	NS	39	Yes HDR BT	NS		4	2	3	**9**
(62)	Montagne et al	2019	IBC and DCIS	IBC and DCIS	LR, OS	143	Yes	NS	143	Yes LDR BT (n=26), HDR BT (n=117)	NS		4	2	3	**9**
(63)	Forster et al	2019	IBC and DCIS	IBC and DCIS	LR, OS	19	Yes	Yes*	19	Yes HDR BT	NS		4	1	3	**8**

										(n=11), PDR BT (n=8)						
(64)	Cozzi et al	2019	IBC and DCIS	IBC and DCIS	LR, OS	40	Yes	NS	40	Yes HDR BT	NS		4	0	3	**7**
(17)	Su et al	2019	IBC	NS	OS	5098	Yes* (n=3687)	NS	1050	Yes* (n=259)	NS		4	2	3	**9**
(29)	Sagona et al†	2020	IBC and DCIS	IBC and DCIS	LR, OS	309	Yes* (n=300)	NS	143	Yes* (n=50)	NS		4	1	3	**8**
(65)	Boehm et al	2020	IBC and DCIS	IBC and DCIS	LR, OS	57	Yes* (n=55)	NS	57	Yes IORT	NS		4	0	3	**7**
(16)	Arthur et al	2020	IBC and DCIS	IBC and DCIS	LR, OS	58	Yes	NS	58	Yes 3D-CRT PBI	NS		4	0	3	**7**
(15)	Van den Bruele et al	2021	IBC	IBC and DCIS	LR	322	Yes* (n=258)	NS	130	Yes* (n=41)	NS		4	2	3	**9**
(14)	Wu et al	2020	IBC	NS	OS	2075	Yes	NS	475	Yes* (n=255)	NS		4	2	3	**9**
(19)	Gentile et al	2021	IBC	IBC and DCIS	LR, OS	309	Yes* (n=300)	NS	143	Yes* (n=50)	NS		4	2	3	**9**
(66)	Li et al	2021	DCIS	IBC and DCIS	LR, OS	5344	Yes* (n=2625)	NS	1812	Yes* (n=735)	NS		4	1	3	**9**

(21)	El Sherif et al	2021	IBC and DCIS	IBC and DCIS	LR, OS	113	Yes* (n=86)	NS	32	Yes* APBI (n=10), IORT (n=1), WBRT (n=2)	NS		4	1	3	**8**
(67)	Wang et al	2021	IBC	NS	LR, OS	5413	Yes	NS	773	Yes* (n=124)	NS		4	2	3	**9**
(68)	Chatzikonstantinou et al	2021	IBC and DCIS	IBC and DCIS	LR, OS	20	Yes	Yes*	20	Yes HDR BT	NS		4	0	3	**7**
(13)	Baek et al	2021	IBC and DCIS	NS	OS	335	Yes* (n=303)	NS	155	Yes* (n=24)	NS		4	3	2	**9**

IBCR: ipsilateral breast cancer recurrence, rBCS: repeat breast conserving surgery, RT: radiotherapy, rRT: repeat radiotherapy, IBC: Invasive breast cancer, DCIS: ductal carcinoma in situ, NS: Not specified, OS: overall survival, LR: local recurrence, EBR: external beam radiotherapy, BT: brachytherapy, LDR: low dose rate, PDR: pulse dose rate, HDR: high dose rate, APBI: Accelerated partial breast irradiation, IORT: intra-operative radiotherapy, 3D-CRT: 3D conformal radiotherapy, PBI: partial breast irradiation, WBRT: whole breast radiotherapy. * Proportion of patients did not receive the respective treatment modality, †Study included in the table but not in the final analysis as it was not explicit if it was duplicate patient population.

Table 2. Pooled rates of second local recurrence with separate subgroup analyses across all studies (single-arm and comparative).

	rBCS				Salvage mastectomy		
Subgroup	2nd LR %	95% CI	Weight (%)		2nd LR %	95% CI	Weight (%)
Primary diagnosis							
IBC	15.59	9.9 – 22.012.5 - 19.4	44.3493.65		8.710.8	4.67.4 – 13.84.8	44.62100.0
IBC and DCIS	15.79.7	3.9 - 15.511.2 – 20.8	55.666.35		11.7.	6.5 – 18.2	55.38
Propensity analysis performed							
Yes	16.05.8	11.41.0 – 21.10.6	7.8233		5.0	2.87 - 7.63	11.8076
No	15.7	11.82.2 – 20.819.2	92.1867		11.19	7.3 - 8.4, 15.64	88.204
Study design							
Comparative	19.63	15.5 - 24.03.2	53.1648.68		9.610.9	7.8 - 13.96.3 – 13.5	9489.2518
Single-arm	11.377	67.56 – 17.215.9	46.8451.32		23.13.5	1.6.0 – 31.73.5	5.7510.82
Concomitant radiotherapy*							
Yes	9.68	5.08 – 15.33.8	43.3897		17.9	12.3 - 24.9	5.9210
No	25.58	16.3 - 35.93	5.574.43		13.19.7	96.1 – 17.713.3	110.532
In selected patients	16.17.0	13.24.3 - 19.37	246.2810		5.611	3.0 - 87.82	339.920
Not reported	232.93	17.45.5 – 31.129.2	265.7570		124.4	78.37 - 1820.51	485.6458
Overall	**15.78**	**12.13 - 19.76**	**100.0**		**10.38**	**6.97.4 - 14.38**	**100.0**

rBCS: repeat breast conserving surgery, LR: local recurrence, 95% CI: 95% Confidence Intervals, IBC: invasive breast cancer, DCIS: ductal carcinoma in situ, *Use and type of repeat radiotherapy for the management of IBCR was not consistently reported and therefore analysis could not be stratified based on specific details.

Table 3. Pooled overall 5-year survival rates with separate subgroup analyses across all studies (single-arm and comparative).

	rBCS			Salvage mastectomy		
Subgroup	%	95% CI	Weight (%)	%	95% CI	Weight (%)
Primary diagnosis						
IBC	805.73	82.476.0 - 88.285.4	90.5056.32	77.875.5	73.970.0 - 81.08	95.7562.55
IBC and DCIS	912.20	86.888.6 - 97.393.7	5.8838.72	81.8	71.8 – 91.8	32.20
DCIS	90.086.5	81.984.4 - 95.388.4	3.624.96	83.387.0	74.085.0 – 90.488.9	54.25
Propensity analysis performed						
Yes	87.1	81.3 - 92.9	23.5226.63	76.077.6	70.774.0 - 81.290.5	72.8028.42
No	85.184.0	81.880.4 - 88.387.6	76.4873.37	82.376.5	74.071.1 - 90.581.9	27.2071.58
Study design						
Comparative	84.082.3	80.378.4 - 87.686.2	64.3363.64	77.60	72.873.3 - 81.93	86.117
Single-arm	88.689.7	865.63 - 91.992.8	35.6736.36	82.8	68.7 - 96.9	13.8930
Concomitant radiotherapy*						
Yes	88.690.2	86.087.2 - 931.2	22.9736.81	56.387.3	37.783.4 - 73.691.1	2.579.45
No	89.982.8	86.477.8 - 93.594.2	19.858.10	89.275.7	86.569.7 - 92.081.8	14.828.26
In selected patients	88.481.9	77.15 - 99.386.7	11.2135.49	81.978.4	86.573.3 - 92.083.5	16.0355.34
Not reported	81.484.2	75.674.2 - 87.294.2	45.9719.60	74.178.8	66.173.1 - 82.084.6	68.7226.95

Overall	**86.~~87~~**	**83.4 - ~~89.690~~**	**100.0**		**79.~~38~~**	**74.~~2~~ ~~7~~ - ~~83.984.5~~**	**100.0**

rBCS: repeat breast conserving surgery, OS: overall survival, 95% CI: 95% Confidence Intervals, IBC: invasive breast cancer, DCIS: ductal carcinoma in situ, *Use and type of repeat radiotherapy for the management of IBCR was not consistently reported and therefore analysis could not be stratified based on specific details.

Table 4. GRADE assessment and recommendations

Question: Repeat breast conserving surgery compared to salvage mastectomy for management of local breast cancer recurrence in patients previously treated with breast conserving surgery and radiotherapy

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	repeat breast conserving surgery	salvage mastectomy	Relative (95% CI)	Absolute (95% CI)		
Second local recurrence after surgical treatment for recurrent breast cancer previously treated with breast conserving surgery and radiotherapy (follow-up: median 720.5 months)												
178	observational studies	serious[a]	serious[b,c]	not serious	serious[b]	all plausible residual confounding would suggest spurious effect, while no effect was observed	202186/973941 (1920.8%)	21836/19552024 (1210.18%)	**RR 1.9502.103** (1.411 535 to 2.695883)	**1195 more per 1 000** (from 580 more to 2035 more)	⨁◯◯◯ Very low	IMPORTANT
Overall survival after surgical treatment for recurrent breast cancer previously treated with breast conserving surgery and radiotherapy (follow-up: median 702 months)												
201	observational studies	serious[a,b,c]	serious[b,c]	not serious	serious[b]	all plausible residual confounding would suggest spurious effect, while no effect was observed	34993368/4075 3932 (85.79%)	77197605/9134 8968 (84.58%)	**RR 1.060040** (1.003118 to 1.104079)	**51 34 more per 1.000** (from 15 3 more to 88 67 more)	⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval; **RR:** risk ratio

Explanations

a. Retrospective single-arm and comparative studies, mostly without matching.

b. Source studies do not accurately report on primary and recurrent tumor biology

c. Outcomes in available studies are often expressed as rates and not Hazard Ratios