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ORIGINAL ARTICLE – BREAST ONCOLOGY

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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ABSTRACT

Introduction. The standard surgical management of ipsilateral breast cancer recurrence (IBCR) in patients previously treated with breast-conserving surgery (BCS) and radiotherapy (RT) 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. The MEDLINE and EMBASE databases were searched for relevant English-language publications, 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 RT were included (PROSPERO registration CRD42021286123).

Results. Forty-two observational studies met the criteria and were included in the analysis. The pooled second LR rate after rBCS was 15.7% (95% confidence interval [CI] 12.1–19.7), and 10.3% (95% CI 6.9–14.3) after salvage mastectomy. On meta-analysis of comparative studies ($n = 17$), the risk ratio (RR) for second LR following rBCS compared with mastectomy was 2.103 (95% CI 1.535–2.883; $p < 0.001$, $I^2 = 55.1\%$). Repeat RT had a protective effect (coefficient: − 0.317, 95% CI − 0.596 to − 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) and 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 favor 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 RT. Shared decision making, appropriate patient selection, and individualized approach are important for optimal outcomes.

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 with 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 (LR) 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]

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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 LR 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 RT.

METHODS

Search Strategy and Inclusion Criteria

A systematic review of the literature was conducted in the 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 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 ductal carcinoma in situ (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 report on the same patients was 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© (Microsoft Corporation, Redmond, WA, USA) working sheet. The data extraction procedure for the whole dataset (including all eligible studies) was standardized 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 Grading of Recommendations, Assessment, Development and Evaluations [GRADE] approach[24] was used to assess the strength of evidence and recommendations by two authors (AV and AK). Knowledge gaps and research priorities were subsequently 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 RT, 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 to guide further subgroup and meta-regression analyses. As the 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 (CIs). Study heterogeneity was assessed using the I^2 statistic.

This 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

After the removal of duplicates, the literature search 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 is presented in Fig. 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 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 10.3% (95% CI 6.9–14.3) after salvage mastectomy. 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

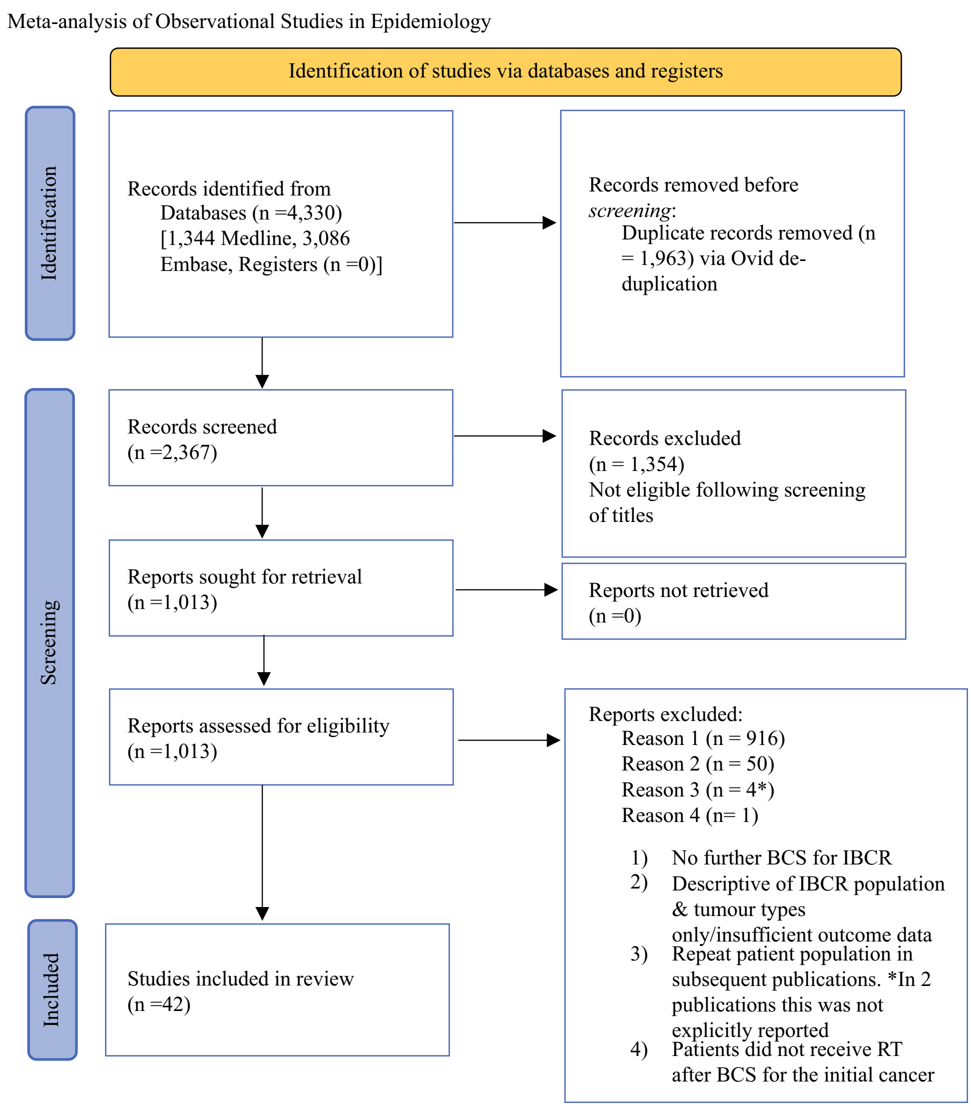


FIG. 1 Flowchart of systematic review and meta-analysis of observational studies in epidemiology. * Two studies were not explicitly described by the authors if they represented the same population as other publications

TABLE 1 Characteristics of the included studies

Reference	Author	Year	Primary diagnosis	IBCR diagnosis	Study outcome	Total no. of patients	Previous breast RT after BCS	Previous RT axilla/regional nodes after BCS	No. of patients rBCS	rRT breast after rBCS	rRT axilla/regional nodes after rBCS	Newcastle-Ottawa Scale: Selection	Comparability	Outcomes	Total
9	Kurtz et al.	1988	IBC	NS	OS	118	Yes	Yes	52	No	No	3	1	3	7
49	Kurtz et al.	1990	IBC	NS	LR	50	Yes	Yes	50	Yes[a] ($n = 11$), EBR ($n = 7$), and BT ($n = 4$)	NS	4	0	3	7
50	Abner et al.	1993	IBC	IBC and DCIS	LR, OS	139	Yes	Yes[a]	16	No	No	3	1	3	7
51	Voogd et al.	1998	IBC	IBC and DCIS	LR	266	Yes	NS	20	Yes[a]	NS	4	0	2	6
18	Dalberg et al	1998	IBC	IBC and DCIS	LR	85	Yes[a] ($n = 67$)	NS	14	Yes[a] ($n = 2$)	NS	4	0	3	7
10	Salvadori et al.	1999	IBC	NS	LR, OS	197	Yes	NS	57	NS	NS	4	0	3	7
52	Deutsch et al.	2002	IBC and DCIS	IBC and DCIS	LR, OS	39	Yes	Yes[a] ($n = 3$)	39	Yes EBR	NS	3	0	3	6
11	Alpert et al.	2004	IBC and DCIS	IBC and DCIS	LR, OS	146	Yes	Yes[a]	30	Yes[a] BT ($n = 1$)	NS	4	1	3	8
53	Hannoun-Levi et al.	2004	IBC and DCIS	IBC and DCIS	LR, OS	69	Yes	NS	69	Yes BT	Yes[a] ($n = 49$)	4	0	3	7
12	Komoike et al.	2005	IBC	NS	LR, OS	136	Yes[a]	NS	55	NS	NS	4	1	3	7
33	Fodor et al.	2007	IBC	IBC and DCIS	LR, OS	124	Yes[a] ($n = 60$)	NS	32	Yes[a] ($n = 4$)	NS	4	2	3	9
41	Chadha et al.	2008	IBC and DCIS	IBC and DCIS	LR, OS	15	Yes	NS	15	Yes LDR BT	NS	4	0	3	7
37	Chen et al.	2008	IBC	IBC and DCIS	OS	747	Yes	NS	180	Yes[a] ($n = 38$)	NS	4	2	3	9
54	Botteri et al.	2009	IBC	IBC	LR, OS	282	Yes	Yes[a]		No	No	4	1	3	8
38	Panet-Raymond et al.	2011	IBC	IBC and DCIS	OS	269	Yes	NS	48	Yes[a] ($n = 33$)	NS	4	2	3	9
55	Kauer-Dorner et al.	2012	IBC	IBC and DCIS	LR, OS	39	Yes	No	39	Yes PDR brachy-therapy	No	4	1	3	8
47	Gentilini et al.	2012	IBC	IBC	LR, OS	161	Yes	Yes[a]	161	No	No	4	2	3	9
56	Shah et al.	2012	IBC and DCIS	IBC and DCIS	OS	18	Yes	NS	4	Yes APBI	NS	4	0	3	7
57	Demicheli et al.	2013	IBC	NS	LR	338	Yes[a]	NS	148	Yes[a] ($n = 43$)	NS	4	1	3	8
40	Hannoun-Levi et al.	2013	IBC	NS	LR, OS	217	Yes	Yes[a]	217	Yes LDR ($n = 27$), PDR ($n = 88$), HDR ($n = 102$),BT	NS	4	2	3	9
28	Ishitobi et al.[b]	2013	IBC	NS	LR, OS	271	Yes[a] ($n = 69$)	NS	143	Yes[a] ($n = 1$)	NS	4	2	3	9

Table 1 (continued)

Reference	Author	Year	Primary diagnosis	IBCR diagnosis	Study outcome	Total no. of patients	Previous breast RT after BCS	Previous RT axilla/regional nodes after BCS	No. of patients rBCS	rRT breast after rBCS	rRT axilla/regional nodes after rBCS	Newcastle-Ottawa Scale: Selection	Comparability	Outcomes	Total
20	Kolben et al.	2015	IBC	IBC and DCIS	LR, OS	170	Yes	NS	58	Yes[a] ($n = 11$)	NS	4	2	3	9
45	Lee et al.	2015	IBC and DCIS	IBC and DCIS	OS	157	Yes[a]	($n = 135$)	NS	23	Yes[a] ($n = 13$)	NS	4	2	3
9															
30	Yoshida et al.	2016	IBC	NS	OS	271	Yes[a]	($n = 133$)	NS	149	NS	NS	4	2	3
9															
58	Wapnir et al.	2017	IBC	IBC	LR, OS	162	Yes[a] ($n = 92$)	NS	16	Yes[a] ($n = 2$)	NS	4	2	3	9
59	Ishitobi et al.	2017	IBC and DCIS	IBC and DCIS	LR, OS	65	Yes	NS	65	No	No	4	2	3	9
46	Sellam et al.	2018	IBC and DCIS	IBC and DCIS	LR, OS	121	Yes	NS	47	Yes[a] ($n = 16$) EBR-PB ($n = 15$), EBR-WB ($n = 1$)	Yes[a] ($n = 1$)	4	2	3	9
60	Houvenaeghel et al.	2018	IBC	NS	LR, OS	348	Yes	NS	116	Yes[a] ($n = 62$) BT ($n = 62$)	NS	4	2	3	9
42	Smanyko et al.	2019	IBC and DCIS	IBC and DCIS	LR, OS	195	Yes	NS	39	Yes HDR BT	NS	4	2	3	9
61	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
62	Forster et al.	2019	IBC and DCIS	IBC and DCIS	LR, OS	19	Yes	Yes[a]	19	Yes HDR BT ($n = 11$), PDR BT ($n = 8$)	NS	4	1	3	8
63	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[a]	($n = 3687$)	NS	1050	Yes[a] ($n = 259$)	NS	4	2	3
9															
29	Sagona et al.[b]	2020	IBC and DCIS	IBC and DCIS	LR, OS	309	Yes[a]	($n = 300$)	NS	143	Yes[a] ($n = 50$)	NS	4	1	3
8															
64	Boehm et al.	2020	IBC and DCIS	IBC and DCIS	LR, OS	57	Yes[a] ($n = 55$)	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[a]	($n = 258$)	NS	130	Yes[a] ($n = 41$)	NS	4	2	3

Table 1 (continued)

Reference	Author	Year	Primary diagnosis	IBCR diagnosis	Study outcome	Total no. of patients	Previous breast RT after BCS	Previous RT axilla/regional nodes after BCS	No. of patients rBCS	rRT breast after rBCS	rRT axilla/regional nodes after rBCS	Newcastle-Ottawa Scale Selection	Comparability	Outcomes	Total
9															
14	Wu et al.	2020	IBC	NS	OS	2075	Yes	NS	475	Yes[a] ($n = 255$)	NS	4	2	3	9
19	Gentile et al.	2021	IBC	IBC and DCIS	LR, OS	309	Yes[a]	($n = 300$)	NS	143	Yes[a] ($n = 50$)	NS	4	2	3
9															
65	Li et al.	2021	DCIS	IBC and DCIS	LR, OS	5344	Yes[a]	($n = 2625$)	NS	1812	Yes[a] ($n = 735$)	NS	4	1	3
9															
21	El Sherif et al.	2021	IBC and DCIS	IBC and DCIS	LR, OS	113	Yes[a] ($n = 86$)	NS	32	Yes[a] APBI ($n = 10$), IORT ($n = 1$), WBRT ($n = 2$)	NS	4	1	3	8
66	Wang et al.	2021	IBC	NS	LR, OS	5413	Yes	NS	773	Yes[a] ($n = 124$)	NS	4	2	3	9
67	Chatzikonstantinou et al.	2021	IBC and DCIS	IBC and DCIS	LR, OS	20	Yes	Yes[a]	20	Yes HDR BT	NS	4	0	3	7
13	Baek et al.	2021	IBC and DCIS	NS	OS	335	Yes[a]	($n = 303$)	NS	155	Yes[a] ($n = 24$)	NS	4	3	2
9															

IBCR Ipsilateral breast cancer recurrence, *BCS* Breast-conserving surgery, *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* Intraoperative radiotherapy, *3D-CRT* 3D Conformal radiotherapy, *PBI* Partial breast irradiation, *WBRT* Whole breast radiotherapy

[a] A proportion of patients did not receive the respective treatment modality

[b] Study included in the table but not in the final analysis as it was not explicit whether it included a duplicate patient population

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

Subgroup	rBCS			Salvage mastectomy		
	Second LR (%)	95% CI	Weight (%)	Second 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[a]						
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, *CI* Confidence interval, *IBC* Invasive breast cancer, *DCIS* Ductal carcinoma in situ

[a]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

received rRT had the lowest pooled second LR rate compared with 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 (RR 2.103, 95% CI 1.535–2.883; $p < 0.001$, $I^2 = 55.1\%$), as shown in Fig. 2. Leave-one-out meta-analysis (electronic supplementary Fig. S1) did not demonstrate any differences. Only concomitant RT retained a protective effect in meta-regression analysis (coefficient − 0.317, 95% CI − 0.596 to − 0.038; $p = 0.026$, $I^2 = 40.4\%$). No publication bias or small-studies effect was detected (Egger's test beta-1 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 favor of rBCS (RR 1.040, 95% CI 1.003–1.079; $p = 0.032$, $I^2 = 70.8\%$) [Fig. 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 (electronic supplementary Fig. 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 (electronic supplementary Table S1). RT 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 regard 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 a small-studies effect (Egger's test beta-1 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

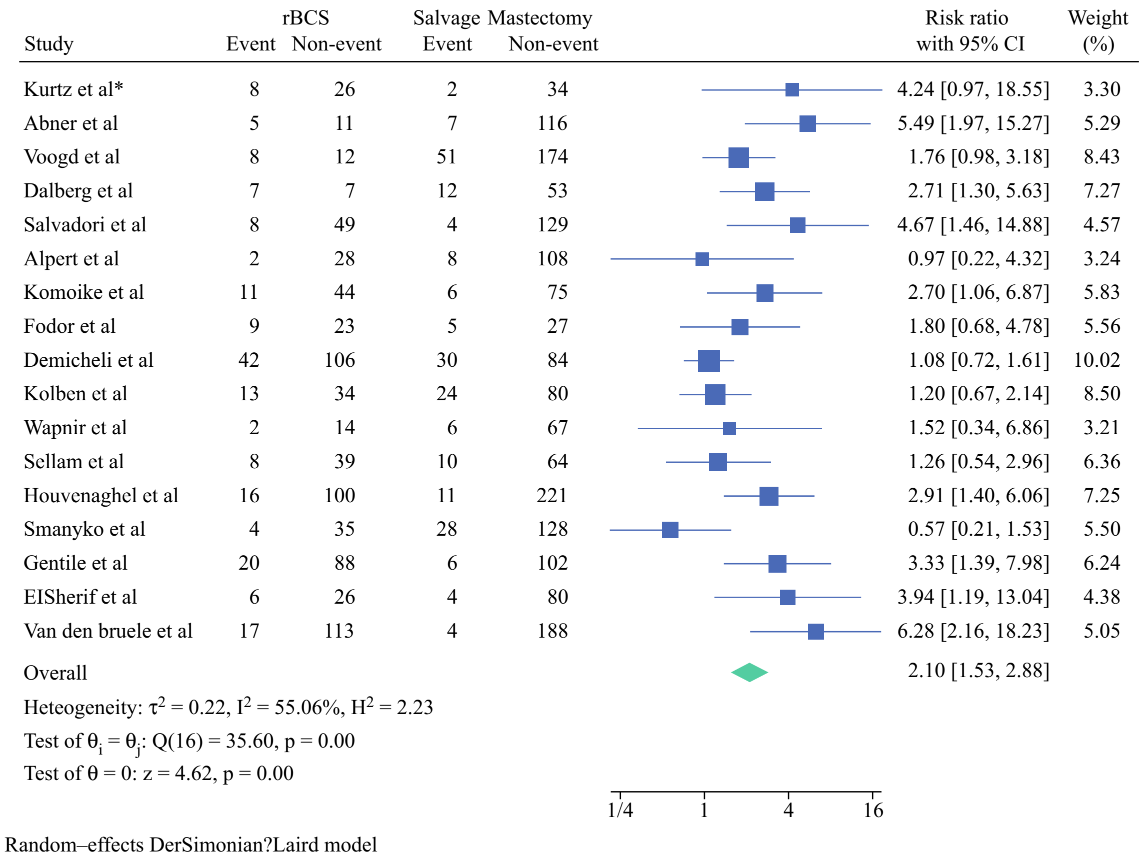


FIG. 2 Forest plot of studies comparing repeat breast-conserving surgery versus salvage mastectomy for second local recurrence. *Study by Kurtz et al.[49]

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[a]						
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, *CI* Confidence interval, *IBC* Invasive breast cancer, *DCIS* Ductal carcinoma in situ

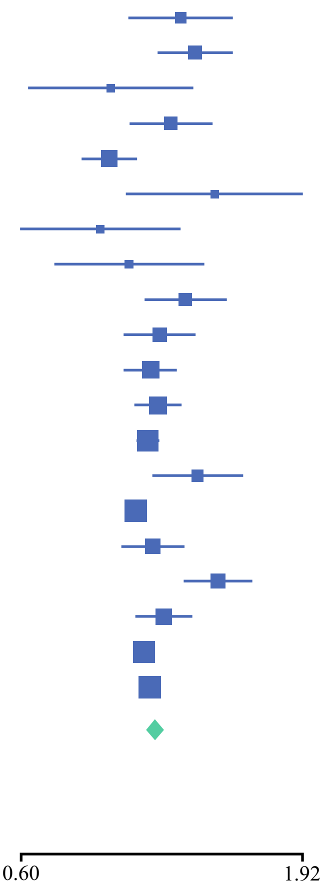
[a]Use and type of repeat radiotherapy for the management of IBCR was not consistently reported and therefore analysis could not be stratified based on specific details

Study	rBCS Non–Event	rBCS Event	Salvage Mastectomy Non–Event	Salvage Mastectomy Event	Risk ratio with 95% CI	Weight (%)
Kurtz et al	41	11	45	21	1.16 [0.93, 1.44]	2.25
Salvadori et al	49	8	93	40	1.23 [1.05, 1.43]	3.80
Alpert et al	17	13	76	40	0.86 [0.62, 1.21]	1.03
Komoike et al	46	9	61	20	1.11 [0.94, 1.32]	3.25
Chen et al	120	59	443	125	0.86 [0.77, 0.96]	5.58
Fodor et al	24	8	18	14	1.33 [0.93, 1.92]	0.90
Panet–Raymond et al	22	26	119	96	0.83 [0.60, 1.15]	1.09
Shah et al	4	0	13	0	0.93 [0.69, 1.27]	1.23
Kolben et al	40	7	75	29	1.18 [1.00, 1.40]	3.30
Lee et al	21	2	93	15	1.06 [0.92, 1.23]	4.01
Yoshida et al	48	3	47	4	1.02 [0.92, 1.13]	5.92
Houvenaeghel et al	100	16	190	42	1.05 [0.96, 1.16]	6.57
Sellam et al	47	0	73	1	1.01 [0.97, 1.05]	10.19
Smanyoko et al	32	7	103	53	1.24 [1.03, 1.50]	2.89
Su et al	710	58	739	29	0.96 [0.94, 0.98]	11.32
Wu et al	164	85	159	90	1.03 [0.91, 1.17]	4.72
Gentile et al	100	8	74	34	1.35 [1.18, 1.55]	4.34
Baek et al	81	9	75	15	1.08 [0.96, 1.21]	5.39
Li et al	1,007	157	1,013	151	0.99 [0.96, 1.03]	10.94
Wang et al	695	78	4,096	544	1.02 [0.99, 1.05]	11.26
Overall					1.04 [1.00, 1.08]	

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 70.82\%$, $H^2 = 3.43$

Test of $\theta_i = \theta_j$: $Q(19) = 65.11$, $p = 0.00$

Test of $\theta = 0$: $z = 2.15$, $p = 0.03$



Random–effects DerSimonian?Laird model

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

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 the form of rates, rather than effect sizes such as HRs that are much more appropriate for time-to-event outcomes, and, finally, that most source studies did not accurately report on primary and recurrent tumor biology as well as adjuvant therapy, for example use of RT after BCS for the management of the initial cancer, or RT for the management of the recurrence, which may play a 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,[6,31] potentially supporting the argument for more aggressive local treatment. However, salvage mastectomy does not eliminate the risk of local or distant recurrence[32,33] and there is increasing data supporting the feasibility of rRT.[16,34] In addition, advances in multidisciplinary management of breast cancer, including systemic therapy and RT options, as well as 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

TABLE 4 GRADE assessment and recommendations

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

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. 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 (1.535–2.883)	119 more per 1000 (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 (1.003–1.079)	34 more per 1.000 (from 3 more to 67 more)	⊕◯◯◯ Very low	IMPORTANT

CI Confidence interval, *RR* Risk ratio

[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

oncologically safe, could be associated with improved patient satisfaction in terms of cosmetic outcome and quality of life[35,36] 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.[9–13,17–20,29,37,38]

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 with 10.3% after salvage mastectomy. However, it should be noted that the included studies are markedly heterogeneous and there was no 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 insufficient 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).[39] The small observed difference may be explained by the fact that the present meta-analysis included 17 studies providing data on second LR compared with 13 studies in the meta-analysis by Mo et al.[39].

On subgroup 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.[34,39] This is an important consideration when individualizing the management plan, especially as a number of rRT options, for example brachytherapy,[40–42] intraoperative RT[43,44] and external beam RT,[16] have been shown to be associated with an acceptable toxicity profile. In the RTOG 1014 prospective phase II clinical trial, three-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.[34]

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 with those treated with salvage mastectomy.[13,15,19,29,30,42,45] 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 that 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. The recent meta-analysis by Mo et al. also supports the findings that rBCS may not be associated with worse OS.[39] The results of the present meta-analysis showed a marginal benefit in OS in favor of rBCS (RR 1.040). The difference between the two meta-analyses may be explained by the different number of included studies (8 vs. 20 in the present analysis). The median NOS of the studies[10–12,33,37,42,45,46] included in the meta-analysis by Mo et al.[39] was 9 (IQR 7–9) and the median NOS of the studies in the present meta-analysis was 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.[39], cautiousness is required due to 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,[17,45] 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 tumor 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 included disease-free interval and the size and histopathology of the recurrence as these have been shown to be independent prognostic factors of OS.[45] Gentilini et al. have suggested that patients with small (≤2 cm), late (>48 months) IBCR would be the ideal candidates for rBCS.[47] 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 of age with unifocal, small (<2–3 cm) IBCR, ≥48 months after primary treatment who are willing to undergo rBCS and this is technically feasible.[48] The St. Gallen International Panel suggests that rBCS can be considered for low-risk recurrent cancers with favorable tumor 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 tumor 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 favored 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

rBCS 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 tumor 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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