



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

Journal:	<i>Annals of Surgical Oncology</i>
Manuscript ID	ASO-2022-05-1294.R1
Manuscript Type:	Am. Soc. Breast Surgeons Manuscript
Date Submitted by the Author:	n/a
Complete List of Authors:	Tollan, Clare Josephine ; Royal Marsden NHS Foundation Trust, Breast Surgery Pantiora, Eirini; Uppsala University Hospital, Department of Surgery; Uppsala University, Department of Surgical Sciences Valachis, Antonios; Örebro University Faculty of Medicine and Health, Department of Oncology Karakatsanis, Andreas; Uppsala University, Department of Surgical Sciences; Tasoulis, Marios Konstantinos; Royal Marsden NHS Foundation Trust, Breast Surgery; The Institute of Cancer Research, Division of Breast Cancer Research

SCHOLARONE™
Manuscripts

1
2
3 **1 Title Page**
4

5
6 **2 A systematic review and meta-analysis on the role of repeat breast conserving surgery for the**
7
8 **3 management of ipsilateral breast cancer recurrence**
9

10
11 **4**
12
13 **5 Running head: Redo breast conserving surgery for recurrence**
14

15 **6**
16
17
18 **7 Clare Josephine Tollan MD¹, Eirini Pantiora MD², Antonios Valachis MD³, Andreas Karakatsanis**
19
20 **8 MD², Marios Konstantinos Tasoulis MD^{1,4}**
21

22
23 **9 ¹ Breast Surgery Unit, The Royal Marsden NHS Foundation Trust, London, SW3 6JJ, UK**
24

25 **10 ² Department of Surgery, Uppsala University Hospital - Department of Surgical Sciences,**
26
27 **11 Uppsala University, Uppsala, 751 85, Sweden**
28

29
30 **12 ³ Department of Oncology, Faculty of Medicine and Health, Örebro University, Örebro, 701 82,**
31
32 **13 Sweden**
33

34
35 **14 ⁴ Division of Breast Cancer Research, The Institute of Cancer Research, Old Brompton Road,**
36
37 **15 London, SW7 3RP, UK**
38

39
40 **16**
41
42 **17 Corresponding author:**
43

44
45 **18 Mr Marios Konstantinos Tasoulis, MD, PhD, FEBS, CEBS, MFSTEd, FRCS**
46

47 **19 Consultant Breast Surgeon**
48

49
50 **20 Breast Surgery Unit, The Royal Marsden NHS Foundation Trust**
51

52 **21 Fulham Road, London, SW3 6JJ, UK**
53

54 **22 Email: marios.tasoulis@rmh.nhs.uk**
55
56
57
58
59
60

1

2 **Disclosures:** The authors have no relevant conflicts of interest to declare

3

4 Preliminary analysis and results were presented as poster at the 23rd Annual Meeting of the

5 American Society of Breast Surgeons, April 6-10, 2022, Las Vegas, NV, USA

For Peer Review

1 **Synopsis**

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

6 **Abstract**

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

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

17 **Results:** 42 observational studies met the criteria and were included in the analysis. The pooled
18 second LR rate after rBCS was 15.7% (95%CI:12.1-19.7) and after salvage mastectomy was
19 10.3% (95%CI:6.9-14.3). On meta-analysis of comparative studies (n=17), the Risk Ratio (RR) for
20 second LR following rBCS compared to mastectomy was 2.103 (95%CI:1.535-2.883, p<0.001,
21 $I^2=55.1%$). Repeat radiotherapy had a protective effect (coefficient:-0.317;95%CI:-0.596,-0.038,
22 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%

1 (95%CI:74.7-84.5) for rBCS and salvage mastectomy respectively. Meta-analysis of comparative
2 studies (n=20) showed a small OS benefit in favour of rBCS (RR:1.040;95%CI:1.003-1.079,
3 p=0.032, $I^2=70.8\%$). Overall evidence certainty was very low.

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

8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For Peer Review

1 Introduction

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

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

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

4 5 **Methods**

6 *Search strategy and Inclusion criteria*

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

1
2
3 1 *Data extraction*
4
5

6 2 Data extraction was performed independently by two authors (CJT and EP) in a preformed
7
8
9 3 Microsoft Excel© working sheet. The data extraction procedure for the whole dataset
10
11 4 (including all eligible studies) was standardised during two training sessions with the senior
12
13 5 authors (AK and MKT) using a random sample of five studies. Disagreement was resolved by
14
15 6 group consensus. The study methodology was registered with PROSPERO International
16
17 7 prospective register of systematic reviews (CRD42021286123,
18
19 https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021286123).
20
21 8
22
23
24 9
25
26

27 10 *Quality assessment*
28
29

30 11 The Newcastle-Ottawa-Scale (NOS) (23) for observational studies, as assessed by two authors
31
32 12 (EP, AK) was used to evaluate the quality of the included studies. Publication bias was assessed
33
34 13 with funnel plots and the Egger's test for small studies. Following analyses and critical appraisal,
35
36 14 the GRADE approach (24) was used to assess the strength of evidence and recommendations by
37
38 15 two authors (AV and AK). Subsequently, knowledge gaps and research priorities were defined.
39
40
41
42
43 16
44
45
46 17
47
48
49 18
50
51

52 19 *Statistical analyses and reporting*
53
54
55
56
57
58
59
60

1 Rates of a second LR and OS at 5 years for rBCS and salvage mastectomy were calculated
2 separately, by pooling the outcomes from single-arm and comparative studies. Subgroup
3 analyses were performed depending on whether the reference population had initially been
4 treated for only DCIS, both DCIS and IBC or IBC only. Subgroup analyses were also undertaken
5 to define the effect of study design (comparative or single-arm), propensity score matching and
6 the effect of radiotherapy, regardless of the technique that was utilized. The median follow-up
7 was also extracted. Meta-analyses of comparative studies were also performed. Additionally,
8 leave-one-out meta-analyses of comparative studies were performed, to allow for the
9 identification of studies with exaggerated effect sizes and guide further subgroup and meta-
10 regression analyses. As literature search was expected to retrieve observational studies, the use
11 of a random-effects model using the DerSimonian Laird method was decided *a priori*. For
12 source studies directly reporting odds ratio (OR), risk ratio (RR) or hazard ratio (HR), the
13 adjusted analyses and Kaplan-Meier curves were considered for data extraction and calculation
14 of 5-year second LR and OS (25, 26). Effect sizes were reported with 95% confidence intervals
15 (95% CI). Study heterogeneity was assessed with the I^2 statistic.

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

20 **Results**

21 *Study selection and characteristics*

1
2
3 1 The literature search, after the removal of duplicates, retrieved 42 studies, with 24 examining
4
5 2 outcomes after a primary IBC, 17 reporting on both IBC and DCIS and 1 on DCIS only (MOOSE
6
7 3 flowchart presented in Figure 1). Twenty-eight studies examined outcomes on both LR and OS,
8
9 4 9 on OS only and 5 on LR only. Study characteristics and NOS scores are shown in Table 1. On
10
11 5 two occasions, it was not explicitly reported by the authors if the study population was the
12
13 6 same as in another publication by the same group (28, 29). Therefore, all the studies were
14
15 7 included in Table 1, but only the most recent studies providing data following propensity score
16
17 8 matching were included in the meta-analysis (19, 30).
18
19
20
21
22
23
24
25
26
27

28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60

10 *Second Local Recurrence*

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

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

1 months, IQR: 52-79). In comparative studies, the pooled second LR rate was higher after rBCS
2 (19.6%, 95% CI: 15.5-24.0) versus after salvage mastectomy (9.6%, 95% CI: 6.3-13.5) (Table 2).
3 On meta-analysis, rBCS was associated with a significantly increased risk of second LR [Risk
4 Ratio (RR) = 2.103; 95% CI: 1.535 - 2.883, $p < 0.001$, $I^2 = 55.1\%$], as shown in Figure 2. Leave-one-
5 out meta-analysis (Supplement, Figure S1) did not demonstrate any differences. Only
6 concomitant radiotherapy retained a protective effect in meta-regression analysis (coefficient: -
7 0.317; 95% CI: -0.596, -0.038, $p = 0.026$, $I^2 = 40.4\%$). No publication bias or small-studies effect
8 was detected (Egger's test β_1 : 1.540, $p = 0.103$).

10 *Overall Survival*

11 Pooled OS rates and subgroup analyses for patients treated with rBCS or salvage mastectomy
12 are presented in Table 3. Overall, at a median follow-up ranging from 30 to 168 months
13 (median of medians 66 months, IQR: 55 - 79), the pooled 5-year OS rate was 86.8% (95% CI:
14 83.4 - 90.0) after rBCS and 79.8% (95% CI: 74.7 - 84.5) after salvage mastectomy. Subgroup
15 analyses (Table 3) did not demonstrate any factor that correlated with difference in outcomes
16 for each group (rBCS or salvage mastectomy). Meta-analysis of comparative studies ($n=20$)
17 showed a small OS benefit in favour of rBCS (RR: 1.040, 95% CI: 1.003 - 1.079, $p = 0.032$, $I^2 =$
18 70.8%) (Figure 3). The median follow-up in these studies ranged from 42 to 168 months
19 (median of medians 72 months, IQR: 59 - 126.6). Leave-one-out meta-analysis (Supplement,
20 Figure S2) showed that the omission of four studies (one at a time) would result in a difference,
21 despite that the numeric value of the RR was not significantly affected. Subsequent subgroup

1 and meta-regression analysis was performed (Supplement, Table S1). Radiotherapy did not
2 affect the outcome on meta-regression analysis (coefficient: 0.0019; 95% CI: -0.0274, 0.0312,
3 $p= 0.898$, $I^2= 70.8\%$). With regards to primary tumor, studies reporting on both DCIS and IBC
4 reported survival benefit for rBCS (RR: 1.119; 95% CI: 1.019 – 1.230, $p=0.019$), but this effect
5 was not retained on meta-regression analysis (coefficient: 0.0721; 95% CI: -0.0017, 0.1458,
6 $p=0.056$). When looking into publication bias, the Egger's test detected small-studies effect
7 (Egger's test beta1: 0.93, $p= 0.041$).

8 9 *Study quality and strength of recommendations*

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

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

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

4 **Discussion**

5 Mastectomy has traditionally been considered as the standard of care for the management of
6 IBCR. This has been recommended by national and international guidelines, including the NCCN
7 guidelines (8). Reasons for this practice include the concerns about rRT and also the fact that
8 IBCR has been associated with poor prognosis (31, 32), potentially supporting the argument for
9 more aggressive local treatment. However, salvage mastectomy does not eliminate the risk of
10 local or distant recurrence (33, 34) and there is increasing data supporting the feasibility of rRT
11 (16, 35). In addition, advances in multidisciplinary management of breast cancer, including
12 systemic therapy and radiotherapy options, and a general trend towards surgical de-escalation
13 have likely contributed to the increasing use of rBCS as part of an individualized, tailored
14 approach (15, 21). This is also now supported by the St. Gallen International Consensus
15 Guidelines (22). Avoidance of mastectomy, if oncologically safe, could be associated with
16 improved patient satisfaction in terms of cosmetic outcome and quality of life (36, 37) apart
17 from cost and resource implications for healthcare providers. However, the existing data do not
18 conclusively support rBCS or salvage mastectomy in terms of oncological outcomes, with a
19 number of studies reporting opposite results (9-13, 17-20, 29, 38, 39).

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

1 salvage mastectomy. However, it should be noted that the included studies are markedly
2 heterogeneous, and there was not a standardized multidisciplinary treatment protocol for the
3 management of IBCR. In addition, it is important to highlight that in a number of studies, a
4 proportion of patients did not receive RT for the management of the primary cancer, with not
5 enough data provided to allow stratification for this in the analysis. On meta-analysis, rBCS was
6 associated with a significantly higher RR for second LR (RR= 2.103), albeit with moderate study
7 heterogeneity. This RR is similar to that reported in a recent meta-analysis (RR = 1.87) (40). The
8 small observed difference may be explained by the fact that the present meta-analysis included
9 17 studies providing data on second LR compared to 13 studies in the meta-analysis by Mo et al
10 (40).

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

1
2
3 1 Despite the finding that rBCS may be associated with a higher risk of second LR, which was two-
4
5
6 2 fold higher based on the results of the present meta-analysis, it may not have a negative impact
7
8 3 on survival. A number of retrospective studies have shown that OS was not inferior or was even
9
10 4 improved in patients treated with rBCS with or without rRT compared to those treated with
11
12 5 salvage mastectomy (13, 15, 19, 29, 30, 43, 46). An analysis of the Surveillance, Epidemiology,
13
14 6 and End Results (SEER) database including data from 1998 to 2013 showed no significant
15
16 7 difference in terms of OS and BCSS in patients treated with rBCS or salvage mastectomy (14).
17
18 8 However, another analysis of the SEER database looking into data from 1973 to 2003 showed
19
20 9 different results (17). In this study the authors found that rBCS was associated with worse OS
21
22 10 and BCSS and that rRT had a protective effect in terms of OS. Although, there is no clear
23
24 11 explanation for the discordant findings, a potential reason may be the different time periods, as
25
26 12 multidisciplinary breast cancer management has significantly evolved over the past decades. A
27
28 13 recent meta-analysis by Mo et al also supports the findings that rBCS may not be associated
29
30 14 with worse OS (40). The results of the present meta-analysis showed a marginal benefit in OS in
31
32 15 favour of rBCS (RR: 1.040). The difference between the two meta-analyses may be explained by
33
34 16 the different number of included studies (8 versus 20 in the present analysis). The median NOS
35
36 17 of the studies (10-12, 34, 38, 43, 46, 47) included in the meta-analysis by Mo et al (40) is 9 (IQR:
37
38 18 7-9), and the median NOS of the studies in the present meta-analysis is also 9 (IQR: 8-9), with
39
40 19 the additional 12 studies having a median NOS of 9 (IQR: 9-9). It has to be noted though that a
41
42 20 small-study effect was found, underlining potential publication bias. While such an effect was
43
44 21 not detected in the meta-analysis by Mo et al (40) cautiousness is required due the small
45
46 22 number of included studies.
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 1 Although rRT was found to have a protective effect in terms of local control and has previously
4
5
6 2 been shown to have a role in improving OS (17, 46), in the present meta-analysis, OS was not
7
8 3 affected by rRT on meta-regression analysis. However, these results should be interpreted with
9
10 4 caution as the included studies were substantially heterogeneous, and the effect size had
11
12
13 5 marginal significance.

14
15
16 6 The findings of this meta-analysis suggest that although rBCS may be associated with higher risk
17
18 7 of subsequent LR, this may not have a negative impact on OS. This suggests that rBCS may be
19
20
21 8 an alternative option in the context of individualized management of IBCR in line with the St.
22
23 9 Gallen International Consensus Guidelines (22), especially for women who want to preserve
24
25
26 10 their breast, following careful consultation about the currently accepted standard
27
28 11 recommendation of salvage mastectomy as per NCCN (8) guidelines. However, appropriate
29
30
31 12 patient selection for such an approach would be of paramount importance. In the first report of
32
33 13 rBCS for IBCR, Kurtz et al suggested an algorithm for patient selection including tumour size < 2
34
35 14 cm, no fixation of the cancer on the skin or chest wall, clinically node negative status and no
36
37
38 15 significant RT changes (9). Other important parameters include disease free interval, and the
39
40
41 16 size and histopathology of the recurrence as these have been shown to be independent
42
43 17 prognostic factors of OS (46). Gentilini et al have suggested that patients with small (≤ 2 cm)
44
45 18 late (> 48 months) IBCR would be the ideal candidates for rBCS (48). Similar selection criteria
46
47
48 19 have been proposed by the German Society of Radiation Oncology (DEGRO) expert panel
49
50 20 suggesting that rBCS can be considered in patients ≥ 50 years with unifocal, small (< 2 – 3 cm)
51
52
53 21 IBCR, ≥ 48 months after primary treatment who are willing to undergo rBCS and this is
54
55 22 technically feasible (49). The St. Gallen International Panel suggests that rBCS can be considered

1
2
3 1 for low-risk recurrent cancers with favourable tumour biology (small, Luminal A) for which rRT
4
5
6 2 may not be required or for IBCR > 5 years after primary treatment (22). The common
7
8 3 denominator of these suggested algorithms for patient selection is an individualized approach
9
10 4 mainly based on tumour biology and anatomical stage. The role of multidisciplinary
11
12 5 management of IBCR, with systemic therapy (endocrine therapy, chemotherapy or targeted
13
14 6 therapy for example anti-HER2) with or without rRT cannot be overemphasized. The potential
15
16 7 effect of such recommendations could not be assessed in this meta-analysis due to lack of
17
18 8 studies providing data that would allow such an analysis.
19
20
21
22

23 9 Although, rBCS is increasingly being used for the management of IBCR (15, 21), and de-
24
25 10 escalated tailored therapeutic approaches are favoured within modern multidisciplinary
26
27 11 working, the quality of the studies providing data on oncological outcomes of rBCS does not
28
29 12 appear to improve over time as demonstrated by the NOS assessment of the studies included in
30
31 13 this meta-analysis. The low quality of available source studies constitutes the limitation of this
32
33 14 meta-analysis, as potentially uncontrolled biases, lack of standardized reports of treatment
34
35 15 modalities and outcomes of interest increase heterogeneity and mandate a careful
36
37 16 interpretation of the results. This fact was illustrated in the outcomes of the GRADE approach
38
39 17 and highlights the importance of collaboration across different specialties to set up prospective
40
41 18 research studies, designed to address the knowledge gaps highlighted.
42
43
44
45
46
47
48
49
50

51 **Conclusions**

52
53
54
55
56
57
58
59
60

1
2
3 1 Repeat BCS may have a role in the management of IBCR in patients previously treated with BCS
4
5
6 2 and RT. This should be based on individualized assessment of tumour and patient factors, and
7
8 3 multidisciplinary working to develop a tailored management plan. Further research in this field
9
10 4 is warranted to allow optimal patient selection and address existing knowledge gaps.
11
12
13
14 5
15
16
17 6
18

19 7 References
20
21 8
22

- 23 9 1. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up
24
25 10 of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for
26
27 11 the treatment of invasive breast cancer. *N Engl J Med*. 2002;347(16):1233-41.
28
29
30 12 2. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of
31
32 13 a randomized study comparing breast-conserving surgery with radical mastectomy for early breast
33
34 14 cancer. *N Engl J Med*. 2002;347(16):1227-32.
35
36
37 15 3. Effects of Radiotherapy and Surgery in Early Breast Cancer — An Overview of the Randomized
38
39 16 Trials. *New England Journal of Medicine*. 1995;333(22):1444-56.
40
41 17 4. Bouganim N, Tsvetkova E, Clemons M, Amir E. Evolution of sites of recurrence after early breast
42
43 18 cancer over the last 20 years: implications for patient care and future research. *Breast Cancer Research*
44
45 19 and Treatment. 2013;139(2):603-6.
46
47
48 20 5. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast
49
50 21 cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials. *The*
51
52 22 *Lancet*. 2011;378(9804):1707-16.
53
54
55
56
57
58
59
60

- 1
2
3 1 6. Wapnir IL, Anderson SJ, Mamounas EP, Geyer CE, Jeong J-H, Tan-Chiu E, et al. Prognosis After
4
5 2 Ipsilateral Breast Tumor Recurrence and Locoregional Recurrences in Five National Surgical Adjuvant
6
7 3 Breast and Bowel Project Node-Positive Adjuvant Breast Cancer Trials. *Journal of Clinical Oncology*.
8
9 4 2006;24(13):2028-37.
10
11
12 5 7. Bosma SCJ, van der Leij F, van Werkhoven E, Bartelink H, Wesseling J, Linn S, et al. Very low local
13
14 6 recurrence rates after breast-conserving therapy: analysis of 8485 patients treated over a 28-year
15
16 7 period. *Breast Cancer Research and Treatment*. 2016;156(2):391-400.
17
18
19 8 8. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Breast
20
21 9 Cancer. v2.2022 https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed 21 Jun
22
23 10 2022.
24
25
26 11 9. Kurtz JM, Amalric R, Brandone H, Ayme Y, Spitalier JM. Results of salvage surgery for mammary
27
28 12 recurrence following breast-conserving therapy. *Ann Surg*. 1988;207(3):347-51.
29
30
31 13 10. Salvadori B, Marubini E, Miceli R, Conti AR, Cusumano F, Andreola S, et al. Reoperation for
32
33 14 locally recurrent breast cancer in patients previously treated with conservative surgery. *The British*
34
35 15 *journal of surgery*. 1999;86(1):84-7.
36
37 16 11. Alpert TE, Kuerer HM, Arthur DW, Lannin DR, Haffty BG. Ipsilateral breast tumor recurrence
38
39 17 after breast conservation therapy: outcomes of salvage mastectomy vs. salvage breast-conserving
40
41 18 surgery and prognostic factors for salvage breast preservation. *International journal of radiation*
42
43 19 *oncology, biology, physics*. 2005;63(3):845-51.
44
45
46 20 12. Komoike Y, Akiyama F, Iino Y, Ikeda T, Tanaka-Akashi S, Ohsumi S, et al. Analysis of ipsilateral
47
48 21 breast tumor recurrences after breast-conserving treatment based on the classification of true
49
50 22 recurrences and new primary tumors. *Breast cancer (Tokyo, Japan)*. 2005;12(2):104-11.
51
52
53
54
55
56
57
58
59
60

- 1 13. Baek SY, Kim J, Chung IY, Ko BS, Kim HJ, Lee JW, et al. Long-term survival outcomes of repeat
2 lumpectomy for ipsilateral breast tumor recurrence: a propensity score-matched analysis. *Breast Cancer*
3 *Research and Treatment*. 2021;185(1):155-64.
- 4 14. Wu Y, Shi X, Li J, Wu G. Prognosis of Surgical Treatment After Ipsilateral Breast Tumor
5 Recurrence. *Journal of Surgical Research*. 2021;258:23-37.
- 6 15. Van den Bruele AB, Chen I, Sevilimedu V, Le T, Morrow M, Braunstein LZ, et al. Management of
7 ipsilateral breast tumor recurrence following breast conservation surgery: a comparative study of re-
8 conservation vs mastectomy. *Breast Cancer Research and Treatment*. 2021;187(1):105-12.
- 9 16. Arthur DW, Winter KA, Kuerer HM, Haffty B, Cuttino L, Todor DA, et al. Effectiveness of Breast-
10 Conserving Surgery and 3-Dimensional Conformal Partial Breast Reirradiation for Recurrence of Breast
11 Cancer in the Ipsilateral Breast: The NRG Oncology/RTOG 1014 Phase 2 Clinical Trial. *JAMA oncology*.
12 2020;6(1):75-82.
- 13 17. Su Y, Guo R, Xue J, Chi Y, Chi W, Wang J, et al. Increased Mortality with Repeat Lumpectomy
14 Alone After Ipsilateral Breast Tumor Recurrence. *The oncologist*. 2019;24(9):e818-e27.
- 15 18. Dalberg K, Mattsson A, Sandelin K, Rutqvist LE. Outcome of treatment for ipsilateral breast
16 tumor recurrence in early-stage breast cancer. *Breast Cancer Res Treat*. 1998;49(1):69-78.
- 17 19. Gentile D, Sagona A, Barbieri E, Antunovic L, Franceschini D, Losurdo A, et al. Breast conserving
18 surgery versus salvage mastectomy for ipsilateral breast cancer recurrence: a propensity score matching
19 analysis. *Updates in Surgery*. 2021.
- 20 20. Kolben T, Schwarz TM, Goess C, Blume C, Degenhardt T, Engel J, et al. Surgical management of
21 ipsilateral breast tumor recurrence. *International Journal of Surgery*. 2015;23:141-6.
- 22 21. ElSherif A, Shah C, Downs-Kelly E, Alhareb A, Valente SA, Tu C, et al. Outcomes of ipsilateral
23 breast tumor recurrence after breast conserving surgery: Repeat lumpectomy as an alternative to
24 salvage mastectomy. *Surgery*. 2022;171(3):673-81.

- 1
2
3 1 22. Burstein HJ, Curigliano G, Thürlimann B, Weber WP, Poortmans P, Regan MM, et al. Customizing
4
5 2 local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus
6
7 3 Guidelines for treatment of early breast cancer 2021. *Annals of oncology : official journal of the*
8
9 4 *European Society for Medical Oncology*. 2021;32(10):1216-35.
- 11
12 5 23. Wells GA, Wells G, Shea B, Shea B, O'Connell D, Peterson J, et al., editors. *The Newcastle-Ottawa*
13
14 6 *Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses* 2014.
- 16
17 7 24. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging
18
19 8 consensus on rating quality of evidence and strength of recommendations. *BMJ (Clinical research ed)*.
20
21 9 2008;336(7650):924-6.
- 23
24 10 25. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the
25
26 11 published literature for survival endpoints. *Statistics in medicine*. 1998;17(24):2815-34.
- 28
29 12 26. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating
30
31 13 summary time-to-event data into meta-analysis. *Trials*. 2007;8(1):16.
- 32
33 14 27. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of
34
35 15 observational studies in epidemiology: a proposal for reporting. *Meta-analysis Of Observational Studies*
36
37 16 *in Epidemiology (MOOSE) group*. *Jama*. 2000;283(15):2008-12.
- 39
40 17 28. Ishitobi M, Okumura Y, Nishimura R, Nakatsukasa K, Tanabe M, Yoshida A, et al. Repeat
41
42 18 lumpectomy for ipsilateral breast tumor recurrence (IBTR) after breast-conserving surgery: the impact of
43
44 19 radiotherapy on second IBTR. *Breast cancer (Tokyo, Japan)*. 2014;21(6):754-60.
- 46
47 20 29. Sagona A, Gentile D, Anghelone CAP, Barbieri E, Marrazzo E, Antunovic L, et al. Ipsilateral Breast
48
49 21 Cancer Recurrence: Characteristics, Treatment, and Long-Term Oncologic Results at a High-Volume
50
51 22 Center. *Clinical breast cancer*. 2021;21(4):329-36.
- 52
53
54
55
56
57
58
59
60

- 1
2
3 1 30. Yoshida A, Takahashi O, Okumura Y, Arima N, Nakatsukasa K, Tanabe M, et al. Prognosis after
4
5 2 mastectomy versus repeat lumpectomy in patients with ipsilateral breast cancer recurrence: A
6
7 3 propensity score analysis. *European Journal of Surgical Oncology*. 2016;42(4):474-80.
8
9
10 4 31. Anderson SJ, Wapnir I, Dignam JJ, Fisher B, Mamounas EP, Jeong JH, et al. Prognosis after
11
12 5 ipsilateral breast tumor recurrence and locoregional recurrences in patients treated by breast-
13
14 6 conserving therapy in five National Surgical Adjuvant Breast and Bowel Project protocols of node-
15
16 7 negative breast cancer. *Journal of clinical oncology : official journal of the American Society of Clinical*
17
18 8 *Oncology*. 2009;27(15):2466-73.
19
20
21 9 32. Wapnir IL, Anderson SJ, Mamounas EP, Geyer CE, Jr., Jeong JH, Tan-Chiu E, et al. Prognosis after
22
23 10 ipsilateral breast tumor recurrence and locoregional recurrences in five National Surgical Adjuvant
24
25 11 Breast and Bowel Project node-positive adjuvant breast cancer trials. *Journal of clinical oncology :*
26
27 12 *official journal of the American Society of Clinical Oncology*. 2006;24(13):2028-37.
28
29
30 13 33. Walstra C, Schipper RJ, Poodt IGM, van Riet YE, Voogd AC, van der Sangen MJC, et al. Repeat
31
32 14 breast-conserving therapy for ipsilateral breast cancer recurrence: A systematic review. *European*
33
34 15 *journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British*
35
36 16 *Association of Surgical Oncology*. 2019;45(8):1317-27.
37
38
39 17 34. Fodor J, Major T, Polgár C, Orosz Z, Sulyok Z, Kásler M. Prognosis of patients with local
40
41 18 recurrence after mastectomy or conservative surgery for early-stage invasive breast cancer. *Breast*
42
43 19 *(Edinburgh, Scotland)*. 2008;17(3):302-8.
44
45
46 20 35. Montagne L, Hannoun A, Hannoun-Levi J-M. Second conservative treatment for second
47
48 21 ipsilateral breast tumor event: A systematic review of the different re-irradiation techniques. *The Breast*.
49
50 22 2020;49:274-80.
51
52
53
54
55
56
57
58
59
60

- 1
2
3 1 36. Al-Ghazal SK, Fallowfield L, Blamey RW. Comparison of psychological aspects and patient
4
5 2 satisfaction following breast conserving surgery, simple mastectomy and breast reconstruction. Eur J
6
7 3 Cancer. 2000;36(15):1938-43.
8
9
10 4 37. Flanagan MR, Zabor EC, Romanoff A, Fuzesi S, Stempel M, Mehrara BJ, et al. A Comparison of
11
12 5 Patient-Reported Outcomes After Breast-Conserving Surgery and Mastectomy with Implant Breast
13
14 6 Reconstruction. Ann Surg Oncol. 2019;26(10):3133-40.
15
16
17 7 38. Chen SL, Martinez SR. The survival impact of the choice of surgical procedure after ipsilateral
18
19 8 breast cancer recurrence. American journal of surgery. 2008;196(4):495-9.
20
21 9 39. Panet-Raymond V, Truong PT, Alexander C, Lesperance M, McDonald RE, Watson PH.
22
23 10 Clinicopathologic factors of the recurrent tumor predict outcome in patients with ipsilateral breast
24
25 11 tumor recurrence. Cancer. 2011;117(10):2035-43.
26
27
28 12 40. Mo C, Ruan W, Lin J, Chen H, Chen X. Repeat Breast-Conserving Surgery Versus Salvage
29
30 13 Mastectomy for Ipsilateral Breast Tumour Recurrence After Breast-Conserving Surgery in Breast Cancer
31
32 14 Patients: A Meta-Analysis. Frontiers in Oncology. 2021;11.
33
34
35 15 41. Hannoun-Levi JM, Resch A, Gal J, Kauer-Dorner D, Strnad V, Niehoff P, et al. Accelerated partial
36
37 16 breast irradiation with interstitial brachytherapy as second conservative treatment for ipsilateral breast
38
39 17 tumour recurrence: multicentric study of the GEC-ESTRO Breast Cancer Working Group. Radiotherapy
40
41 18 and oncology : journal of the European Society for Therapeutic Radiology and Oncology.
42
43 19 2013;108(2):226-31.
44
45
46 20 42. Chadha M, Feldman S, Boolbol S, Wang L, Harrison LB. The feasibility of a second lumpectomy
47
48 21 and breast brachytherapy for localized cancer in a breast previously treated with lumpectomy and
49
50 22 radiation therapy for breast cancer. Brachytherapy. 2008;7(1):22-8.
51
52
53
54
55
56
57
58
59
60

- 1
2
3 1 43. Smanyakó V, Mészáros N, Újhelyi M, Fröhlich G, Stelczer G, Major T, et al. Second breast-
4
5 2 conserving surgery and interstitial brachytherapy vs. salvage mastectomy for the treatment of local
6
7 3 recurrences: 5-year results. *Brachytherapy*. 2019;18(3):411-9.
8
9
10 4 44. Thangarajah F, Heilmann J, Malter W, Kunze S, Marnitz S, Mallmann P, et al. Breast conserving
11
12 5 surgery in combination with intraoperative radiotherapy after previous external beam therapy: an
13
14 6 option to avoid mastectomy. *Breast Cancer Research and Treatment*. 2018;168(3):739-44.
15
16
17 7 45. Kraus-Tiefenbacher U, Bauer L, Scheda A, Schoeber C, Schaefer J, Steil V, et al. Intraoperative
18
19 8 radiotherapy (IORT) is an option for patients with localized breast recurrences after previous external-
20
21 9 beam radiotherapy. *BMC cancer*. 2007;7:178.
22
23
24 10 46. Lee JH, Lee SK, Park SM, Ryu JM, Paik HJ, Yi HW, et al. Independent Prognostic Factors for
25
26 11 Overall Survival after Salvage Operation for Ipsilateral Breast Tumor Recurrence Following Breast-
27
28 12 Conserving Surgery. *Journal of breast cancer*. 2015;18(4):386-93.
29
30
31 13 47. Sellam Y, Shahadi ID, Gelernter I, Zippel D, Sklair-Levy M, Symon Z, et al. Local recurrence of
32
33 14 breast cancer: Salvage lumpectomy as an option for local treatment. *The breast journal*. 2019;25(4):619-
34
35 15 24.
36
37 16 48. Gentilini O, Botteri E, Veronesi P, Sangalli C, Del Castillo A, Ballardini B, et al. Repeating
38
39 17 conservative surgery after ipsilateral breast tumor reappearance: criteria for selecting the best
40
41 18 candidates. *Ann Surg Oncol*. 2012;19(12):3771-6.
42
43
44 19 49. Harms W, Budach W, Dunst J, Feyer P, Fietkau R, Haase W, et al. DEGRO practical guidelines for
45
46 20 radiotherapy of breast cancer VI: therapy of locoregional breast cancer recurrences. *Strahlentherapie*
47
48 21 *und Onkologie : Organ der Deutschen Röntgengesellschaft [et al]*. 2016;192(4):199-208.
49
50
51 22 50. Kurtz JM, Spitalier JM, Amalric R, Brandone H, Ayme Y, Jacquemier J, et al. The prognostic
52
53 23 significance of late local recurrence after breast-conserving therapy. *International journal of radiation*
54
55 24 *oncology, biology, physics*. 1990;18(1):87-93.
56
57
58
59
60

- 1
2
3 1 51. Abner AL, Recht A, Eberlein T, Come S, Shulman L, Hayes D, et al. Prognosis following salvage
4
5 2 mastectomy for recurrence in the breast after conservative surgery and radiation therapy for early-stage
6
7 3 breast cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*.
8
9 4 1993;11(1):44-8.
- 10
11
12 5 52. Voogd AC, van Tienhoven G, Peterse HL, Crommelin MA, Rutgers EJ, van de Velde CJ, et al. Local
13
14 6 recurrence after breast conservation therapy for early stage breast carcinoma: detection, treatment,
15
16 7 and outcome in 266 patients. Dutch Study Group on Local Recurrence after Breast Conservation
17
18 8 (BORST). *Cancer*. 1999;85(2):437-46.
- 19
20
21 9 53. Deutsch M. Repeat high-dose external beam irradiation for in-breast tumor recurrence after
22
23 10 previous lumpectomy and whole breast irradiation. *International journal of radiation oncology, biology,*
24
25 11 *physics*. 2002;53(3):687-91.
- 26
27
28 12 54. Hannoun-Levi JM, Houvenaeghel G, Ellis S, Teissier E, Alzieu C, Lallement M, et al. Partial breast
29
30 13 irradiation as second conservative treatment for local breast cancer recurrence. *International journal of*
31
32 14 *radiation oncology, biology, physics*. 2004;60(5):1385-92.
- 33
34
35 15 55. Botteri E, Rotmensz N, Sangalli C, Toesca A, Peradze N, De Oliveira Filho HR, et al. Unavoidable
36
37 16 mastectomy for ipsilateral breast tumour recurrence after conservative surgery: patient outcome.
38
39 17 *Annals of Oncology*. 2009;20(6):1008-12.
- 40
41
42 18 56. Kauer-Dorner D, Pötter R, Resch A, Handl-Zeller L, Kirchheiner K, Meyer-Schell K, et al. Partial
43
44 19 breast irradiation for locally recurrent breast cancer within a second breast conserving treatment:
45
46 20 alternative to mastectomy? Results from a prospective trial. *Radiotherapy and oncology : journal of the*
47
48 21 *European Society for Therapeutic Radiology and Oncology*. 2012;102(1):96-101.
- 49
50
51 22 57. Shah C, Wilkinson JB, Jawad M, Wobb J, Berry S, Mitchell C, et al. Outcome after ipsilateral
52
53 23 breast tumor recurrence in patients with early-stage breast cancer treated with accelerated partial
54
55 24 breast irradiation. *Clinical breast cancer*. 2012;12(6):392-7.

- 1
2
3 1 58. Demicheli R, Ardoino I, Ambrogi F, Agresti R, Biganzoli E. Significance of ipsilateral breast tumor
4
5 2 recurrence after breast conserving treatment: role of surgical removal. Chinese journal of cancer
6
7 3 research = Chung-kuo yen cheng yen chiu. 2013;25(1):22-31.
8
9
10 4 59. Wapnir IL, Gelber S, Anderson SJ, Mamounas EP, Robidoux A, Martín M, et al. Poor Prognosis
11
12 5 After Second Locoregional Recurrences in the CALOR Trial. Ann Surg Oncol. 2017;24(2):398-406.
13
14 6 60. Ishitobi M, Fukui R, Hashimoto Y, Kittaka N, Nakayama T, Tamaki Y. Safety for Repeat
15
16 7 Lumpectomy Without Radiotherapy for Ipsilateral Breast Tumor Recurrence. Anticancer research.
17
18 8 2017;37(9):5293-9.
19
20
21 9 61. Houvenaeghel G, Boher JM, Michel V, Bannier M, Minsat M, Tallet A, et al. Survival after breast
22
23 10 cancer local recurrence according to therapeutic strategies. European journal of surgical oncology : the
24
25 11 journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology.
26
27 12 2017;43(8):1409-14.
28
29
30 13 62. Montagne L, Gal J, Chand ME, Schiappa R, Falk AT, Kinj R, et al. GEC-ESTRO APBI classification as
31
32 14 a decision-making tool for the management of 2nd ipsilateral breast tumor event. Breast Cancer Res
33
34 15 Treat. 2019;176(1):149-57.
35
36
37 16 63. Forster T, Akbaba S, Schmitt D, Krug D, El Shafie R, Oelmann-Avendano J, et al. Second breast
38
39 17 conserving therapy after ipsilateral breast tumor recurrence - a 10-year experience of re-irradiation.
40
41 18 Journal of contemporary brachytherapy. 2019;11(4):312-9.
42
43
44 19 64. Cozzi S, Jamal DN, Slocker A, Laplana M, Tejedor AG, Krengli M, et al. Second breast-conserving
45
46 20 therapy with interstitial brachytherapy (APBI) as a salvage treatment in ipsilateral breast tumor
47
48 21 recurrence: a retrospective study of 40 patients. Journal of contemporary brachytherapy.
49
50 22 2019;11(2):101-7.
51
52
53
54
55
56
57
58
59
60

- 1
2
3 1 65. Boehm KM, Chen J, Trichter S, Abdallah H, Zhuo R, Nowak EJ, et al. Characterization of
4
5 2 Recurrences Following Second Breast-Conserving Surgery with Intraoperative Radiotherapy. *Annals of*
6
7 3 *Surgical Oncology*. 2020;27(5):1638-44.
8
9
10 4 66. Li Q, Wang K, Yang L, Wu Q, Zhu W, Li Z, et al. Long-term Survival Comparison of Repeated
11
12 5 Breast-conserving Surgery Versus Mastectomy for Patients with DCIS with Ipsilateral Breast Tumor
13
14 6 Recurrence: A Real-world Longitudinal Study. *Clinical breast cancer*. 2021;21(4):360-72.
15
16
17 7 67. Wang J, Tang H, Yin K, Li X, Xie X, Hughes KS. Second invasive breast cancers in patients treated
18
19 8 with breast-conserving therapy. *European journal of surgical oncology : the journal of the European*
20
21 9 *Society of Surgical Oncology and the British Association of Surgical Oncology*. 2021;47(10):2492-8.
22
23 10 68. Chatzikonstantinou G, Strouthos I, Scherf C, Köhn J, Solbach C, Rödel C, et al. Interstitial
24
25 11 multicatheter HDR-brachytherapy as accelerated partial breast irradiation after second breast-
26
27 12 conserving surgery for locally recurrent breast cancer. *Journal of radiation research*. 2021;62(3):465-72.
28
29
30
31 13
32
33
34 14
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **1 Figure legends**
4
5

6 **2 Figure 1.** Flowchart of systematic review and meta-analysis of observational studies in
7 epidemiology. *2 studies were not explicitly described by the authors if they represented same
8 population as other publications
9
10

11
12
13 **6 Figure 2.** Forest plot of studies comparing repeat breast conserving surgery versus salvage
14 mastectomy for second local recurrence. * Study by Kurtz et al *International journal of radiation*
15 *oncology, biology, physics* 1990
16
17
18

19
20
21 **10 Figure 3.** Forest plot of studies comparing repeat breast conserving surgery versus salvage
22 mastectomy for overall survival.
23
24

25
26
27 **13 Supplemental Figure 1.** Leave-one-out meta-analysis forest plot of studies comparing repeat
28 breast conserving surgery versus salvage mastectomy for second local recurrence
29
30

31
32
33 **16 Supplemental Figure 2.** Leave-one-out meta-analysis forest plot of studies comparing repeat
34 breast conserving surgery versus salvage mastectomy for overall survival.
35
36

37 18

38 19

39 20

40 21
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Tables

Table 1. Characteristics of Included Studies.

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	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
(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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

	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

1
2

3 4 5 6 7 8	(56)	Kauer-Dorner et al	2012	IBC	IBC and DCIS	LR, OS	39	Yes	No	39	Yes PDR brachytherapy	No	4	1	3	8
9 10 11	(48)	Gentilini et al	2012	IBC	IBC	LR, OS	161	Yes	Yes*	161	No	No	4	2	3	9
12 13 14 15	(57)	Shah et al	2012	IBC and DCIS	IBC and DCIS	OS	18	Yes	NS	4	Yes APBI	NS	4	0	3	7
16 17 18	(58)	Demicheli et al	2013	IBC	NS	LR	338	Yes*	NS	148	Yes* (n=43)	NS	4	1	3	8
19 20 21 22 23 24 25 26 27 28	(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
29 30 31 32	(28)	Ishitobi et al†	2013	IBC	NS	LR, OS	271	Yes* (n=69)	NS	143	Yes* (n=1)	NS	4	2	3	9
33 34 35	(20)	Kolben et al	2015	IBC	IBC and DCIS	LR, OS	170	Yes	NS	58	Yes* (n=11)	NS	4	2	3	9
36 37 38 39	(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

40
41
42
43
44
45
46
47

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

(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

1
2

3										(n=11),					
4										PDR BT					
5										(n=8)					
6															
7															
8										Yes					
9	(64)	Cozzi et al	2019	IBC and DCIS	IBC and DCIS	LR, OS	40	Yes	NS	40	NS	4	0	3	7
10										HDR BT					
11															
12															
13	(17)	Su et al	2019	IBC	NS	OS	5098	Yes* (n=3687)	NS	1050	NS	4	2	3	9
14										Yes* (n=259)					
15															
16	(29)	Sagona et al†	2020	IBC and DCIS	IBC and DCIS	LR, OS	309	Yes* (n=300)	NS	143	NS	4	1	3	8
17										Yes* (n=50)					
18															
19	(65)	Boehm et al	2020	IBC and DCIS	IBC and DCIS	LR, OS	57	Yes* (n=55)	NS	57	NS	4	0	3	7
20										IORT					
21															
22															
23	(16)	Arthur et al	2020	IBC and DCIS	IBC and DCIS	LR, OS	58	Yes	NS	58	NS	4	0	3	7
24										Yes					
25										3D-CRT					
26										PBI					
27															
28	(15)	Van den Bruele et al	2021	IBC	IBC and DCIS	LR	322	Yes* (n=258)	NS	130	NS	4	2	3	9
29										Yes* (n=41)					
30															
31															
32	(14)	Wu et al	2020	IBC	NS	OS	2075	Yes	NS	475	NS	4	2	3	9
33										Yes* (n=255)					
34															
35	(19)	Gentile et al	2021	IBC	IBC and DCIS	LR, OS	309	Yes* (n=300)	NS	143	NS	4	2	3	9
36										Yes* (n=50)					
37															
38	(66)	Li et al	2021	DCIS	IBC and DCIS	LR, OS	5344	Yes* (n=2625)	NS	1812	NS	4	1	3	9
39										Yes* (n=735)					
40															
41															

42
43
44
45
46
47

1
2

3 4 5 6 7 8 9 10 11 12 13	(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
14 15 16	(67)	Wang et al	2021	IBC	NS	LR, OS	5413	Yes	NS	773	Yes* (n=124)	NS	4	2	3	9
17 18 19 20 21	(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
22 23 24	(13)	Baek et al	2021	IBC and DCIS	NS	OS	335	Yes* (n=303)	NS	155	Yes* (n=24)	NS	4	3	2	9

25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

IBC: 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).

Subgroup	rBCS			Salvage mastectomy		
	2 nd LR %	95% CI	Weight (%)	2 nd 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).

<i>Subgroup</i>	rBCS			Salvage mastectomy		
	%	95% CI	Weight (%)	%	95% CI	Weight (%)
<i>Primary diagnosis</i>						
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
<i>Propensity analysis performed</i>						
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
<i>Study design</i>						
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
<i>Concomitant radiotherapy*</i>						
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							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 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

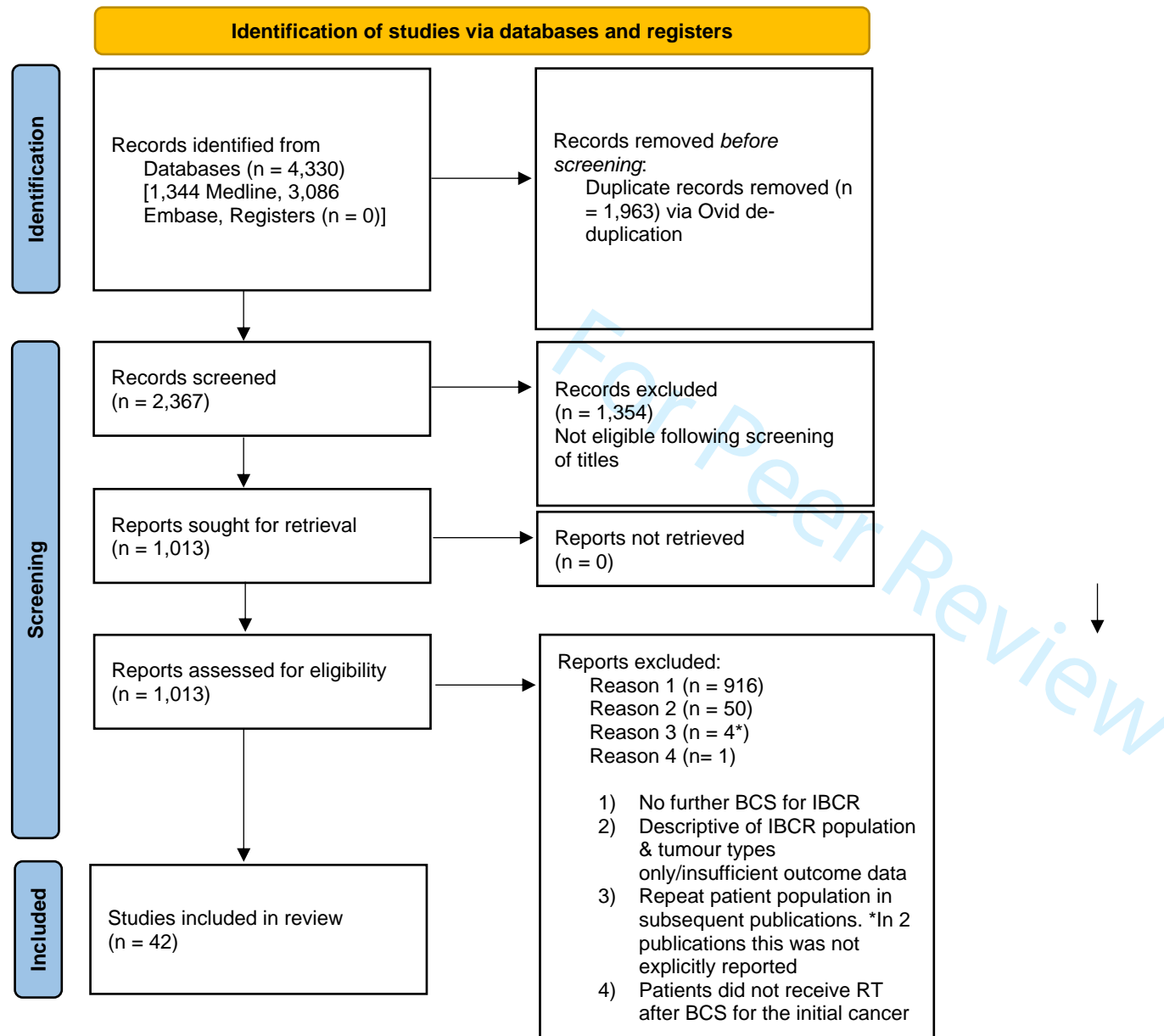
CI: confidence interval; RR: risk ratio

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

For Peer Review

Meta-analysis of Observational Studies in Epidemiology



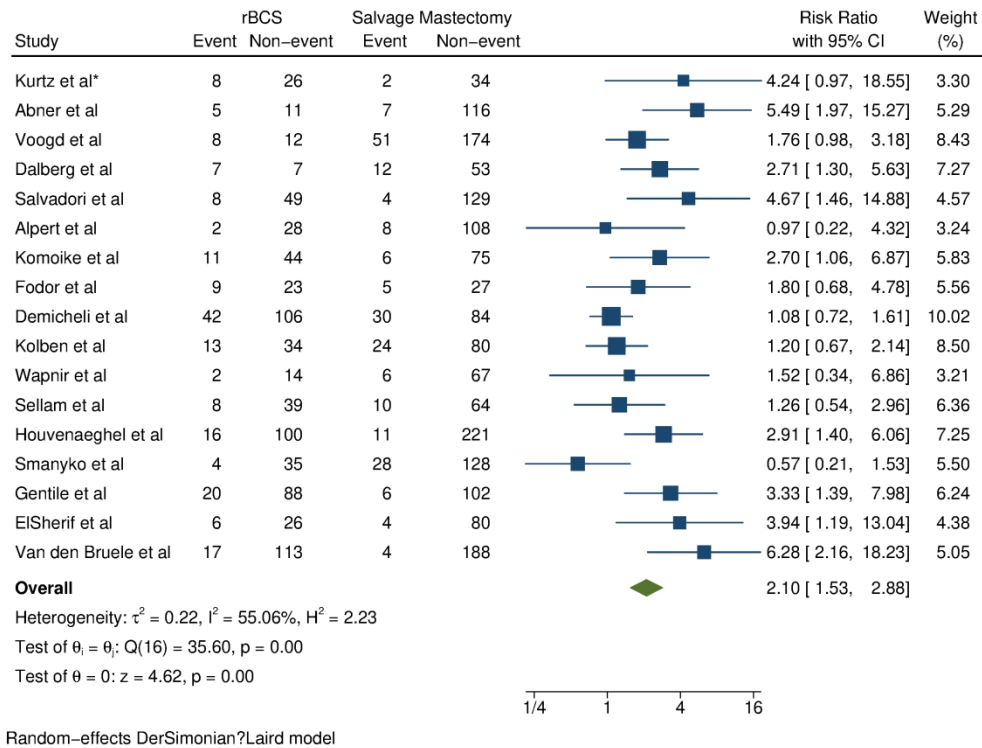


Figure 2. Forest plot of studies comparing repeat breast conserving surgery versus salvage mastectomy for second local recurrence. * Study by Kurtz et al International journal of radiation oncology, biology, physics 1990

571x433mm (118 x 118 DPI)

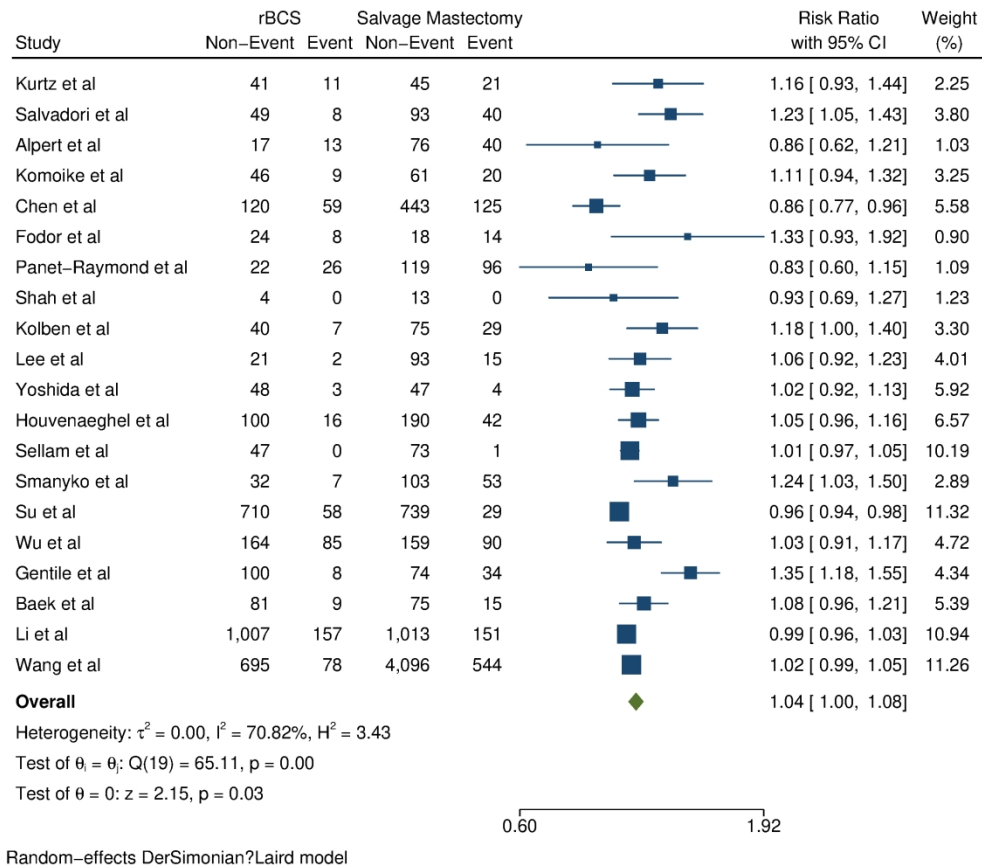


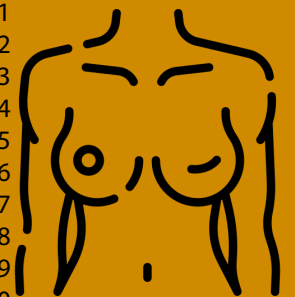
Figure 3. Forest plot of studies comparing repeat breast conserving surgery versus salvage mastectomy for overall survival.

551x484mm (118 x 118 DPI)

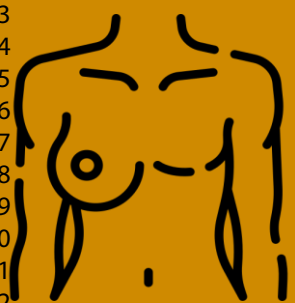
A Systematic Review and Meta-analysis on the role of

Repeat Breast Conserving Surgery for the Management of Ipsilateral Breast Cancer Recurrence

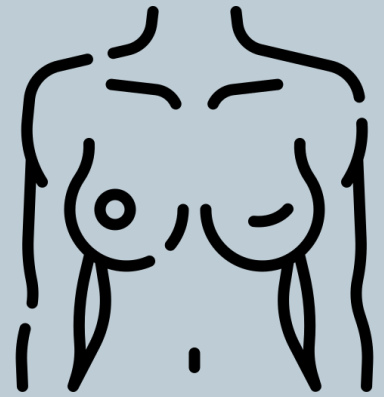
Breast conserving surgery standard of care for early-stage breast cancer



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

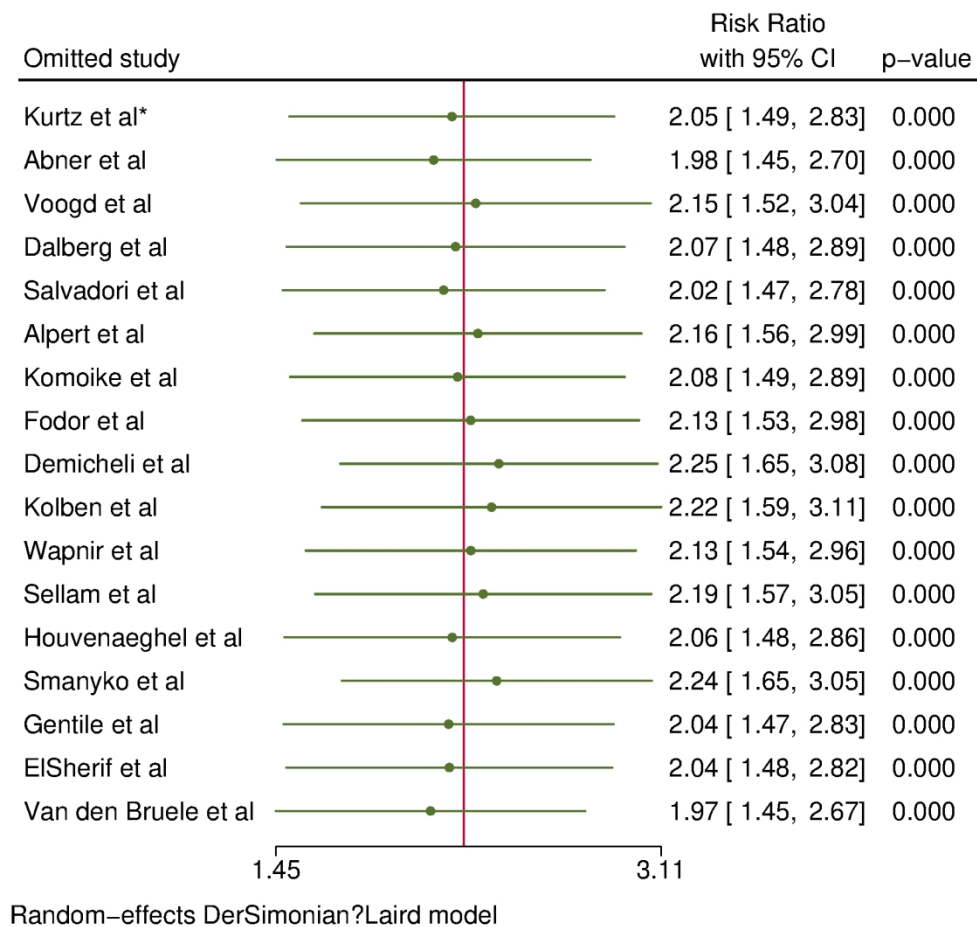
Repeat radiotherapy protective effect on 2nd LR

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

GRADE: very low certainty of evidence

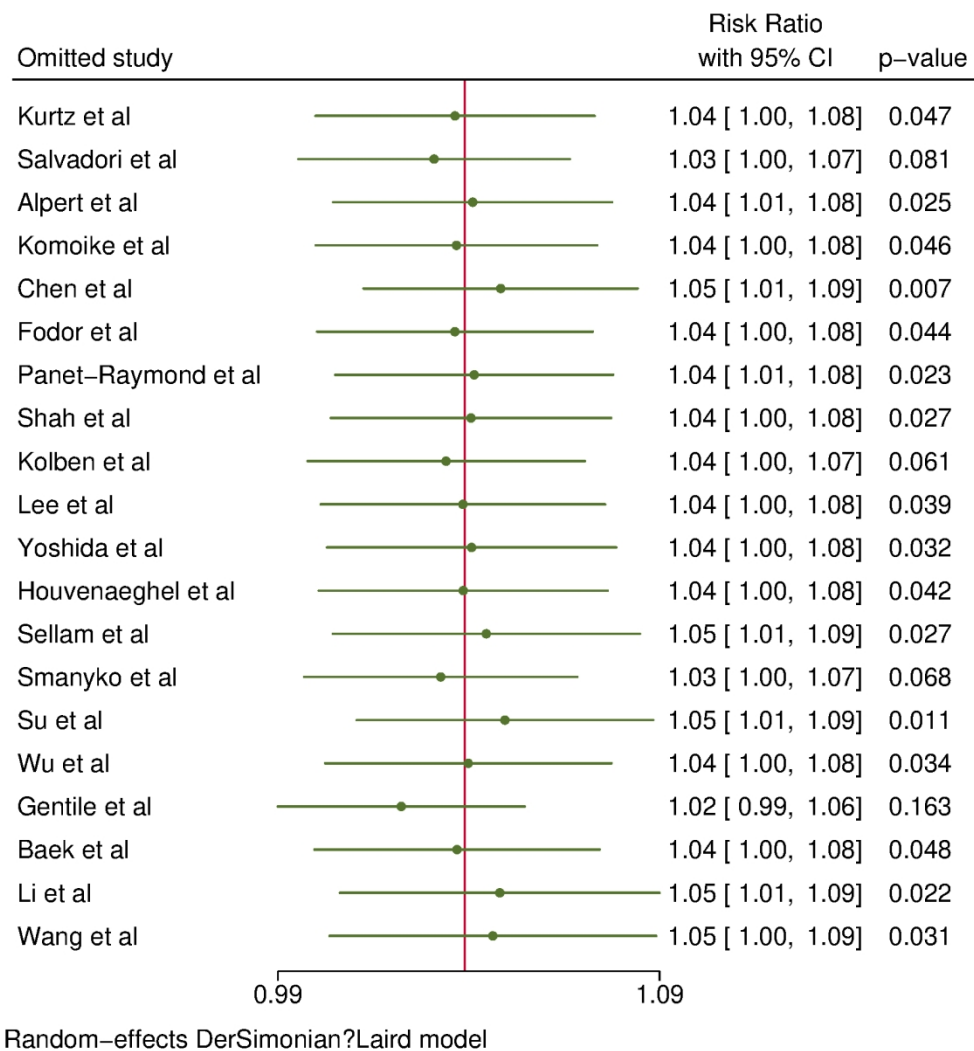
Tollan et al. *Ann Surg Oncol*.
Visual Abstract @CjSivarajan for @AnnSurgOncol

To contact the Journal office: info@asoeditorial.org



386x365mm (118 x 118 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



390x417mm (118 x 118 DPI)

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			

1
2
3 **1 Title Page**
4

5
6 **2 A systematic review and meta-analysis on the role of repeat breast conserving surgery for the**
7
8 **3 management of ipsilateral breast cancer recurrence**
9

10
11 **4**
12
13 **5 Running head: Redo breast conserving surgery for recurrence**
14

15 **6**
16
17
18 **7 Clare Josephine Tollan MD¹, Eirini Pantiora MD², Antonios Valachis MD³, Andreas Karakatsanis**
19
20 **8 MD², Marios Konstantinos Tasoulis MD^{1,4}**
21

22
23 **9 ¹ Breast Surgery Unit, The Royal Marsden NHS Foundation Trust, London, SW3 6JJ, UK**
24

25 **10 ² Department of Surgery, Uppsala University Hospital - Department of Surgical Sciences,**
26
27 **11 Uppsala University, Uppsala, 751 85, Sweden**
28

29
30 **12 ³ Department of Oncology, Faculty of Medicine and Health, Örebro University, Örebro, 701 82,**
31
32 **13 Sweden**
33

34
35 **14 ⁴ Division of Breast Cancer Research, The Institute of Cancer Research, Old Brompton Road,**
36
37 **15 London, SW7 3RP, UK**
38

39
40 **16**
41
42 **17 Corresponding author:**
43

44
45 **18 Mr Marios Konstantinos Tasoulis, MD, PhD, FEBS, CEBS, MFSTEd, FRCS**
46

47 **19 Consultant Breast Surgeon**
48

49
50 **20 Breast Surgery Unit, The Royal Marsden NHS Foundation Trust**
51

52 **21 Fulham Road, London, SW3 6JJ, UK**
53

54 **22 Email: marios.tasoulis@rmh.nhs.uk**
55
56
57
58
59
60

1

2 **Disclosures:** The authors have no relevant conflicts of interest to declare

3

4 Preliminary analysis and results were presented as poster at the 23rd Annual Meeting of the
5 American Society of Breast Surgeons, April 6-10, 2022, Las Vegas, NV, USA

For Peer Review

1 Synopsis

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

6 Abstract

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

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

17 **Results:** ~~425~~ observational studies met the criteria and were included in the analysis. The
18 pooled second LR rate after rBCS was ~~15.78%~~ (95%CI:~~12.13-19.76~~) and after salvage
19 mastectomy was ~~10.3% (95%CI:6.9-14.3)~~ 10.8% (95%CI:7.4-14.8). On meta-analysis of
20 comparative studies (n=~~178~~), the Risk Ratio (RR) for second LR following rBCS compared to
21 mastectomy was ~~2.103 (95%CI:1.535-2.883, p<0.001, I²=55.1%)~~ 1.950 (95%CI:1.411-2.695,
22 p<0.001, I²=60.1%). Repeat radiotherapy had a protective effect (coefficient:-0.317;95%CI:-

1 0.596, -0.038, p=0.026, I²=40.4%~~coefficient: -0.333; 95%CI: -0.617, -0.049, p= 0.022, I²=46.6%~~) for
2 second LR. Pooled 5-year OS was 86.78% (95%CI:83.4-89.690.0) vs 79.38% (95%CI:74.27-
3 834.95) for rBCS and salvage mastectomy respectively. Meta-analysis of comparative studies
4 (n=2024) showed a small OS benefit in favour of rBCS (RR:1.060040; 95%CI:1.018003-1.10079,
5 p<=0.001032, I²=7770.518%). Overall evidence certainty~~quality~~ was~~ranged from moderate to~~
6 very low.

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

1 Introduction

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

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

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

4 5 **Methods**

6 *Search strategy and Inclusion criteria*

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

1
2
3 1 *Data extraction*
4
5

6 2 Data extraction was performed independently by two authors (CJT and EP) in a preformed
7
8
9 3 Microsoft Excel© working sheet, ~~after two training sessions with the senior authors (AK and~~
10
11 4 ~~MKT) in a random sample of five studies, to standardize the extraction procedure.~~ The data
12
13 5 extraction procedure for the whole dataset (including all eligible studies) was standardised
14
15 6 during two training sessions with the senior authors (AK and MKT) using a random sample of
16
17 7 five studies. Disagreement was resolved by group consensus. The study methodology was
18
19 8 registered with PROSPERO International prospective register of systematic reviews
20
21 9 (CRD42021286123,
22
23 10 https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021286123).
24
25
26
27
28
29
30
31

32 12 *Quality assessment*
33
34

35 13 The Newcastle-Ottawa-Scale (NOS) (23) for observational studies, as assessed by two authors
36
37 14 (EP, AK) was used to evaluate the quality of the included studies. Publication bias was assessed
38
39 15 with funnel plots and the Egger's test for small studies. Following analyses and critical appraisal,
40
41 16 the GRADE approach (24) was used to assess the strength of evidence and recommendations by
42
43 17 two authors (AV and AK). Subsequently, knowledge gaps and research priorities were defined.
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 1 *Statistical analyses and reporting*
4
5

6 2 Rates of a second LR and OS at 5 years for rBCS and salvage mastectomy were calculated
7
8 3 separately, by pooling the outcomes from single-arm and comparative studies. Subgroup
9
10 4 analyses were performed depending on whether the reference population had initially been
11
12 5 treated for only DCIS, both DCIS and IBC or IBC only. Subgroup analyses were also undertaken
13
14 6 to define the effect of study design (comparative or single-arm), propensity score matching and
15
16 7 the effect of radiotherapy, regardless of the technique that was utilized. The median follow-up
17
18 8 was also extracted. Meta-analyses of comparative studies were also performed. ~~If preliminary
19
20 9 subgroup analyses had denoted any difference, meta-regression for the respective factor was
21
22 10 undertaken. Additionally, leave-one-out meta-analyses of comparative studies were performed,
23
24 11 to allow for the identification of studies with exaggerated effect sizes and guide further
25
26 12 subgroup and meta-regression analyses.~~ As literature search was expected to retrieve
27
28 13 observational studies, the use of a random-effects model using the DerSimonian Laird method
29
30 14 was decided *a priori*. For source studies directly reporting odds ratio (OR), risk ratio (RR) or
31
32 15 hazard ratio (HR), the adjusted analyses and Kaplan-Meier curves were considered for data
33
34 16 extraction and calculation of 5-year second LR and OS (25, 26). Effect sizes were reported with
35
36 17 95% confidence intervals (95% CI). Study heterogeneity was assessed with the I^2 statistic.
37
38
39
40
41
42
43
44
45

46 18 The manuscript was prepared according to the Meta-analysis Of Observational Studies in
47
48 19 Epidemiology (MOOSE) guidelines (27). Stata v17 (StataCorp. 2021. Stata Statistical Software:
49
50 20 Release 17. College Station, TX: StataCorp LLC.) was used for all statistical analyses.
51
52
53

54 21
55
56
57
58
59
60

1 Results

2 *Study selection and characteristics*

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

12 *Second Local Recurrence*

13 Source studies reporting on a second LR had a median follow-up ranging from 24.5 to 165.6
14 months [median of medians 7062 months, interquartile range (IQR): 52-732.5]. The overall
15 pooled incidence of a second LR after rBCS was 15.78% (95% CI: 12.13-19.76) and after salvage
16 mastectomy was 10.38% (95% CI: 76.49-14.38). Despite the fact these were separately pooled
17 outcomes without comparison, the confidence intervals were numerically overlapping,
18 suggesting that the difference may not be significant, but study heterogeneity was high. The
19 results of the subgroup analyses across all included studies are summarized in Table 2. Overall,
20 among patients treated with rBCS, those who received rRT had the lowest pooled second LR
21 rate compared to the other subgroups (9.68%, 95% CI: 5.08-15.38).

1 A total of 178 studies provided comparative data on second LR after rBCS and salvage
2 mastectomy. The median follow-up ranged from 30 to 165.5 months (median of medians 72.0-5
3 months, IQR: 52.5-79.6). In comparative studies, the pooled second LR rate was higher after
4 rBCS (19.63%, 95% CI: 15.5--24.02) versus after salvage mastectomy (9.61-9%, 95% CI: 6.7.38
5 --13.59) (Table 2). On meta-analysis, rBCS was associated with a significantly increased risk of
6 second LR [Risk Ratio (RR) = 2.1.103950; 95% CI: 1.535411 - 2.883695, $p < 0.001$, $I^2 = 55.60.1\%$),
7 as shown in Figure 2. Leave-one-out meta-analysis (Supplement, Figure S1) did not
8 demonstrate any differences. Only concomitant radiotherapy retained a protective effect in
9 meta-regression analysis (coefficient: -0.31733; 95% CI: -0.596617, -0.03849, $p = 0.0262$, $I^2 =$
10 40.6.46%). No publication bias or small-studies effect was detected (Egger's test beta1:
11 1.5400.11, $p = 0.103917$).

13 Overall Survival

14 Pooled OS rates and subgroup analyses for patients treated with rBCS or salvage mastectomy
15 are presented in Table 3. Overall, in-at a median follow-up ranging from 30 to 168 months
16 (median of medians 65.6 months, IQR: 57.5 - 73.9), the pooled 5-year OS rate was 86.78% (95%
17 CI: 83.4 - 89.690.0) after rBCS and 79.38% (95% CI: 74.2.7 - 83.84.95) after salvage mastectomy.
18 Subgroup analyses (Table 3) did not demonstrate any factor that correlated with difference in
19 outcomes for each group (rBCS or salvage mastectomy). Meta-analysis of comparative studies
20 (n=2021) showed a small OS benefit in favour of rBCS (RR: 1.060040, 95% CI: 1.018-003 -
21 1.104079, $p \leq 0.001032$, $I^2 = 77.70.518\%$) (Figure 3). The median follow-up in these studies

1 ranged from 42 to 168 months (median of medians 71.52 months, IQR: 59 – 130126.6). Leave-
2 one-out meta-analysis (Supplement, Figure S2) showed that the omission of four studies (one at
3 a time) would result in a difference, despite that the numeric value of the RR was not
4 significantly affected. Subsequent subgroup and meta-regression analysis was performed
5 (Supplement, Table S1). Radiotherapy did not affect the outcome on meta-regression analysis
6 (coefficient: 0.0260019; 95% CI: -0.0110274, 0.0640312, $p= 0.170898$, $I^2= 7870.58\%$). With
7 regards to primary tumor, studies reporting on both DCIS and IBC reported survival benefit for
8 rBCS (RR: 1.119; 95% CI: 1.019 – 1.230, $p=0.019$), but this effect was not retained on meta-
9 regression analysis (coefficient: 0.0721; 95% CI: -0.0017, 0.1458, $p=0.056$). When looking into
10 publication bias, the Egger's test detected small-studies effect (Egger's test beta1: 0.93, $p=$
11 0.041).~~No publication bias or small studies effect was detected (Egger's test beta1: 0.94, $p=$~~
12 0.062).

14 *Study quality and strength of recommendations*

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

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

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

9 Discussion

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

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

4 The present systematic literature review showed variable second LR rates after rBCS. The
5 overall pooled second LR rate was found to be 15.87% after rBCS compared to 10.83% after
6 salvage mastectomy. However, it should be noted that the included studies are markedly
7 heterogeneous, and there was not a standardized multidisciplinary treatment protocol for the
8 management of IBCR. In addition, it is important to highlight that in a number of studies, a
9 proportion of patients did not receive RT for the management of the primary cancer, with not
10 enough data provided to allow stratification for this in the analysis. On meta-analysis, rBCS was
11 associated with a significantly higher RR for second LR (RR= 2.1031-950), albeit with moderate
12 study heterogeneity. This RR is similar to that reported in a recent meta-analysis (RR = 1.87)
13 (40). The small observed difference may be explained by the fact that the present meta-analysis
14 included 187 studies providing data on second LR compared to 13 studies in the meta-analysis
15 by Mo et al (40).

16 On sub-group analysis, the lowest second LR rate among patients treated with rBCS was
17 observed in those receiving rRT (9.68%). The protective effect of rRT was also demonstrated in
18 meta-regression analysis. This finding is in line with previous reports highlighting the potentially
19 important role of rRT in improving local control after rBCS for IBCR (35, 40). This is an important
20 consideration when individualizing the management plan especially as a number of rRT options,
21 for example brachytherapy (41-43), intraoperative radiotherapy (44, 45) and external beam
22 radiotherapy (16) have been shown to be associated with acceptable toxicity profile. In the

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

6 Despite the finding that rBCS may be associated with a higher risk of second LR, which was
7 ~~almost~~ two-fold higher based on the results of the present meta-analysis, it may not have a
8 negative impact on survival. A number of retrospective studies have shown that OS was not
9 inferior or was even improved in patients treated with rBCS with or without rRT compared to
10 those treated with salvage mastectomy (13, 15, 19, 29, 30, 43, 46). An analysis of the
11 Surveillance, Epidemiology, and End Results (SEER) database including data from 1998 to 2013
12 showed no significant difference in terms of OS and BCSS in patients treated with rBCS or
13 salvage mastectomy (14). However, another analysis of the SEER database looking into data
14 from 1973 to 2003 showed different results (17). In this study the authors found that rBCS was
15 associated with worse OS and BCSS and that rRT had a protective effect in terms of OS.
16 Although, there is no clear explanation for the discordant findings, a potential reason may be
17 the different time periods, as multidisciplinary breast cancer management has significantly
18 evolved over the past decades. A recent meta-analysis by Mo et al also supports the findings
19 that rBCS may not be associated with worse OS (40). The results of the present meta-analysis
20 showed a ~~small~~ [marginal](#) benefit in OS in favour of rBCS (RR: 1.0640). The difference between
21 the two meta-analyses may be explained by the different number of included studies (8 versus
22 ~~2021~~ in the present analysis). The median NOS of the studies (10-12, 34, 38, 43, 46, 47) included

1 in the meta-analysis by Mo et al (40) is 9 (IQR: 7-9), and the median NOS of the studies in the
2 present meta-analysis is also 9 (IQR: 8-9), with the additional ~~13~~12 studies having a median
3 NOS of 9 (IQR: ~~8.59~~9). It has to be noted though that a small-study effect was found,
4 underlining potential publication bias. While such an effect was not detected in the meta-
5 analysis by Mo et al (40) cautiousness is required due the small number of included studies.

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

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

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

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

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

4 **Conclusions**

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

12 **References**

- 14 1. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up
15 of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for
16 the treatment of invasive breast cancer. *N Engl J Med.* 2002;347(16):1233-41.
- 17 2. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of
18 a randomized study comparing breast-conserving surgery with radical mastectomy for early breast
19 cancer. *N Engl J Med.* 2002;347(16):1227-32.
- 20 3. Effects of Radiotherapy and Surgery in Early Breast Cancer — An Overview of the Randomized
21 Trials. *New England Journal of Medicine.* 1995;333(22):1444-56.

- 1 4. Bouganim N, Tsvetkova E, Clemons M, Amir E. Evolution of sites of recurrence after early breast
2 cancer over the last 20 years: implications for patient care and future research. *Breast Cancer Research
3 and Treatment*. 2013;139(2):603-6.
- 4 5. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast
5 cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials. *The
6 Lancet*. 2011;378(9804):1707-16.
- 7 6. Wapnir IL, Anderson SJ, Mamounas EP, Geyer CE, Jeong J-H, Tan-Chiu E, et al. Prognosis After
8 Ipsilateral Breast Tumor Recurrence and Locoregional Recurrences in Five National Surgical Adjuvant
9 Breast and Bowel Project Node-Positive Adjuvant Breast Cancer Trials. *Journal of Clinical Oncology*.
10 2006;24(13):2028-37.
- 11 7. Bosma SCJ, van der Leij F, van Werkhoven E, Bartelink H, Wesseling J, Linn S, et al. Very low local
12 recurrence rates after breast-conserving therapy: analysis of 8485 patients treated over a 28-year
13 period. *Breast Cancer Research and Treatment*. 2016;156(2):391-400.
- 14 8. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Breast
15 Cancer. v2.2022 https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed 21 Jun
16 2022.
- 17 9. Kurtz JM, Amalric R, Brandone H, Ayme Y, Spitalier JM. Results of salvage surgery for mammary
18 recurrence following breast-conserving therapy. *Ann Surg*. 1988;207(3):347-51.
- 19 10. Salvadori B, Marubini E, Miceli R, Conti AR, Cusumano F, Andreola S, et al. Reoperation for
20 locally recurrent breast cancer in patients previously treated with conservative surgery. *The British
21 journal of surgery*. 1999;86(1):84-7.
- 22 11. Alpert TE, Kuerer HM, Arthur DW, Lannin DR, Haffty BG. Ipsilateral breast tumor recurrence
23 after breast conservation therapy: outcomes of salvage mastectomy vs. salvage breast-conserving

- 1
2
3 1 surgery and prognostic factors for salvage breast preservation. International journal of radiation
4
5 2 oncology, biology, physics. 2005;63(3):845-51.
6
7
8 3 12. Komoike Y, Akiyama F, Iino Y, Ikeda T, Tanaka-Akashi S, Ohsumi S, et al. Analysis of ipsilateral
9
10 4 breast tumor recurrences after breast-conserving treatment based on the classification of true
11
12 5 recurrences and new primary tumors. Breast cancer (Tokyo, Japan). 2005;12(2):104-11.
13
14 6 13. Baek SY, Kim J, Chung IY, Ko BS, Kim HJ, Lee JW, et al. Long-term survival outcomes of repeat
15
16 7 lumpectomy for ipsilateral breast tumor recurrence: a propensity score-matched analysis. Breast Cancer
17
18 8 Research and Treatment. 2021;185(1):155-64.
19
20 9 14. Wu Y, Shi X, Li J, Wu G. Prognosis of Surgical Treatment After Ipsilateral Breast Tumor
21
22 10 Recurrence. Journal of Surgical Research. 2021;258:23-37.
23
24 11 15. Van den Bruele AB, Chen I, Sevilimedu V, Le T, Morrow M, Braunstein LZ, et al. Management of
25
26 12 ipsilateral breast tumor recurrence following breast conservation surgery: a comparative study of re-
27
28 13 conservation vs mastectomy. Breast Cancer Research and Treatment. 2021;187(1):105-12.
29
30 14 16. Arthur DW, Winter KA, Kuerer HM, Haffty B, Cuttino L, Todor DA, et al. Effectiveness of Breast-
31
32 15 Conserving Surgery and 3-Dimensional Conformal Partial Breast Reirradiation for Recurrence of Breast
33
34 16 Cancer in the Ipsilateral Breast: The NRG Oncology/RTOG 1014 Phase 2 Clinical Trial. JAMA oncology.
35
36 17 2020;6(1):75-82.
37
38 18 17. Su Y, Guo R, Xue J, Chi Y, Chi W, Wang J, et al. Increased Mortality with Repeat Lumpectomy
39
40 19 Alone After Ipsilateral Breast Tumor Recurrence. The oncologist. 2019;24(9):e818-e27.
41
42 20 18. Dalberg K, Mattsson A, Sandelin K, Rutqvist LE. Outcome of treatment for ipsilateral breast
43
44 21 tumor recurrence in early-stage breast cancer. Breast Cancer Res Treat. 1998;49(1):69-78.
45
46 22 19. Gentile D, Sagona A, Barbieri E, Antunovic L, Franceschini D, Losurdo A, et al. Breast conserving
47
48 23 surgery versus salvage mastectomy for ipsilateral breast cancer recurrence: a propensity score matching
49
50 24 analysis. Updates in Surgery. 2021.
51
52
53
54
55
56
57
58
59
60

- 1 20. Kolben T, Schwarz TM, Goess C, Blume C, Degenhardt T, Engel J, et al. Surgical management of
2 ipsilateral breast tumor recurrence. *International Journal of Surgery*. 2015;23:141-6.
- 3 21. ElSherif A, Shah C, Downs-Kelly E, Alhareb A, Valente SA, Tu C, et al. Outcomes of ipsilateral
4 breast tumor recurrence after breast conserving surgery: Repeat lumpectomy as an alternative to
5 salvage mastectomy. *Surgery*. 2022;171(3):673-81.
- 6 22. Burstein HJ, Curigliano G, Thürlimann B, Weber WP, Poortmans P, Regan MM, et al. Customizing
7 local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus
8 Guidelines for treatment of early breast cancer 2021. *Annals of oncology : official journal of the*
9 *European Society for Medical Oncology*. 2021;32(10):1216-35.
- 10 23. Wells GA, Wells G, Shea B, Shea B, O'Connell D, Peterson J, et al., editors. The Newcastle-Ottawa
11 Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses 2014.
- 12 24. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging
13 consensus on rating quality of evidence and strength of recommendations. *BMJ (Clinical research ed)*.
14 2008;336(7650):924-6.
- 15 25. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the
16 published literature for survival endpoints. *Statistics in medicine*. 1998;17(24):2815-34.
- 17 26. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating
18 summary time-to-event data into meta-analysis. *Trials*. 2007;8(1):16.
- 19 27. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of
20 observational studies in epidemiology: a proposal for reporting. *Meta-analysis Of Observational Studies*
21 *in Epidemiology (MOOSE) group*. *Jama*. 2000;283(15):2008-12.
- 22 28. Ishitobi M, Okumura Y, Nishimura R, Nakatsukasa K, Tanabe M, Yoshida A, et al. Repeat
23 lumpectomy for ipsilateral breast tumor recurrence (IBTR) after breast-conserving surgery: the impact of
24 radiotherapy on second IBTR. *Breast cancer (Tokyo, Japan)*. 2014;21(6):754-60.

- 1
2
3 1 29. Sagona A, Gentile D, Anghelone CAP, Barbieri E, Marrazzo E, Antunovic L, et al. Ipsilateral Breast
4
5 2 Cancer Recurrence: Characteristics, Treatment, and Long-Term Oncologic Results at a High-Volume
6
7 3 Center. *Clinical breast cancer*. 2021;21(4):329-36.
8
9
10 4 30. Yoshida A, Takahashi O, Okumura Y, Arima N, Nakatsukasa K, Tanabe M, et al. Prognosis after
11
12 5 mastectomy versus repeat lumpectomy in patients with ipsilateral breast cancer recurrence: A
13
14 6 propensity score analysis. *European Journal of Surgical Oncology*. 2016;42(4):474-80.
15
16
17 7 31. Anderson SJ, Wapnir I, Dignam JJ, Fisher B, Mamounas EP, Jeong JH, et al. Prognosis after
18
19 8 ipsilateral breast tumor recurrence and locoregional recurrences in patients treated by breast-
20
21 9 conserving therapy in five National Surgical Adjuvant Breast and Bowel Project protocols of node-
22
23 10 negative breast cancer. *Journal of clinical oncology : official journal of the American Society of Clinical*
24
25 11 *Oncology*. 2009;27(15):2466-73.
26
27
28 12 32. Wapnir IL, Anderson SJ, Mamounas EP, Geyer CE, Jr., Jeong JH, Tan-Chiu E, et al. Prognosis after
29
30 13 ipsilateral breast tumor recurrence and locoregional recurrences in five National Surgical Adjuvant
31
32 14 Breast and Bowel Project node-positive adjuvant breast cancer trials. *Journal of clinical oncology :*
33
34 15 *official journal of the American Society of Clinical Oncology*. 2006;24(13):2028-37.
35
36
37 16 33. Walstra C, Schipper RJ, Poodt IGM, van Riet YE, Voogd AC, van der Sangen MJC, et al. Repeat
38
39 17 breast-conserving therapy for ipsilateral breast cancer recurrence: A systematic review. *European*
40
41 18 *journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British*
42
43 19 *Association of Surgical Oncology*. 2019;45(8):1317-27.
44
45
46 20 34. Fodor J, Major T, Polgár C, Orosz Z, Sulyok Z, Kásler M. Prognosis of patients with local
47
48 21 recurrence after mastectomy or conservative surgery for early-stage invasive breast cancer. *Breast*
49
50 22 *(Edinburgh, Scotland)*. 2008;17(3):302-8.
51
52
53
54
55
56
57
58
59
60

- 1
2
3 1 35. Montagne L, Hannoun A, Hannoun-Levi J-M. Second conservative treatment for second
4
5 2 ipsilateral breast tumor event: A systematic review of the different re-irradiation techniques. *The Breast*.
6
7 3 2020;49:274-80.
8
9
10 4 36. Al-Ghazal SK, Fallowfield L, Blamey RW. Comparison of psychological aspects and patient
11
12 5 satisfaction following breast conserving surgery, simple mastectomy and breast reconstruction. *Eur J*
13
14 6 *Cancer*. 2000;36(15):1938-43.
15
16
17 7 37. Flanagan MR, Zabor EC, Romanoff A, Fuzesi S, Stempel M, Mehrara BJ, et al. A Comparison of
18
19 8 Patient-Reported Outcomes After Breast-Conserving Surgery and Mastectomy with Implant Breast
20
21 9 Reconstruction. *Ann Surg Oncol*. 2019;26(10):3133-40.
22
23
24 10 38. Chen SL, Martinez SR. The survival impact of the choice of surgical procedure after ipsilateral
25
26 11 breast cancer recurrence. *American journal of surgery*. 2008;196(4):495-9.
27
28 12 39. Panet-Raymond V, Truong PT, Alexander C, Lesperance M, McDonald RE, Watson PH.
29
30 13 Clinicopathologic factors of the recurrent tumor predict outcome in patients with ipsilateral breast
31
32 14 tumor recurrence. *Cancer*. 2011;117(10):2035-43.
33
34
35 15 40. Mo C, Ruan W, Lin J, Chen H, Chen X. Repeat Breast-Conserving Surgery Versus Salvage
36
37 16 Mastectomy for Ipsilateral Breast Tumour Recurrence After Breast-Conserving Surgery in Breast Cancer
38
39 17 Patients: A Meta-Analysis. *Frontiers in Oncology*. 2021;11.
40
41
42 18 41. Hannoun-Levi JM, Resch A, Gal J, Kauer-Dorner D, Strnad V, Niehoff P, et al. Accelerated partial
43
44 19 breast irradiation with interstitial brachytherapy as second conservative treatment for ipsilateral breast
45
46 20 tumour recurrence: multicentric study of the GEC-ESTRO Breast Cancer Working Group. *Radiotherapy*
47
48 21 *and oncology : journal of the European Society for Therapeutic Radiology and Oncology*.
49
50 22 2013;108(2):226-31.
51
52
53
54
55
56
57
58
59
60

- 1
2
3 1 42. Chadha M, Feldman S, Boolbol S, Wang L, Harrison LB. The feasibility of a second lumpectomy
4 and breast brachytherapy for localized cancer in a breast previously treated with lumpectomy and
5 radiation therapy for breast cancer. *Brachytherapy*. 2008;7(1):22-8.
6
7
8 43. Smanyakó V, Mészáros N, Újhelyi M, Fröhlich G, Stelczer G, Major T, et al. Second breast-
9 conserving surgery and interstitial brachytherapy vs. salvage mastectomy for the treatment of local
10 recurrences: 5-year results. *Brachytherapy*. 2019;18(3):411-9.
11
12
13 44. Thangarajah F, Heilmann J, Malter W, Kunze S, Marnitz S, Mallmann P, et al. Breast conserving
14 surgery in combination with intraoperative radiotherapy after previous external beam therapy: an
15 option to avoid mastectomy. *Breast Cancer Research and Treatment*. 2018;168(3):739-44.
16
17
18 45. Kraus-Tiefenbacher U, Bauer L, Scheda A, Schoeber C, Schaefer J, Steil V, et al. Intraoperative
19 radiotherapy (IORT) is an option for patients with localized breast recurrences after previous external-
20 beam radiotherapy. *BMC cancer*. 2007;7:178.
21
22
23 46. Lee JH, Lee SK, Park SM, Ryu JM, Paik HJ, Yi HW, et al. Independent Prognostic Factors for
24 Overall Survival after Salvage Operation for Ipsilateral Breast Tumor Recurrence Following Breast-
25 Conserving Surgery. *Journal of breast cancer*. 2015;18(4):386-93.
26
27
28 47. Sellam Y, Shahadi ID, Gelernter I, Zippel D, Sklair-Levy M, Symon Z, et al. Local recurrence of
29 breast cancer: Salvage lumpectomy as an option for local treatment. *The breast journal*. 2019;25(4):619-
30 24.
31
32
33 48. Gentilini O, Botteri E, Veronesi P, Sangalli C, Del Castillo A, Ballardini B, et al. Repeating
34 conservative surgery after ipsilateral breast tumor reappearance: criteria for selecting the best
35 candidates. *Ann Surg Oncol*. 2012;19(12):3771-6.
36
37
38 49. Harms W, Budach W, Dunst J, Feyer P, Fietkau R, Haase W, et al. DEGRO practical guidelines for
39 radiotherapy of breast cancer VI: therapy of locoregional breast cancer recurrences. *Strahlentherapie
40 und Onkologie : Organ der Deutschen Röntgengesellschaft [et al]*. 2016;192(4):199-208.
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 1 50. Kurtz JM, Spitalier JM, Amalric R, Brandone H, Ayme Y, Jacquemier J, et al. The prognostic
4
5 2 significance of late local recurrence after breast-conserving therapy. *International journal of radiation*
6
7 3 *oncology, biology, physics*. 1990;18(1):87-93.
8
9
10 4 51. Abner AL, Recht A, Eberlein T, Come S, Shulman L, Hayes D, et al. Prognosis following salvage
11
12 5 mastectomy for recurrence in the breast after conservative surgery and radiation therapy for early-stage
13
14 6 breast cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*.
15
16 7 1993;11(1):44-8.
17
18
19 8 52. Voogd AC, van Tienhoven G, Peterse HL, Crommelin MA, Rutgers EJ, van de Velde CJ, et al. Local
20
21 9 recurrence after breast conservation therapy for early stage breast carcinoma: detection, treatment,
22
23 10 and outcome in 266 patients. Dutch Study Group on Local Recurrence after Breast Conservation
24
25 11 (BORST). *Cancer*. 1999;85(2):437-46.
26
27
28 12 53. Deutsch M. Repeat high-dose external beam irradiation for in-breast tumor recurrence after
29
30 13 previous lumpectomy and whole breast irradiation. *International journal of radiation oncology, biology,*
31
32 14 *physics*. 2002;53(3):687-91.
33
34
35 15 54. Hannoun-Levi JM, Houvenaeghel G, Ellis S, Teissier E, Alzieu C, Lallement M, et al. Partial breast
36
37 16 irradiation as second conservative treatment for local breast cancer recurrence. *International journal of*
38
39 17 *radiation oncology, biology, physics*. 2004;60(5):1385-92.
40
41
42 18 55. Botteri E, Rotmensz N, Sangalli C, Toesca A, Peradze N, De Oliveira Filho HR, et al. Unavoidable
43
44 19 mastectomy for ipsilateral breast tumour recurrence after conservative surgery: patient outcome.
45
46 20 *Annals of Oncology*. 2009;20(6):1008-12.
47
48
49 21 56. Kauer-Dorner D, Pötter R, Resch A, Handl-Zeller L, Kirchheiner K, Meyer-Schell K, et al. Partial
50
51 22 breast irradiation for locally recurrent breast cancer within a second breast conserving treatment:
52
53 23 alternative to mastectomy? Results from a prospective trial. *Radiotherapy and oncology : journal of the*
54
55 24 *European Society for Therapeutic Radiology and Oncology*. 2012;102(1):96-101.
56
57
58
59
60

- 1
2
3 1 57. Shah C, Wilkinson JB, Jawad M, Wobb J, Berry S, Mitchell C, et al. Outcome after ipsilateral
4
5 2 breast tumor recurrence in patients with early-stage breast cancer treated with accelerated partial
6
7 3 breast irradiation. *Clinical breast cancer*. 2012;12(6):392-7.
8
9
10 4 58. Demicheli R, Ardoino I, Ambrogi F, Agresti R, Biganzoli E. Significance of ipsilateral breast tumor
11
12 5 recurrence after breast conserving treatment: role of surgical removal. *Chinese journal of cancer*
13
14 6 research = *Chung-kuo yen cheng yen chiu*. 2013;25(1):22-31.
15
16
17 7 59. Wapnir IL, Gelber S, Anderson SJ, Mamounas EP, Robidoux A, Martin M, et al. Poor Prognosis
18
19 8 After Second Locoregional Recurrences in the CALOR Trial. *Ann Surg Oncol*. 2017;24(2):398-406.
20
21 9 60. Ishitobi M, Fukui R, Hashimoto Y, Kittaka N, Nakayama T, Tamaki Y. Safety for Repeat
22
23 10 Lumpectomy Without Radiotherapy for Ipsilateral Breast Tumor Recurrence. *Anticancer research*.
24
25 11 2017;37(9):5293-9.
26
27
28 12 61. Houvenaeghel G, Boher JM, Michel V, Bannier M, Minsat M, Tallet A, et al. Survival after breast
29
30 13 cancer local recurrence according to therapeutic strategies. *European journal of surgical oncology : the*
31
32 14 *journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology*.
33
34 15 2017;43(8):1409-14.
35
36
37 16 62. Montagne L, Gal J, Chand ME, Schiappa R, Falk AT, Kinj R, et al. GEC-ESTRO APBI classification as
38
39 17 a decision-making tool for the management of 2nd ipsilateral breast tumor event. *Breast Cancer Res*
40
41 18 *Treat*. 2019;176(1):149-57.
42
43
44 19 63. Forster T, Akbaba S, Schmitt D, Krug D, El Shafie R, Oelmann-Avendano J, et al. Second breast
45
46 20 conserving therapy after ipsilateral breast tumor recurrence - a 10-year experience of re-irradiation.
47
48 21 *Journal of contemporary brachytherapy*. 2019;11(4):312-9.
49
50
51 22 64. Cozzi S, Jamal DN, Slocker A, Laplana M, Tejedor AG, Krengli M, et al. Second breast-conserving
52
53 23 therapy with interstitial brachytherapy (APBI) as a salvage treatment in ipsilateral breast tumor
54
55
56
57
58
59
60

- 1
2
3 1 recurrence: a retrospective study of 40 patients. *Journal of contemporary brachytherapy*.
4
5 2 2019;11(2):101-7.
6
7 3 65. Boehm KM, Chen J, Trichter S, Abdallah H, Zhuo R, Nowak EJ, et al. Characterization of
8
9 4 Recurrences Following Second Breast-Conserving Surgery with Intraoperative Radiotherapy. *Annals of*
10
11 5 *Surgical Oncology*. 2020;27(5):1638-44.
12
13
14 6 66. Li Q, Wang K, Yang L, Wu Q, Zhu W, Li Z, et al. Long-term Survival Comparison of Repeated
15
16 7 Breast-conserving Surgery Versus Mastectomy for Patients with DCIS with Ipsilateral Breast Tumor
17
18 8 Recurrence: A Real-world Longitudinal Study. *Clinical breast cancer*. 2021;21(4):360-72.
19
20
21 9 67. Wang J, Tang H, Yin K, Li X, Xie X, Hughes KS. Second invasive breast cancers in patients treated
22
23 10 with breast-conserving therapy. *European journal of surgical oncology : the journal of the European*
24
25 11 *Society of Surgical Oncology and the British Association of Surgical Oncology*. 2021;47(10):2492-8.
26
27
28 12 68. Chatzikonstantinou G, Strouthos I, Scherf C, Köhn J, Solbach C, Rödel C, et al. Interstitial
29
30 13 multicatheter HDR-brachytherapy as accelerated partial breast irradiation after second breast-
31
32 14 conserving surgery for locally recurrent breast cancer. *Journal of radiation research*. 2021;62(3):465-72.
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **1 Figure legends**
4
5

6 **2 Figure 1.** Flowchart of systematic review and meta-analysis of observational studies in
7 epidemiology. *2 studies were not explicitly described by the authors if they represented same
8 population as other publications
9
10
11
12

13 **6 Figure 2.** Forest plot of studies comparing repeat breast conserving surgery versus salvage
14 mastectomy for second local recurrence. * Study by Kurtz et al *International journal of radiation*
15 *oncology, biology, physics* 1990
16
17
18
19

20
21 **10 Figure 3.** Forest plot of studies comparing repeat breast conserving surgery versus salvage
22 mastectomy for overall survival.
23
24
25

26
27 **13 Supplemental Figure 1.** Leave-one-out meta-analysis forest plot of studies comparing repeat
28 breast conserving surgery versus salvage mastectomy for second local recurrence
29
30

31
32
33 **16 Supplemental Figure 2.** Leave-one-out meta-analysis forest plot of studies comparing repeat
34 breast conserving surgery versus salvage mastectomy for overall survival.
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Tables

Table 1. Characteristics of Included Studies.

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	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
(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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

	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

1
2

3 4 5 6 7 8	(56)	Kauer-Dorner et al	2012	IBC	IBC and DCIS	LR, OS	39	Yes	No	39	Yes PDR brachytherapy	No	4	1	3	8
9 10 11	(48)	Gentilini et al	2012	IBC	IBC	LR, OS	161	Yes	Yes*	161	No	No	4	2	3	9
12 13 14 15	(57)	Shah et al	2012	<u>IBC and DCIS</u>	IBC and DCIS	OS	18	Yes	NS	4	Yes APBI	NS	4	0	3	7
16 17 18	(58)	Demicheli et al	2013	IBC	NS	LR	338	Yes*	NS	148	Yes* (n=43)	NS	4	1	3	8
19 20 21 22 23 24 25 26 27 28	(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
29 30 31 32	(28)	Ishitobi et al†	2013	IBC	NS	LR, OS	271	Yes* (n=69)	NS	143	Yes* (n=1)	NS	4	2	3	9
33 34 35	(20)	Kolben et al	2015	IBC	IBC and DCIS	LR, OS	170	Yes	NS	58	Yes* (n=11)	NS	4	2	3	9
36 37 38 39	(46)	Lee et al	2015	<u>IBC and DCIS</u>	IBC and DCIS	OS	157	Yes* (n=135)	NS	23	Yes* (n=13)	NS	4	2	3	9

40
41
42
43
44
45
46
47

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

(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

1
2

3										(n=11),					
4										PDR BT					
5										(n=8)					
6															
7															
8										Yes					
9	(64)	Cozzi et al	2019	<u>IBC and DCIS</u>	IBC and DCIS	LR, OS	40	Yes	NS	40	NS	4	0	3	7
10										HDR BT					
11															
12															
13	(17)	Su et al	2019	IBC	NS	OS	5098	Yes* (n=3687)	NS	1050	NS	4	2	3	9
14															
15										Yes* (n=259)					
16															
17	(29)	Sagona et al†	2020	<u>IBC and DCIS</u>	IBC and DCIS	LR, OS	309	Yes* (n=300)	NS	143	NS	4	1	3	8
18										Yes* (n=50)					
19															
20	(65)	Boehm et al	2020	<u>IBC and DCIS</u>	IBC and DCIS	LR, OS	57	Yes* (n=55)	NS	57	NS	4	0	3	7
21										IORT					
22															
23										Yes					
24	(16)	Arthur et al	2020	IBC and DCIS	IBC and DCIS	LR, OS	58	Yes	NS	58	NS	4	0	3	7
25										3D-CRT					
26										PBI					
27															
28															
29	(15)	Van den Bruele et al	2021	IBC	IBC and DCIS	LR	322	Yes* (n=258)	NS	130	NS	4	2	3	9
30										Yes* (n=41)					
31															
32	(14)	Wu et al	2020	IBC	NS	OS	2075	Yes	NS	475	NS	4	2	3	9
33										Yes* (n=255)					
34															
35	(19)	Gentile et al	2021	IBC	IBC and DCIS	LR, OS	309	Yes* (n=300)	NS	143	NS	4	2	3	9
36										Yes* (n=50)					
37															
38															
39	(66)	Li et al	2021	DCIS	IBC and DCIS	LR, OS	5344	Yes* (n=2625)	NS	1812	NS	4	1	3	9
40										Yes* (n=735)					
41															

42
43
44
45
46
47

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

(21)	El Sherif et al	2021	IBC <u>and</u> <u>DCIS</u>	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 <u>and</u> <u>DCIS</u>	IBC and DCIS	LR, OS	20	Yes	Yes*	20	Yes HDR BT	NS	4	0	3	7
(13)	Baek et al	2021	IBC <u>and</u> <u>DCIS</u>	NS	OS	335	Yes* (n=303)	NS	155	Yes* (n=24)	NS	4	3	2	9

IBC: 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		
<i>Subgroup</i>	2 nd LR %	95% CI	Weight (%)	2 nd LR %	95% CI	Weight (%)
Primary diagnosis						
IBC	15.59	9.9 – 22.0 12.5 – 19.4	44.34 93.65	8.7 10.8	4.67 – 4 – 13.8 7.4 – 8	44.62 100.0
IBC and DCIS	15.79 7	3.9 – 15.5 11.2 – 20.8	55.66 6.35	11.7	6.5 – 18.2	55.38
Propensity analysis performed						
Yes	16.05 8	11.41 – 0 – 21.10 6	7.82 33	5.0	2.87 – 7.63	11.80 76
No	15.7	11.82 – 2 – 20.81 9.2	92.18 67	11.19	7.3 – 8.4, 15.64	88.20 4
Study design						
Comparative	19.63	15.5 – 24.0 3.2	53.16 48.68	9.6 10.9	7.8 – 13.96 3 – 13.5	94.89 25.18
Single-arm	11.37 7	6.75 – 6 – 17.21 5.9	46.84 45.32	23.13 5	1.6 – 0 – 31.73 5	5.75 10.82
Concomitant radiotherapy*						
Yes	9.68	5.08 – 15.33 8	43.38 97	17.9	12.3 – 24.9	5.92 10
No	25.58	16.3 – 35.93	5.57 4.43	13.19 7	96.1 – 17.71 3.3	110.5 32
In selected patients	16.17 0	13.24 – 3 – 19.37	24.62 810	5.61 1	3.0 – 87.82	339.9 20
Not reported	23.29 3	17.45 – 5 – 31.12 9.2	26.57 570	12.4	7.837 – 1820.51	485.64 58
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).

Subgroup	rBCS			Salvage mastectomy		
	%	95% CI	Weight (%)	%	95% CI	Weight (%)
Primary diagnosis						
IBC	<u>805.73</u>	<u>82.476.0 - 88.285.4</u>	<u>90.5056.3</u> <u>2</u>	<u>77.875.</u> <u>5</u>	<u>73.970.0 - 81.08</u>	<u>95.7562.5</u> <u>5</u>
IBC and DCIS	<u>912.20</u>	<u>86.888.6 - 97.393.7</u>	<u>5.8838.72</u>	<u>81.8</u>	<u>71.8 - 91.8</u>	<u>32.20</u>
DCIS	<u>90.086.</u> <u>5</u>	<u>81.984.4 - 95.388.4</u>	<u>3.624.96</u>	<u>83.387.</u> <u>0</u>	<u>74.085.0 - 90.488.9</u>	<u>54.25</u>
Propensity analysis performed						
Yes	87.1	81.3 - 92.9	<u>23.5226.6</u> <u>3</u>	<u>76.077.</u> <u>6</u>	<u>70.774.0 - 81.290.5</u>	<u>72.8028.4</u> <u>2</u>
No	<u>85.184.</u> <u>0</u>	<u>81.880.4 - 88.387.6</u>	<u>76.4873.3</u> <u>7</u>	<u>82.376.</u> <u>5</u>	<u>74.071.1 - 90.581.9</u>	<u>27.2071.5</u> <u>8</u>
Study design						
Comparative	<u>84.082.</u> <u>3</u>	<u>80.378.4 - 87.686.2</u>	<u>64.3363.6</u> <u>4</u>	<u>77.60</u>	<u>72.873.3 - 81.93</u>	<u>86.117</u>
Single-arm	<u>88.689.</u> <u>7</u>	<u>865.63 - 91.992.8</u>	<u>35.6736.3</u> <u>6</u>	<u>82.8</u>	<u>68.7 - 96.9</u>	<u>13.8930</u>
Concomitant radiotherapy*						
Yes	<u>88.690.</u> <u>2</u>	<u>86.087.2 - 931.2</u>	<u>22.9736.8</u> <u>1</u>	<u>56.387.</u> <u>3</u>	<u>37.783.4 - 73.691.1</u>	<u>2.579.45</u>
No	<u>89.982.</u> <u>8</u>	<u>86.477.8 - 93.594.2</u>	<u>19.858.10</u>	<u>89.275.</u> <u>7</u>	<u>86.569.7 - 92.081.8</u>	<u>14.828.26</u>
In selected patients	<u>88.481.</u> <u>9</u>	<u>77.15 - 99.386.7</u>	<u>11.2135.4</u> <u>9</u>	<u>81.978.</u> <u>4</u>	<u>86.573.3 - 92.083.5</u>	<u>16.0355.3</u> <u>4</u>
Not reported	<u>81.484.</u> <u>2</u>	<u>75.674.2 - 87.294.2</u>	<u>45.9719.6</u> <u>0</u>	<u>74.178.</u> <u>8</u>	<u>66.173.1 - 82.084.6</u>	<u>68.7226.9</u> <u>5</u>

Overall	86.87	83.4 - 89.690	100.0		79.38	74.27 - 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.

For Peer Review

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	202186/97394 1 (1920.8%)	21836/1955 2024 (1210.18%)	RR 1.9502.10 3 (1.411-535 to 2.695883)	1195 more per 1 000 (from 589 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	34993368/407 5-3932 (85.79%)	77197605/913 4-8968 (84.58%)	RR 1.060040 (1.00318 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

For Peer Review