European Journal of Surgical Oncology 45 (2019) 1317–1327

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Repeat breast-conserving therapy for ipsilateral breast cancer recurrence: A systematic review

Coco J.E.F. Walstra [a, *], Robert-Jan Schipper [a], Ingrid G.M. Poodt [a], Yvonne E. van Riet [a], Adri C. Voogd [b, c, d], Maurice J.C. van der Sangen [e], Grard A.P. Nieuwenhuijzen [a]

[a] Department of Surgery, Catharina Hospital Eindhoven, the Netherlands
[b] Department of Epidemiology, Maastricht University Medical Center, Maastricht, the Netherlands
[c] Department of Research, Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, the Netherlands
[d] GROW-School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, the Netherlands
[e] Department of Radiotherapy, Catharina Hospital Eindhoven, the Netherlands

ARTICLE INFO

Article history:
Received 6 September 2018
Received in revised form
27 January 2019
Accepted 6 February 2019
Available online 10 February 2019

Keywords:
IBTR
Recurrent breast cancer
Breast-conserving therapy
Repeat breast-conserving therapy
Repeat breast irradiation

ABSTRACT

The standard of care for patients with an ipsilateral breast tumour recurrence (IBTR) after breast-conserving therapy (BCT) is a salvage mastectomy. However, there is growing interest in the feasibility of repeat BCT for these patients. This systematic review contains the latest insights on BCT options for patients with an IBTR after initial BCT.

A PubMed literature search was performed for articles on BCT options for IBTR after primary lumpectomy followed by radiotherapy. Weighted estimates were calculated for 5- and 10-year local control, distant metastasis-free and overall survival rates. Secondary outcomes were toxicity, cosmesis and quality of life.

In total, 34 studies were eligible for analysis, of which 5 reported on repeat breast-conserving surgery (BCS) alone, 10 with mixed populations (BCS ± RT and/or mastectomy), 18 on repeat BCS followed by re-irradiation (whole-breast or partial) and one on quality of life. The weighted estimates for 5-year overall survival for repeat BCS and repeat BCS followed by reirradiation were 77% and 87%, respectively. Five-year local control was 76% for repeat BCS alone and 89% for repeat BCS followed by re-irradiation. Grade III-IV toxicity rates after re-irradiation varied from 0 to 21%, whereas the cosmesis was excellent-good in 29–100% of patients and unacceptable in 0–18%.

Repeat BCS followed by re-irradiation, with either whole breast or partial breast re-irradiation, seems a feasible alternative to mastectomy in case of IBTR, in selected patients. Toxicity rates are low and the cosmetic outcome is good, but the size and follow-up of the published patient series is limited.

Introduction

The treatment of patients with an ipsilateral breast cancer recurrence (IBTR) after initial breast-conserving therapy (BCT) remains challenging. With constant improvement of multimodality treatment options for primary breast cancer, the 10-year local recurrence rate has decreased from more than 15% to less than 5% in patients treated with BCT in recent cohorts [1–6]. However, since 1.67 million women worldwide are diagnosed with breast cancer every year [7], a significant number of patients will continue to develop an IBTR.

Several treatment-, tumour- and patient-related factors are associated with a higher risk of IBTR: omission of adjuvant radiotherapy after breast-conserving surgery (BCS) [8–10], higher tumour grade [3,11] positive excision margins [12,13], younger patient age [3,14] and presence of extensive, concomitant lobular or ductal carcinoma in situ (LCIS or DCIS) [11,15].

Ipsilateral breast tumour recurrence is associated with dismal long-term outcomes [16–19], especially when this occurs earlier after primary treatment [3,20–22]. Recurrent disease is regarded as a sign of aggressiveness of the tumour and IBTR can be an indicator of regional or distant progression of disease [16,17].

* Corresponding author. Department of Surgery, Catharina Hospital Eindhoven, Michelangelolaan 2, 5623 EJ, Eindhoven, the Netherlands.
E-mail address: coco-walstra@live.nl (C.J.E.F. Walstra).

https://doi.org/10.1016/j.ejso.2019.02.008
0748-7983/

The surgical standard of care in case of an IBTR after BCT as recommended by international guidelines is, and has always been, salvage mastectomy. This recommendation is based on expert opinion, considering the possibly unacceptable cosmetic result after repeat lumpectomy, the increased risk for a second IBTR and controversy regarding the possibility of renewed irradiation of the breast as part of repeat BCT. However, also salvage mastectomy does not eliminate the risk of (second) locoregional recurrence, metastatic disease or breast-cancer related death. Chest wall recurrences after salvage mastectomy occur in around 10% within 5 years [23–26], metastatic disease in about 20% [23,25,26] and overall survival rates after 5 years are approximately 80% [26,27].

To date, no prospective randomized trials have been performed to challenge the view that salvage mastectomy is the preferred treatment option for patients with IBTR.

The inferiority of mastectomy compared to BCS with respect to peroperative risks, cosmesis and quality of life (QoL) has been extensively described for primary breast cancer treatment [28–35]. Literature on these topics after salvage mastectomy is scarce. With improving overall survival of patients with IBTR [36,37], more attention is warranted with respect to the quality of life of these survivors. More and more treatment strategies are suggested in order to perform a repeat BCT in patients with IBRT after initial BCT. These include repeat BCS alone or followed by whole-breast external beam re-irradiation or partial breast re-irradiation, e.g. external partial irradiation, brachytherapy or intra-operative radiotherapy (IORT). The aim of the current study is to provide an overview of the latest insights on breast-preserving treatment options for IBTR, focusing on oncological safety, morbidity, cosmesis and QoL.

Methods

Search

A PubMed literature search according to the PRISMA method (Fig. 1) was performed in June 2018 for all available articles on BCT options for IBTR using the following combinations of search terms: [1] repeat lumpectomy breast cancer, [2] "recurrent breast cancer" AND breast-conserving therapy [3] ipsilateral recurrence breast cancer treatment [4] ipsilateral recurrent breast cancer treatment and [5] IBTR repeat breast-conserving therapy. All studies concerning BCT options for IBTR after previous BCT were included. Excluded were studies with patients who underwent primary BCS without radiotherapy, review articles, duplicate publications, comments, editorials, and letters to the editor. In case of multiple articles with the same study population, the survival data from the article with the longest follow-up were included in the analysis.

Data extraction

Data extraction was performed independently by two authors (CW and RS). Discrepancies were resolved by discussion. With the extracted data, an attempt was made to answer the following research questions:

1. Which repeat BCT regimens are currently used for IBTR?
2. What is the IBTR-free, distant metastasis-free and overall survival after repeat BCT in the various treatment regimens?
3. Which patients with IBTR are considered eligible for repeat BCT?
4. What are the acute and late toxicity rates of re-irradiation of the breast in various radiotherapy regimens for IBTR?
5. How is the cosmetic outcome after repeat BCT for IBTR?

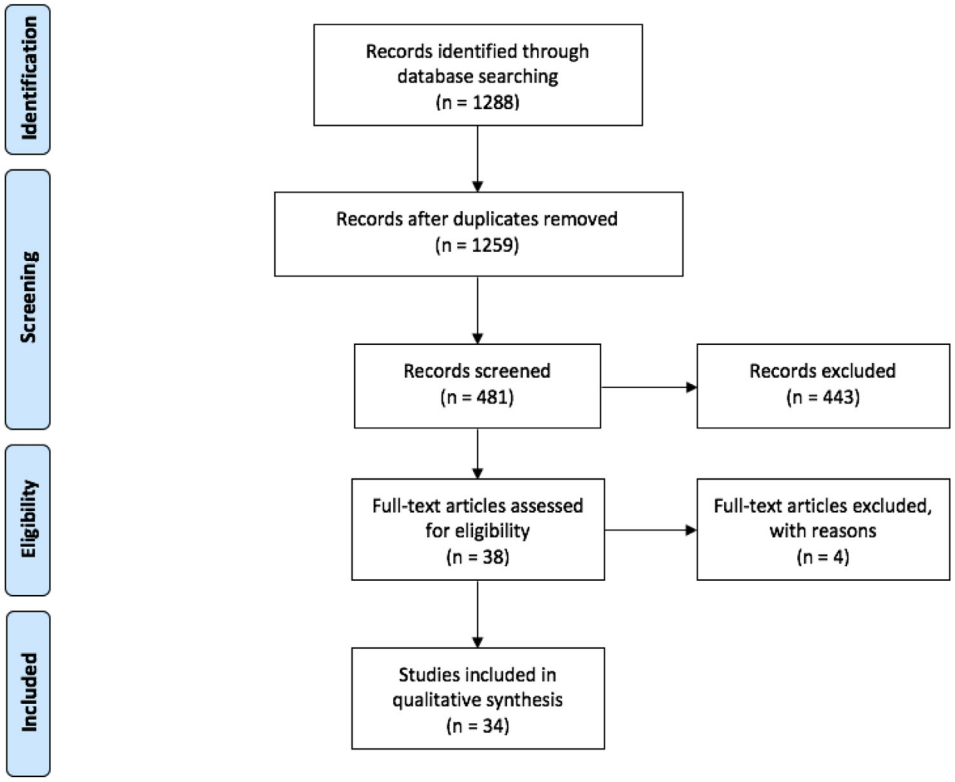

Fig. 1. Flowchart of literature search procedure.

6. What do we know about QoL in patients with IBTR treated with repeat BCT in comparison to salvage mastectomy?

Outcomes

With respect to the aim of this review, follow-up data of second IBTR after repeat BCT, distant disease-free survival and overall survival were extracted. For studies investigating repeat radiotherapy, data on acute and late toxicities and cosmetic outcome were assessed. Lastly, data were collected reporting on QoL after repeat BCT.

Statistical analysis

The derived survival data were pooled to calculate weighted estimates and corresponding 95% confidence intervals. Data analysis was performed using SPSS version 25 (SPSS Inc, Chicago, IL, USA).

Results

Search

The Pubmed search yielded 1288 hits. After removal of duplicates and screening the records, 38 studies were found eligible (See Fig. 1). Four articles were duplicate publications on the same population and were not individually included in the analysis.

Different BCT regimens for IBTR

For the included studies, the proposed BCT strategies were divided in three categories. Firstly, repeat BCS alone, secondly repeat BCS followed by several modalities of partial breast re-irradiation, e.g. 3D-conformal external beam therapy, brachytherapy or intraoperative radiotherapy (IORT), and thirdly repeat BCS followed by whole-breast re-irradiation. Five studies investigated the oncological safety of repeat BCS alone in patients with IBTR after primary BCS and radiotherapy (Table 1).

In 10 studies, the authors did not report separate outcomes for different treatment strategies for IBTR; nine did not report separate outcomes for repeat BCS with and without radiotherapy (two of these did not specify how many patients underwent adjuvant radiotherapy) and one article reported outcomes for a highly heterogenic group of repeat BCS±radiotherapy and salvage mastectomy. These studies are summarized in Table 2. No weighted estimates were calculated for these populations because these would not differentiate between repeat BCS alone and followed by radiotherapy or even mastectomy.

Table 3 contains 18 studies on repeat BCS followed by some modality of re-irradiation. Five of these administered external beam therapy (three to the whole breast and two by 3D-conformal partial radiation), nine interstitial brachytherapy (either high-dose, low-dose or pulse-dose-rate), and four IORT. Three studies analyzed and compared different modalities of radiotherapy (either by dose variation or different techniques). Data on adjuvant systemic therapy were available in 18 studies.

Outcomes reported after repeat BCT for IBTR

There is a wide variety of outcomes in the included studies. The most frequently reported survival outcomes were overall, disease-free and IBTR-free survival (OS, DFS, IBTRFS), but Dalberg et al. [38,39] reported "uncontrolled local disease" as a primary outcome. Four studies provided 10-year follow-up. Three others published

Table 1
Studies on repeat BCS alone.

Study	N	Eligibility criteria for repeat BCS	Median FU	Treatment	Systemic therapy	5-yr OS	5-yr DDFS	5-yr IBTRFS	10-yr OS	10-yr DDFS	10-yr IBTRFS
Salvadori 1999 [76]	57	NR	73 mo	Repeat BCS	NR	85%	NR	NR	NR	NR	NR
Komoike 2003 [77]	30	N0	43 mo	Repeat BCS	Adjuvant ET 57% Adjuvant CT 13% Adjuvant ET + CT 3%	90%	83%	63%	NR	NR	NR
Alpert 2005 [78]	30	Tumour <3 cm, <3 positive lymph nodes, M0, no lymphovascular invasion	166 mo	Repeat BCS	NR	NR	NR	NR	58%	76%	97%
Ishitobi 2017 [79]	65	M0	62 mo	Repeat BCS	Adjuvant ET 69% Adjuvant CT 15%	NR	NR	83%	NR	NR	NR
Houvenaeghel 2017 [66]	54	Tumour <2 cm, time to IBTR >2years, negative margins, recurrence in other quadrant, absence of LVI, low tumour grade	73 mo	Repeat BCS	NR	72%	68%	74%	65%	58%	NR
Total/weighted estimate (95% CI)	236		83 mo			77% (76.13–78.67%) *N = 143, 3 studies*	73% (71.78–74.93) *N = 84, 2 studies*	76% (74.49–76.94) *N = 149, 3 studies*	55% (53.09–56.61) *N = 84, 2 studies*	64% (62.55–66.31) *N = 84, 2 studies*	97% (not calculated) *N = 30, 1 study*

Abbreviations: FU follow-up, OS overall survival, DDFS distant-disease free survival, IBTRFS IBTR-free survival, NR not reported, ET endocrine therapy, CT chemotherapy.

Table 2
Studies with mixed populations (BCS ± RT and/or mastectomy).

Study	N	Eligibility criteria BCT	Median FU	Treatment	Systemic therapy	5-yr OS	5-yr DDFS	5-yr IBTRFS	10-yr OS	10-yr DDFS	10-yr IBTRFS
Kurtz 1991 [80]	50	NR	51 mo	Repeat BCS (22% with RT)	Adjuvant ET 34% Adjuvant CT 30%	67%	NR	62%	42%	NR	NR
Dalberg 1998 [38]	14	NR	72 mo	Repeat BCS (14% with RT)	Adjuvant ET 25% Adjuvant CT 10%	NR	NR	66% (ULD)	NR	NR	NR
Voogd 1999 [81]	266	Clinical N0M0	NR	SM/rBCS ± RT (8% BCT)	NR	61%	47%	NR	NR	NR	NR
Dalberg 2003 [39]	62	NR	NR	Repeat BCS ± RT	Unclear	NR	NR	84%	NR	NR	NR
Galper 2005 [82]	27	NR	NR	Repeat BCS (11% with RT)	Unclear	61%	NR	NR	NR	NR	NR
Chen 2008 [83]	179	NR	NR	Repeat BCS (21% with RT)	NR	67%	NR	NR	57%	NR	NR
Shah 2012 [84]	4	NR	49 mo	Repeat BCS ± RT	Neo-adj ET 67% Neo-adj CT 11%	100%	100%	100%	NR	NR	NR
Lee 2015 [36]	23	NR	NR	Repeat BCS (57% with RT)	Adjuvant ET 48% Adjuvant CT 53%	93%	NR	NR	NR	NR	NR
Kolben 2015 [27]	47	Unifocality, favourable breast-to-tumour ratio	49 mo	Repeat BCS (19% with RT)	Adjuvant ET 60% Adjuvant CT 2%	85%	NR	80%	NR	NR	NR
Yoshida 2016 [85]	149	M0 disease, unilateral	55 mo	Repeat BCS (38% with RT)	Adjuvant ET 68% Adjuvant CT 15%	95%	80%	NR	NR	NR	NR

Abbreviations: FU follow-up, OS overall survival, DDFS distant-disease free survival, IBTRFS IBTR-free survival, NR not reported, ET endocrine therapy, CT chemotherapy, RT radiotherapy, SM salvage mastectomy.

relatively short follow-up data (1 and 3 years). In some studies, there were no 5-year follow-up data available, but only the number of patients alive or free of recurrence at the time of analysis. These data are not displayed in Tables 1–3 but are presented (when available) in Appendix A. For two studies, a 3-year OS and IBTRFS is included in Table 3, but not taken into the weighted analysis for 5-year OS.

Sixteen out of 18 studies on repeat BCS followed by reirradiation reported on toxicity. Some authors differentiated between acute and late toxicities, others did not. Toxicity was assessed according to the criteria of the Radiation Therapy Oncology Group (RTOG) [40].

Cosmesis was assessed in 10 studies with repeat irradiation of the breast according to either the 5-point Harvard Cosmesis scale [41] or the 4-point NSABP Breast Cosmesis Grading Scale. Trombetta also used a modified scale [42] to assess cosmesis after salvage surgery and radiotherapy in comparison to the cosmetic outcome after primary treatment - these data are not taken into analysis.

Patient selection for repeat BCT

The inclusion criteria and eligibility criteria for repeat BCS with or without radiotherapy, when available, are displayed in Tables 1–3 In 14 studies, there are no clear inclusion criteria. Seven studies included patients with a primary tumour in a previously irradiated breast due to another malignancy.

Repeat BCS

In the five included studies on repeat BCS alone, the mean median follow-up was 83 months. Weighted estimates for 5-year local control, distant metastasis-free and overall survival were 76%, 73%, and 77%, respectively and 97%, 64% and 55% respectively after 10 years (see Table 1). In the two studies with availability of data on systemic therapy, 73–85% of patients received adjuvant systemic therapy of some sort: 57–69% endocrine therapy, 13–15% chemotherapy and 3% a combination of both.

Repeat BCS followed by re-irradiation

Weighted estimates of 5-year local control, distant-metastasis free and overall survival for repeat BCS followed by re-irradiation were 89%, 87% and 87%, respectively and 93%, 78% and 79% after 10 years (all calculated for subgroups of the total population with available data; see Table 3).

In the 10 studies with availability of data on systemic treatment, adjuvant chemotherapy was administered in 6–29% of patients and endocrine therapy in 18–93%.

Weighted estimates for 5-year overall survival per reirradiation technique were 76% for whole-breast irradiation (based on two studies), 89% for brachytherapy (based on five studies) and 89% for IORT (based on two studies). The 5-year local control rate was reported in only one study for whole-breast irradiation (68%), in two studies for IORT (weighted estimate 91%) and in three studies for brachytherapy (weighted estimate 89%).

Toxicity after repeat BCS followed by re-irradiation

Sixteen studies reported toxicity rates after repeat radiotherapy. In five of these, no grade III to IV toxicities occurred, and 11 studies had toxicity rates varying from 2 to 21%. Seven articles reported separately on acute and late toxicities, whereas most toxicities tend to occur late rather than acute. Taken acute and late toxicity together, weighted estimates for grade III and IV complications were 11% for whole-breast re-irradiation, 9% for external PBI, 9% for interstitial brachytherapy and 18% for IORT (estimates not displayed in Table 3).

Cosmesis after repeat BCS followed by re-irradiation

Twelve studies reported on cosmesis after repeat lumpectomy followed by radiotherapy. Overall, the cosmesis was “excellent to good” in 29–100% of patients with a weighted estimate of 75% (77% for brachytherapy, 62% for IORT and 75% for whole-breast re-irradiation). Cosmesis was described as unacceptable in four studies (Kauer-Dorner 4%, Adkison 18%, Hannoun-Levi 2013 2%, Smanyko 18%, all multi-catheter brachytherapy). The weighted estimate of overall unacceptable cosmesis in IBT was 3% (not reported in Table 3).

Quality of life

Only one study provided data on QoL as a primary outcome for

Table 3
Studies with repeat BCS followed by reirradiation.

Study	N	Inclusion criteria	Median FU	Treatment	Systemic therapy	5-yr OS	5-yr DDFS	5-yr IBTRFS	10-yr OS	10-yr DDFS	10-yr IBTRFS	Toxicity	Cosmesis
Mullen 1997 [86]	16	NR	55 mo	Repeat BCS + WBI	Adj ET 63% Adj CT 6%	70%	69%	68%	NR	NR	NR	No grade III-IV	NR
Deutsch 2002 [87]	39	NR	52 mo	Repeat BCS + WBI	Adj ET 49% Adj CT 7%	78%	NR	NR	NR	NR	NR	NR	Excellent-good 75%
Resch 2002 [88]	17	Small tumours	59 mo	Repeat BCS + WBI&IBT or PDR	Adj ET 18% Adj CT 29% Adj CT + ET 12%	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	No grade III-IV	Excellent-good 29%, moderate 47%
Hannoun-Levi 2004 [89]	69	Denied mastectomy	50 mo	Repeat BCS + IBT	NR	92%	87%	77%	NR	NR	NR	Acute: no grade III-IV Late: 10% grade III, (unclear which)	NR
Kauer-Dorner 2011 [44]	39	Unicentric, M0, IBTR >1 year after primary treatment	57 mo	Repeat BCS + PDR	Adj ET 62% Adj CT 26%	87%	NR	NR	NR	NR	NR	3% grade III fibrosis 8% grade III breast pain	Excellent-good 37%, fair 38%
Kraus-Tiefenbacher 2007 [90]	15	NR	26 mo	Repeat BCS + IORT	Adj ET 93% Adj CT 20%	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	No grade III-IV	Excellent-good 82%
Trombetta 2008[71]/2009[70]/ 2011 [91]	36	cTis − T2N0M0, 1 with primary tumour after EBT for Hodgkin lymphoma	34 mo	Repeat BCS + 21 LDR, 11 HDR, 3 3DCRT	NR	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	LDR: 11% grade III ulceration HDR: no grade III-IV 3DCRT: no grade III-IV	Excellent-good 92%
Chadha 2008 [92]	15	NR	36 mo	Repeat BCS + LDR	Adj ET 53% Adj CT 20%	100% (3-yr)	NR	89% (3-yr)	NR	NR	NR	No grade III-IV	Excellent-good 100%
Adkison 2010 [67]	11	Tumour <2 cm, N0M0, 6 with primary tumour after EBT for other malignancy	53 mo	Repeat BCS + IBT	NR	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	9% grade III necrosis	Excellent-good 69%
Hannoun-Levi 2013 [93]	217	M0, no skin involvement	47 mo	Repeat BCS + IBT (low-, PDR and high-dose)	NR	89%	89%	94%	77%	80%	93%	Late: 10% grade III, 1% grade IV (unclear which)	Excellent-good 85%
Trombetta 2014 [57]	18	NR, 2 with primary tumour after EBT for Hodgkin lymphoma	40 mo	Repeat BCS + HDR	NR	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	No grade III-IV	Excellent-good 83%
Merino 2015 [94]	13	NR	17 mo	Repeat BCS + WBI	Unclear	NR	NR	NR	NR	NR	NR	Acute: 8% grade III, 2% grade IV dermatitis Late: 8% grade III fibrosis, 6% grade III telangiectasia	NR
Chin 2017 [68]	12	Unifocal, 3 with previous EBT for other malignancy	14 mo	Repeat BCS + IORT	Adj ET 75% Adj CT 8%	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	Late: 8% grade III abscess	NR
Arthur 2016/ 2017 [51,52]	58/ 55	Tumour <3 cm, no skin	44 mo	Repeat BCS + 3DCRT		95% (3-yr)	95% (3-yr)	96% (3-yr)	NR	NR	NR	Acute: 2% grade III fibrosis	NR

(*continued on next page*)

Table 3 (*continued*)

Study	N	Inclusion criteria	Median FU	Treatment	Systemic therapy	5-yr OS	5-yr DDFS	5-yr IBTRFS	10-yr OS	10-yr DDFS	10-yr IBTRFS	Toxicity	Cosmesis
		involvement, M0, >3 positive lymph nodes, >1 year to IBTR, >30% radiation field-to-breast ratio			Adj ET 38% Adj CT 11% Adj CT + ET 2%							Late: 7% grade III (unclear which)	
Houvenaeghel 2017 [66]	62	Tumour <2 cm, time to IBTR >2years, negative margins, recurrence in other quadrant, absence of LVI, low tumour grade	73 mo	Repeat BCS + IBT	NR	87%	83%	NR	87%	70%	NR	NR	NR
Blandino 2017	29	Unicentric, M0, 3 with previous EBT for other malignancy	47 mo	Repeat BCS + IORT	Adj ET 88% Adj CT 8% Adj CT + ET 4%	91%	NR	92%	NR	NR	NR	Acute: 10% grade III fibrosis Late: 21% grade III fibrosis	Excellent-good 51%, fair 28%
Smanyko 2018 [95]	33	Tumour <3 cm, N0M0	61 mo	Repeat BCS + HDR	Adj ET 73% Adj CT 18%	89%	94%	85%	NR	NR	NR	Late: 3% grade III fibrosis	Excellent-good 70%
Thangarajah 2018 [69]	41	NR, 2 with primary tumour after radiation for Hodgkin	58 mo	Repeat BCS + IORT	NR	83%	80%	90%	NR	NR	NR	No grade III-IV	NR
Total/weighted estimate (95%-CI)	740		46 mo			87.31% (86.93 −87.71%) *N = 545, 9 studies*	86.64% (86.18 −87.10%) *N = 438, 6 studies*	88.56% (87.91 −89.20%) *N = 405, 6 studies*	79% (78,73-79-71%) *N = 279, 2 studies*	78% (77.29 −78.27) *N = 279, 2 studies*	93% (not calculcated) *N = 217, 1 study*		

Abbreviations: FU follow-up, WBI whole-breast irradiation, adj adjuvant, ET endocrine therapy, CT chemotherapy, NR not reported, PDR pulse-dose-rate brachytherapy, LDR low-dose-rate brachytherapy, HDR high-dose-rate brachytherapy, 3DCRT 3D-conformal external beam radiation, EBT external beam radiotherapy, IBT interstitial brachytherapy, IORT intraoperative radiotherapy, 95%-CI 95%-confidence interval.

[a] No 5- or 10-year follow-up data available: see Appendix A for more information.

IBTR surgery. Jendrian et al. [43] addressed QoL in patients after a salvage mastectomy or repeat BCT for recurrent breast cancer after primary BCT. They reported a significantly better score for body image and overall QoL in women after repeat BCT compared to salvage mastectomy. More importantly, no differences in anxiety, depression and fear of progression between the groups were reported in this study. Kauer-Dorner et al. [44] presented QoL as a secondary outcome after repeat lumpectomy followed by interstitial brachytherapy and found no differences compared to healthy controls.

Discussion

This systematic review provides an overview of the latest insights on repeat BCT options for patients with an IBTR after initial BCT, focusing on oncological safety, morbidity, cosmesis and QoL. A total of 34 studies were included. According to the available evidence and the pooled data, there seems to be an oncological advantage of adding radiotherapy to repeat BCS for IBTR, without unacceptable toxicity or worse cosmetic outcome.

The increasing survival of patients with an IBTR [36,37] calls for attention to QoL after salvage surgery. There is substantial evidence for a better QoL after lumpectomy compared to a mastectomy in the primary treatment setting [35,45]. Only two studies addressed this outcome after salvage surgery. They suggested a better QoL in patients treated with repeat BCS compared to salvage mastectomy. This underlines the importance to pursue breast-conserving treatment options, also in case of an IBTR.

Regarding oncological safety and in particular local control, there seems to be an advantage of adding radiotherapy to repeat BCS. Second IBTR rates are reduced by an estimate of 18% after adding radiotherapy, which is concordant with the evidence for radiotherapy after primary BCS [46].

Although not evidence-based, it seems important to prevent a second IBTR. The negative influence of a first IBTR on overall survival is well-documented [10,47] and radiotherapy is known to diminish the risk of local recurrences in comparison to BCS alone [8]. Therefore, adding radiotherapy to the multidisciplinary treatment of patients with IBTR opting for repeat BCS seems preferable to optimize local control whilst preserving the breast.

Two issues in the addition of radiotherapy to the previously irradiated breast are the higher risk of late skin toxicity and a possible unacceptable cosmetic outcome. The evidence provided in this review does not support these concerns, with Grade III-IV toxicity rates reported in 0–21% of cases. These percentages are calculated taking acute and late skin toxicity together, as only 44% of the studies with toxicity as an outcome reported acute and late toxicities separately. When calculated separately, the maximum rate of acute Grade III-IV toxicity was 21% and the maximum rate of late Grade III-IV toxicity was 14%. These rates are comparable to those reported after primary radiotherapy [48–50]. However, with a mean median follow-up of 44 months in the studies reporting on toxicity, the long-term effects of re-irradiation are not clear yet. Arthur et al. [51,52] has published promising preliminary results of a relatively large prospective trial on 3D-conformal PBI (NRG Oncology/RTOG 1014, 65 patients); their longer follow-up data are awaited with interest.

To minimize skin toxicity, partial breast irradiation is considered superior, at least in primary treatment [53]. With the limited available data, the weighted estimates in this review seem to show less toxicity after partial breast re-irradiation than after whole-breast external beam therapy, with comparable local control and overall survival rates.

Regarding patient convenience, IORT seems preferable, as there is no need to travel for radiotherapy. Sorrentino et al. [54] reported a better QoL and faster return to daily activities for IORT compared to whole-breast irradiation for primary treatment. Unfortunately, relatively few hospitals dispose of an IORT device, which results in longer waiting lists and limited availability for patients living in a rural area.

Oncoplastic surgery could become an important component of repeat BCT, as the breast is even more mutilated than during primary BCS. However, in The Netherlands, oncoplastic surgery is considered a relative contraindication for external beam PBI since the tumour bed volume can no longer be estimated reliably. Intraoperative radiotherapy provides the opportunity to perform an oncoplastic reconstruction of the breast after the irradiation to the tumour bed is completed. Furthermore, the skin surface will not be exposed to radiation like in external beam irradiation and this may result in better wound healing and cosmesis. To date, there is no literature on oncoplastic reconstructions in repeat BCS and the effect of various radiotherapy regimes on the cosmetic result.

Two other important factors in the selection of patients feasible for repeat BCS followed by re-irradiation are the interval between primary and re-irradiation and the perceived high risk of radiation-induced heart disease in case of a left-sided IBTR. To date, no studies addressed the first issue in terms of a safe radiation-free interval when considering re-irradiation. The selection of patients in the studies in this analysis is merely based on favourable tumour characteristics, of which a longer IBTR-free interval is one. Inclusion criteria regarding minimum time to IBTR from the studies in this review vary from 1 to 2 years. Hence, a radiation-free interval of at least 1 year seems safe to consider re-irradiation. Regarding radiation-induced heart disease after re-irradiation of the left breast, no data are available in the included studies which have a limited follow-up, whereas the latency of cardiotoxicity can be more than 10 years [55]. To minimize the radiation dose to the heart and surrounding tissue during primary treatment, new techniques like the deep inspiration breath holding (DIBH) and state of the art treatment planning have been implemented during the last decade [56]. Partial breast irradiation is also assumed to diminish collateral damage, and in particular IORT, since the skin is moved away from the irradiated field and ribs, lungs and heart are properly shielded. Long-term data on radiation-induced heart disease in patients with IBTR and repeat BCS followed by re-irradiation are needed to confirm this hypothesis.

The most solid evidence regarding partial breast re-irradiation is available for brachytherapy. In general, brachytherapy is administered either by multiple catheter placement, radioactive seeds or via an interstitial balloon device. The latter offers the opportunity of high-dose brachytherapy and is less time-consuming but experience with balloon brachytherapy in this setting is limited [57].

Cost-effectiveness is becoming a more and more important factor in the choice of breast cancer treatment. For primary treatment, partial breast irradiation techniques seems to be more cost-effective in comparison to conservative whole-breast external beam radiotherapy [58], in terms of hospital and societal costs, whereas insurance coverage varies widely between countries and health insurance companies.

Hence, until now toxicity does not seem to be an issue in treating patients with IBTR with repeat BCT, and the use of partial breast re-irradiation seems to be the treatment of preference regarding patient convenience and long-term cost-efficacy.

Few studies described specific inclusion and exclusion criteria and therefore generalization of the evidence is impossible. Overall, the 3 most frequently mentioned eligibility criteria for repeat BCT include (1) small tumours, (2) long time to IBTR, (3) unicentric disease. The Veronesi group [59–61] evaluated patient and tumour characteristics related to a safe repeat BCS in IBTR. They recommended considering repeat BCT in case of small tumours (<2 cm)

and late recurrences (>4 years). These characteristics have been associated before with general better prognosis [3,22,62].

As mentioned before, repeat BCT is only feasible in selected patients with IBTR. In accordance with the scarce available evidence we would recommend considering a repeat BCT under the following circumstances: 1) patient's preference to preserve the breast, 2) a tumour-to-breast ratio that allows for an acceptable cosmetic outcome, regardless the size of the tumour, and 3) the possibility to apply radiotherapy to the tumour bed without unacceptable toxicity.

Whereas most authors are fairly specific in their description of performed surgery and applied method and doses of radiotherapy, there is limited information on the use of adjuvant systemic treatment regimens in the included studies. The role of chemotherapy is not to be underestimated: as shown in the CALOR trial, patients with isolated local recurrences benefit significantly from adjuvant chemotherapy after salvage surgery [63,64], especially in patients with estrogen receptor-negative tumours. Probably, with the use of adjuvant systemic therapy, also the risks of a second IBTR after repeat BCS in case of IBRT could be reduced.

Limitations

Due to the scarce information on the specific inclusion criteria, high heterogeneity and different endpoints in the included studies, it was not possible to perform an adequate meta-analysis. The large variety in selection criteria and outcomes in breast cancer literature has been described by Moosdorff et al. [65] The second best option was to calculate a weighted estimate for all available outcomes. However, some estimates (for example the 10-year IBTR-free survival after repeat BCS alone in Table 1) are based on a single study with a limited number of patients. Therefore, the weighted estimates should be interpreted with caution.

Another issue in the included studies is the risk of selection bias due to the retrospective design of the studies and the lack of randomized controlled trials. Some authors stated that they included patients who refused a mastectomy for various reasons. The pooled estimates in this study for local control, distant disease-free and overall survival after repeat BCS followed by re-irradiation were non-inferior or better compared to salvage mastectomy [23–27]. However, this comparison is susceptible to selection bias, since tumours that are considered eligible for repeat BCS are generally smaller and have better prognostic features (longer time to IBTR, clinically lymph node-negative). Houvenaeghel et al. [66] addressed this important issue by matching two groups of patients (60 repeat BCT vs 120 salvage mastectomy) for factors that appeared significantly associated with poor prognosis in a multivariate analysis, being tumour size and time to IBTR. After matching, they observed no significant differences in distant metastasis-free and overall survival between mastectomy and repeat BCS followed by brachytherapy.

Another contributing factor in possible selection bias is the inclusion of patients with primary breast cancer. Some studies (Adkison [67], Chin [68], Thangarajah [69], Trombetta [57,70,71], Blandino [72]) included patients with a breast tumour after previous radiation on the chest for another malignancy and thus strictly had no IBTR. This may have led to an overestimation of local control and overall survival. However, these studies focused on toxicity as primary endpoint rather than oncological safety.

Interestingly, none of the studies elaborated on whether the IBTR was a true in field recurrence or a second primary tumour. This may have affected the outcome as evidence suggests that second primary tumours occur later after primary treatment, have in general a better prognosis than true in field recurrences [73,74] and may therefore be more suitable for a second breast-conserving treatment. It could be useful to include determination of tumour characteristics and for instance clonality analysis [75] in the workup of IBTR and take this knowledge into account in the decision-making process.

Conclusion

With all limitations in mind, based on the current available evidence repeat BCT seems to be a feasible alternative to salvage mastectomy in selected patients with IBTR. With the use of re-irradiation, lower local recurrence rates are reported compared to repeat BCS alone with acceptable toxicity. Partial breast re-irradiation seems to be the preferable option, but it is not clear whether one specific technique is superior. Available data show good disease-free and overall survival rates, at least within relatively short follow-up. The long-term effects of re-irradiation of the breast are yet unknown.

Conflict of interest

The authors declare that there is no conflict of interest.

Funding statement

None.

Acknowledgments

None.

Appendix A. Raw data from studies without 5-year OS/DDFS/IBTRFS

Study	N	Treatment	Median FU	Patients alive	Patients free of metastasis	Patients free of second IBTR
Resch 2002	17	Repeat BCS + WBI&IBT or PDR	59 mo	14 (82%)	13 (77%)	13 (77%)
Kraus-Tiefenbacher 2007	17	Repeat BCS + IORT	26 mo	16 (94%))	14 (82%)	17 (100%)
Trombetta 2008/2009/2011	26	Repeat BCS + 21 LDR, 11 HDR, 3 3DCRT	38 mo	22 (85%)	23 (88%)	25 (96%)
Adkison 2010	11	Repeat BCS + IBT	54 mo	10 (91%)	10 (91%)	10 (91%)
Trombetta 2014	18	Repeat BCS + HDR	40 mo	17 (94%)	17 (94%)	16 (89%)
Chin 2017	12	Repeat BCS + IORT	14 mo	11 (92%)	11 (92%)	11 (92%)

Abbreviations: FU follow-up, WBI whole-breast irradiation, NR not reported, PDR pulse-dose-rate brachytherapy, LDR low-dose-rate brachytherapy, HDR high-dose-rate brachytherapy, 3DCRT 3D-conformal external beam radiation, EBT external beam radiotherapy, IBT interstitial brachytherapy, IORT intraoperative radiotherapy, 95%-CI 95%-confidence interval.

References

[1] Fisher B. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. TT. New Engl J Med TA - 2002;347(16):1233–41.

[2] van Laar C, van der Sangen MJC, Poortmans PMP, Nieuwenhuijzen GA, Roukema JA, Roumen RM, et al. Local recurrence following breast-conserving treatment in women aged 40 years or younger: trends in risk and the impact on prognosis in a population-based cohort of 1143 patients TT. Eur J Cancer TA - 2013;49(15):3093–101.

[3] Bosma SCJ, van der Leij F, van Werkhoven E, Bartelink H, Wesseling J, Linn S, et al. Very low local recurrence rates after breast-conserving therapy: analysis of 8485 patients treated over a 28-year period. Breast Canc Res Treat 2016;156(2):391–400. https://doi.org/10.1007/s10549-016-3732-0.

[4] Takahashi S, Murakami Y, Imano N, Kaneyasu Y, Doi Y, Kenjo M, et al. Long-term results after 12-year follow-up of patients treated with whole-breast and boost irradiation after breast-conserving surgery. Jpn J Radiol 2016;34(9):595–604. https://doi.org/10.1007/s11604-016-0562-2.

[5] Jobsen J, Palen Job van der, Riemersma S, Heijmans H, Ong F, Struikmans H. Pattern of ipsilateral breast tumor recurrence after breast-conserving therapy TT -. Int J Radiat Oncol Biol Phys TA - 2014;89:1006–14.

[6] Giuliano AE, Ballman K, Mccall L, Beitsch P, Whitworth PW, Blumencranz P, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: long-term follow-up from the American college of surgeons Oncology group (alliance) ACOSOG Z0011 randomized trial HHS public access, vol. 264; 2016. p. 413–20. https://doi.org/10.1097/SLA.0000000000001863. 3.

[7] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015;65(2):87–108. https://doi.org/10.3322/caac.21262.

[8] Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet (London, England) 2005;366(9503):2087–106. https://doi.org/10.1016/S0140-6736(05)67887-7.

[9] Yu J Il, Choi DH, Huh SJ, Park W, Nam SJ, Kim SW, et al. Proportion and clinical outcomes of postoperative radiotherapy omission after breast-conserving surgery in women with breast cancer. J Breast Cancer 2015;18(1):50–6. http://synapse.koreamed.org/DOIx.php?id=10.4048%2Fjbc.2015.18.1.50.

[10] Yoshida T, Takei H, Kurosumi M, Arima N, Nakatsukasa K, Tanabe M, et al. Ipsilateral breast tumor relapse after breast conserving surgery in women with breast cancer. Breast 2009;18(4):238–43. https://doi.org/10.1016/J.BREAST.2009.06.001.

[11] Vrieling C, van Werkhoven E, Maingon P, Poortmans P, Weltens C, Fourquet A, et al. Prognostic factors for local control in breast cancer after long-term follow-up in the eortc boost vs no boost trial: a randomized clinical trial. JAMA Oncol 2017;3(1):42–8. https://doi.org/10.1001/jamaoncol.2016.3031.

[12] Moran MS, Schnitt SJ, Giuliano AE, Harris JR, Khan SA, Horton J, et al. SSO-ASTRO consensus guideline on margins for breast-conserving surgery with whole breast irradiation in stage I and II invasive breast cancer. Int J Radiat Oncol Biol Phys 2014;88(3):553–64. https://doi.org/10.1016/j.ijrobp.2013.11.012.

[13] Bodilsen A, Bjerre K, Offersen BV, Vahl P, Ejlertsen B, Overgaard J, et al. The influence of repeat surgery and residual disease on recurrence after breast-conserving surgery: a Danish breast cancer cooperative group study. Ann Surg Oncol 2015;22(Suppl 3):S476–85. https://doi.org/10.1245/s10434-015-4707-9.

[14] van der L F, E PH, Bartelink H, van de V MJ. Predictive factors for local recurrence in breast cancer. TT -. Semin Radiat Oncol TA - 2012;22(2):100–7.

[15] Mechera R, Viehl CT, Oertli D. Factors predicting in-breast tumor recurrence after breast-conserving surgery. Breast Canc Res Treat 2009;116(1):171–7. https://doi.org/10.1007/s10549-008-0187-y.

[16] Fisher B, Anderson S, Fisher ER, Redmond C, Wickerham DL, Wolmark N, et al. Significance of ipsilateral breast tumour recurrence after lumpectomy. Lancet (London, England) 1991;338(8763):327–31.

[17] Fortin A, Larochelle M, Laverdiére J, Lavertu S, Tremblay D. Breast cancer - local failure is responsible for the decrease in survival for patients with breast cancer treated with conservative surgery and postoperative radiotherapy. TT -. J Clin Oncol TA 1999;17(1):101–9.

[18] Tanis E, van de Velde CJH, Bartelink H, van de Vijver MJ, Putter H, van der Hage JA. Locoregional recurrence after breast-conserving therapy remains an independent prognostic factor even after an event free interval of 10years in early stage breast cancer. Eur J Cancer 2012;48(12):1751–6. https://doi.org/10.1016/j.ejca.2012.02.051.

[19] Voogd AC, van Oost FJ, Rutgers EJT, Elkhuizen PH, van Geel AN, Scheijman LJ, et al. Long-term prognosis of patients with local recurrence after conservative surgery and radiotherapy for early breast cancer. Eur J Cancer 2005;41(17):2637–44. https://doi.org/10.1016/j.ejca.2005.04.040.

[20] van der Sangen MJC, van de Poll-Franse LV, Roumen RMH, Rutten HJ, Coebergh JW, Vreugdenhil G, et al. The prognosis of patients with local recurrence more than five years after breast conservation therapy for invasive breast carcinoma. Eur J Surg Oncol 2006;32(1):34–8. https://doi.org/10.1016/j.ejso.2005.10.005.

[21] Neri A, Marrelli D, Rossi S, De Stefano A, Mariani F, De Marco G, et al. Breast cancer local recurrence: risk factors and prognostic relevance of early time to recurrence. World J Surg 2007;31(1):36–45. https://doi.org/10.1007/s00268-006-0097-2.

[22] Gosset M, Hamy A-S, Mallon P, Delomenie M, Mouttet D, Pierga JY, et al. Prognostic impact of time to ipsilateral breast tumor recurrence after breast conserving surgery. PLoS One 2016;11(8). https://doi.org/10.1371/journal.-pone.0159888. e0159888.

[23] Abner AL, Recht A, Eberlein T, Come S, Shulman L, Hayes D, et al. Prognosis following salvage mastectomy for recurrence in the breast after conservative surgery and radiation therapy for early-stage breast cancer. J Clin Oncol 1993;11(1):44–8. https://doi.org/10.1200/JCO.1993.11.1.44.

[24] Beard HR, Cantrell EF, Russell GB, Howard-McNatt M, Shen P, Levine EA. Outcome after mastectomy for ipsilateral breast tumor recurrence after breast conserving surgery. Am Surg 2010;76(8):829–34.

[25] Tanabe M, Iwase T, Okumura Y, Yoshida A, Masuda N, Nakatsukasa K, et al. Local recurrence risk after previous salvage mastectomy. Eur J Surg Oncol 2016;42(7):980–5. https://doi.org/10.1016/j.ejso.2016.03.008.

[26] Shaikh T, Li T, Avkshtol V, Weiss S, Sigurdson E, Hayes S, et al. (P013) outcomes after salvage mastectomy for an ipsilateral breast tumor recurrence after breast conservation therapy. Int J Radiat Oncol 2017;98(2):E18–9. https://doi.org/10.1016/j.ijrobp.2017.02.110.

[27] Kolben T, Schwarz TM, Goess C, Blume C, Degenhardt T, Engel J, et al. Surgical management of ipsilateral breast tumor recurrence. Int J Surg 2015;23(Pt A):141–6. https://doi.org/10.1016/j.ijsu.2015.08.084.

[28] Bartelink H, Van Dam F, Van Dongen J. Psychological effects of breast conserving therapy in comparison with radical mastectomy. Int J Radiat Oncol 1985;11(2):381–5. https://doi.org/10.1016/0360-3016(85)90161-0.

[29] Margolis G, Goodman RL, Rubin A. Psychological effects of breast-conserving cancer treatment and mastectomy. Psychosomatics 1990;31(1):33–9. https://doi.org/10.1016/S0033-3182(90)72214-1.

[30] Al-Hilli Z, Thomsen KM, Habermann EB, Jakub JW, Boughey JC. Reoperation for complications after lumpectomy and mastectomy for breast cancer from the 2012 national surgical quality improvement program (ACS-NSQIP). Ann Surg Oncol 2015;22(Suppl 3):S459–69. https://doi.org/10.1245/s10434-015-4741-7.

[31] Curran D, van Dongen JP, Aaronson NK, Kiebert G, Fentiman IS, Mignolet F, et al. Quality of life of early-stage breast cancer patients treated with radical mastectomy or breast-conserving procedures: results of EORTC Trial 10801. The European Organization for Research and Treatment of Cancer (EORTC), Breast Cancer Co-operative Group. Eur J Cancer 1998;34(3):307–14.

[32] Chatterjee A, Pyfer B, Czerniecki B, Rosenkranz K, Tchou J, Fisher C. Early postoperative outcomes in lumpectomy versus simple mastectomy. J Surg Res 2015;198(1):143–8. https://doi.org/10.1016/j.jss.2015.01.054.

[33] Chow R, Pulenzas N, Zhang L, Ecclestone C, Leahey A, Hamer J, et al. Quality of life and symptom burden in patients with breast cancer treated with mastectomy and lumpectomy. Support Care Canc Off J Multinatl Assoc Support Care Canc 2016;24(5):2191–9. https://doi.org/10.1007/s00520-015-3027-8.

[34] Nowicki A, Licznerska B, Rhone P. Evaluation of the quality of life of women treated due to breast cancer using amputation or breast conserving surgery in the early postoperative period. Pol Przegl Chir 2015;87(4):174–80. https://doi.org/10.1515/pjs-2015-0040.

[35] Aerts L, Christiaens MR, Enzlin P, Neven P, Amant F. Sexual functioning in women after mastectomy versus breast conserving therapy for early-stage breast cancer: a prospective controlled study. Breast 2014;23(5):629–36. https://doi.org/10.1016/j.breast.2014.06.012.

[36] Lee JH, Lee SK, Park SM, Ryu JM, Paik HJ, Yi HW, et al. Independent prognostic factors for overall survival after salvage operation for ipsilateral breast tumor recurrence following breast-conserving surgery. J Breast Cancer 2015;18(4):386–93. https://doi.org/10.4048/jbc.2015.18.4.386.

[37] Poodt IGM, Vugts G, Schipper R-J, Nieuwenhuijzen GAP. Repeat sentinel lymph node biopsy for ipsilateral breast tumor recurrence: a systematic review of the results and impact on prognosis. Ann Surg Oncol 2018;25(5):1329–39. https://doi.org/10.1245/s10434-018-6358-0.

[38] Dalberg K, Mattsson A, Sandelin K, Rutqvist LE. Outcome of treatment for ipsilateral breast tumor recurrence in early-stage breast cancer. Breast Canc Res Treat 1998;49(1):69–78.

[39] Dalberg K, Liedberg A, Johansson U, Rutqvist LE. Uncontrolled local disease after salvage treatment for ipsilateral breast tumour recurrence. Eur J Surg Oncol 2003;29(2):143–54.

[40] Cox JD, Stetz J, Pajak TF. Toxicity criteria of the radiation therapy Oncology group (RTOG) and the European organization for research and treatment of cancer (EORTC). Int J Radiat Oncol 1995;31(5):1341–6. https://doi.org/10.1016/0360-3016(95)00060-C.

[41] Rose M, Olivotto I, Cady B, al et. Conservative surgery and radiation therapy for early breast cancer: long-term cosmetic results. Arch Surg 1989;124(2):153–7. https://doi.org/10.1001/archsurg.1989.01410020023002.

[42] Trombetta M, Julian TB, Kim Y, Werts ED, Parda D. The allegheny general modification of the Harvard Breast Cosmesis Scale for the retreated breast. Oncology (Williston Park) 2009;23(11):954–6.

[43] Jendrian S, Steffens K, Schmalfeldt B, Laakmann E, Bergelt C, Witzel I. Quality of life in patients with recurrent breast cancer after second breast-conserving therapy in comparison with mastectomy: the German experience. Breast Canc Res Treat 2017;163(3):517–26. https://doi.org/10.1007/s10549-017-4208-6.

[44] Kauer-Dorner D, Pötter R, Resch A, Handl-Zeller L, Kirchheiner K, Meyer-

Schell K, et al. Partial breast irradiation for locally recurrent breast cancer within a second breast conserving treatment: alternative to mastectomy? Results from a prospective trial TT -. Radiother Oncol TA 2012;102(1):96–101.
[45] Tsai H-Y, Kuo RN-C, Chung K-P. Quality of life of breast cancer survivors following breast-conserving therapy versus mastectomy: a multicenter study in Taiwan. Jpn J Clin Oncol 2017;47(10):909–18. https://doi.org/10.1093/jjco/hyx099.
[46] Fisher B, Costantino J, Redmond C, Fisher E, Margolese R, Dimitrov N, et al. Lumpectomy compared with lumpectomy and radiation therapy for the treatment of intraductal breast cancer. N Engl J Med 1993;328(22):1581–6. https://doi.org/10.1056/NEJM199306033282201.
[47] Wapnir IL, Anderson SJ, Mamounas EP, Geyer Jr CE, Jeong JH, Tan-Chiu E, et al. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five National Surgical Adjuvant Breast and Bowel Project node-positive adjuvant breast cancer trials. J Clin Oncol 2006;24(13):2028–37. https://doi.org/10.1200/JCO.2005.04.3273.
[48] Harris EER, Small W. Intraoperative radiotherapy for breast cancer. Front Oncol 2017;7:317. https://www.frontiersin.org/article/10.3389/fonc.2017.00317.
[49] Kindts I, Laenen A, Depuydt T, Weltens C. Tumour bed boost radiotherapy for women after breast-conserving surgery. Cochrane Database Syst Rev 2017;11:CD011987. https://doi.org/10.1002/14651858.CD011987.pub2.
[50] Shaitelman SF, Amendola B, Khan A, Beriwal S, Rabinovitch R, Demanes DJ, et al. American Brachytherapy Society Task Group Report: long-term control and toxicity with brachytherapy for localized breast cancer. Brachytherapy 2017;16(1):13–21. https://doi.org/10.1016/j.brachy.2016.04.392.
[51] Arthur DW, Moughan J, Kuerer HM, Haffty BG, Cuttino LW, Todor D, et al. NRG Oncology/RTOG 1014: 3 Year efficacy report from a phase II study of repeat breast preserving surgery and 3D conformal partial breast Re-irradiation (PBrI) for in-breast recurrence. Int J Radiat Oncol 2016;96(5):941. https://doi.org/10.1016/J.IJROBP.2016.09.054.
[52] Arthur DW, Winter KA, Kuerer HM, Haffty BG, Cuttino LW, Todor D, et al. NRG oncology—radiation therapy Oncology group study 1014: 1-year toxicity report from a phase 2 study of repeat breast-preserving surgery and 3-dimensional conformal partial-breast reirradiation for in-breast recurrence. Int J Radiat Oncol Biol Phys 2018;98(5):1028–35. https://doi.org/10.1016/j.ijrobp.2017.03.016.
[53] Vaidya JS, Joseph DJ, Tobias JS, Bulsara M, Wenz F, Saunders C, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. Lancet 2010;376(9735):91–102. https://doi.org/10.1016/S0140-6736(10)60837-9.
[54] Sorrentino L, Fissi S, Meaglia I, Bossi D, Caserini O, Mazzucchelli S, et al. One-step intraoperative radiotherapy optimizes conservative treatment of breast cancer with advantages in quality of life and work resumption. Breast 2018;39:123–30. https://doi.org/10.1016/j.breast.2018.04.004.
[55] Bouillon K, Haddy N, Delaloge S, Garbay JR, Garsi JP, Brindel P, et al. Long-term cardiovascular mortality after radiotherapy for breast cancer. J Am Coll Cardiol 2011;57(4):445–52. https://doi.org/10.1016/j.jacc.2010.08.638.
[56] Shah C, Ahlawat S, Khan A, Tendulkar RD, Wazer DE, Shah SS, et al. The role of MRI in the follow-up of women undergoing breast-conserving therapy. Am J Clin Oncol 2016;39(3):314–9. https://doi.org/10.1097/COC.0000000000000290.
[57] Trombetta M, Hall M, Julian TB. Long-term followup of breast preservation by re-excision and balloon brachytherapy after ipsilateral breast tumor recurrence. Brachytherapy 2014;13(5):488–92. https://doi.org/10.1016/j.brachy.2014.05.017.
[58] Monten C, Lievens Y. Adjuvant breast radiotherapy: how to trade-off cost and effectiveness? Radiother Oncol 2018;126(1):132–8. https://doi.org/10.1016/j.radonc.2017.11.005.
[59] Gentilini O, Botteri E, Rotmensz N, Santillo B, Peradze N, Saihum RC, et al. When can a second conservative approach be considered for ipsilateral breast tumour recurrence? Ann Oncol 2007;18(3):468–72. https://doi.org/10.1093/annonc/mdl424.
[60] Gentilini O, Botteri E, Veronesi P, Sangalli C, Del Castillo A, Ballardini B, et al. Repeating conservative surgery after ipsilateral breast tumor reappearance: criteria for selecting the best candidates. Ann Surg Oncol 2012;19(12):3771–6. https://doi.org/10.1245/s10434-012-2404-5.
[61] Botteri E, Rotmensz N, Sangalli C, Toesca A, Peradze N, De Oliveira Filho HR, et al. Unavoidable mastectomy for ipsilateral breast tumour recurrence after conservative surgery: patient outcome. Ann Oncol 2009;20(6):1008–12. https://doi.org/10.1093/annonc/mdn732.
[62] Ishitobi M, Fukui R, Hashimoto Y, Kittaka N, Nakayama T, Tamaki Y. pTis and pT1a ipsilateral breast tumor recurrence is associated with good prognosis after salvage surgery. Oncology 2018;94(1):12–8. https://www.karger.com/DOI/10.1159/000480516.
[63] Aebi S, Gelber S, Anderson SJ, Láng I, Robidoux A, Martín M, et al. Chemotherapy for isolated locoregional recurrence of breast cancer (CALOR): a randomised trial. Lancet Oncol 2014;15(2):156–63. https://doi.org/10.1016/S1470-2045(13)70589-8.
[64] Wapnir IL, Price KN, Anderson SJ, Robidoux A, Martín M, Nortier JWR, et al. Efficacy of chemotherapy for ER-negative and ER-positive isolated locoregional recurrence of breast cancer: final analysis of the CALOR trial. J Clin Oncol 2018;36(11):1073–9. https://doi.org/10.1200/JCO.2017.76.5719.
[65] Moossdorff M, van Roozendaal LM, Schipper R-J, Strobbe LJ, Voogd AC, Tjan-Heijnen VC, et al. Inconsistent selection and definition of local and regional endpoints in breast cancer research. Br J Surg 2014;101(13):1657–65. https://doi.org/10.1002/bjs.9644.
[66] Houvenaeghel G, Boher JM, Michel V, Bannier M, Minsat M, Tallet A, et al. Survival after breast cancer local recurrence according to therapeutic strategies TT. Eur J Surg Oncol TA 2017;43(8):1409–14.
[67] Adkison JB, Kuske RR, Patel RR. Breast conserving surgery and accelerated partial breast irradiation after prior breast radiation therapy. Am J Clin Oncol 2010;33(5):427–31. https://doi.org/10.1097/COC.0b013e3181b20426.
[68] Chin C, Jadeja P, Taback B, Horowitz DP, Feldman SM, Ha R, et al. Evaluation of partial breast reirradiation with intraoperative radiotherapy after prior thoracic radiation: a single-institution report of outcomes and toxicity TT. Front Oncol TA 2017;7.
[69] Thangarajah F, Heilmann J, Malter W, Kunze S, Marnitz S, Mallmann P, et al. Breast conserving surgery in combination with intraoperative radiotherapy after previous external beam therapy: an option to avoid mastectomy TT. Breast Cancer Res Treat TA 2018;168(3):739–44.
[70] Trombetta M, Julian TB, Werts DE, McWilliams W, Kim Y, Miften M, et al. Long-term cosmesis after lumpectomy and brachytherapy in the management of carcinoma of the previously irradiated breast. Am J Clin Oncol 2009;32(3):314–8. https://doi.org/10.1097/COC.0b013e31818af0b9.
[71] Trombetta M, Julian T, Bhandari T, Werts ED, Miften M, Parda D. Breast conservation surgery and interstitial brachytherapy in the management of locally recurrent carcinoma of the breast: the Allegheny General Hospital experience. Brachytherapy 2008;7(1):29–36. https://doi.org/10.1016/j.brachy.2007.12.001.
[72] Blandino G, Guenzi M, Belgioia L, Bonzano E, Configliaccio E, Tornari E, et al. Adjuvant intraoperative radiotherapy for selected breast cancers in previously irradiated women: evidence for excellent feasibility and favorable outcomes. Reports Pract Oncol Radiother J Gt Cancer Cent Pozn Polish Soc Radiat Oncol 2017;22(4):277–83. https://doi.org/10.1016/j.rpor.2017.02.009.
[73] Nishimura S, Takahashi K, Akiyama F, Oguchi M, Tada K, Makita M, et al. Classification of ipsilateral breast tumor recurrence after breast-conserving therapy: new primary cancer allows a good prognosis. Breast Canc 2005;12(2):112–7. https://doi.org/10.2325/jbcs.12.112.
[74] Yi M, Buchholz TA, Meric-Bernstam F, Bedrosian I, Hwang RF, Ross MI, et al. Classification of ipsilateral breast tumor recurrences after breast conservation therapy can predict patient prognosis and facilitate treatment planning. Ann Surg 2011;253(3):572–9. https://doi.org/10.1097/SLA.0b013e318208fc2a.
[75] Biermann J, Parris TZ, Nemes S, Danielsson A, Engqvist H, Werner Rönnerman E, et al. Clonal relatedness in tumour pairs of breast cancer patients. Breast Cancer Res 2018;20(1):96. https://doi.org/10.1186/s13058-018-1022-y.
[76] Salvadori B, Marubini E, Miceli R, Conti AR, Cusumano F, Andreola S, et al. Reoperation for locally recurrent breast cancer in patients previously treated with conservative surgery. Br J Surg 2003;86(1):84–7. https://doi.org/10.1046/j.1365-2168.1999.00961.x.
[77] Komoike Y, Motomura K, Inaji H, Kasugai T, Koyama H. Repeat lumpectomy for patients with ipsilateral breast tumor recurrence after breast-conserving surgery. Oncology 2003;64(1):1–6. https://www.karger.com/DOI/10.1159/000066512.
[78] Alpert TE, Kuerer HM, Arthur DW, Lannin DR, Haffty BG. Ipsilateral breast tumor recurrence after breast conservation therapy: outcomes of salvage mastectomy vs. salvage breast-conserving surgery and prognostic factors for salvage breast preservation. Int J Radiat Oncol Biol Phys 2005;63(3):845–51. https://doi.org/10.1016/j.ijrobp.2005.02.035.
[79] Ishitobi M, Fukui R, Hashimoto Y, Kittaka N, Nakayama T, Tamaki Y. Safety for repeat lumpectomy without radiotherapy for ipsilateral breast tumor recurrence. Anticancer Res 2017;37(9):5293–9. https://doi.org/10.21873/anticanres.11955.
[80] Kurtz JM, Jacquemier J, Amalric R, Brandone H, Ayme Y, et al. Is breast conservation after local recurrence feasible? Eur J Cancer 1991;27(3):240–4.
[81] Voogd AC, van Tienhoven G, Peterse HL, Crommelin MA, Rutgers EJ, et al. Local recurrence after breast conservation therapy for early stage breast carcinoma: detection, treatment, and outcome in 266 patients. Dutch Study Group on Local Recurrence after Breast Conservation (BORST). Cancer 1999;85(2):437–46.
[82] Galper S, Blood E, Gelman R, Abner A, Recht A, Kohli A, et al. Prognosis after local recurrence after conservative surgery and radiation for early-stage breast cancer. Int J Radiat Oncol 2005;61(2):348–57. https://doi.org/10.1016/J.IJROBP.2004.06.011.
[83] Chen SL, Martinez SR. The survival impact of the choice of surgical procedure after ipsilateral breast cancer recurrence. Am J Surg 2008;196(4):495–9. https://doi.org/10.1016/J.AMJSURG.2008.06.018.
[84] Shah C, Wilkinson J Ben, Jawad M, Wobb J, Berry S, Mitchell C, et al. Outcome after ipsilateral breast tumor recurrence in patients with early-stage breast cancer treated with accelerated partial breast irradiation. Clin Breast Canc 2012;12(6):392–7. https://doi.org/10.1016/j.clbc.2012.09.006.
[85] Yoshida A, Takahashi O, Okumura Y, Arima N, Nakatsukasa K, Tanabe M, et al. Prognosis after mastectomy versus repeat lumpectomy in patients with ipsilateral breast cancer recurrence: a propensity score analysis. Eur J Surg Oncol 2016;42(4):474–80. https://doi.org/10.1016/j.ejso.2016.01.011.
[86] Mullen EE, Deutsch M, Bloomer WD. Salvage radiotherapy for local failures of lumpectomy and breast irradiation. Radiother Oncol 1997;42(1):25–9.
[87] Deutsch M. Repeat high-dose external beam irradiation for in-breast tumor

recurrence after previous lumpectomy and whole breast irradiation. Int J Radiat Oncol Biol Phys 2002;53(3):687–91.
[88] Resch A, Fellner C, Mock U, Handl-Zeller L, Biber E, Seitz W, et al. Locally recurrent breast cancer: pulse dose rate brachytherapy for repeat irradiation following lumpectomy– a second chance to preserve the breast. Radiology 2002;225(3):713–8. https://doi.org/10.1148/radiol.2253011913.
[89] Hannoun-Levi J-M, Houvenaeghel G, Ellis S, Teissier E, Alzieu C, Lallement M, et al. Partial breast irradiation as second conservative treatment for local breast cancer recurrence. Int J Radiat Oncol Biol Phys 2004;60(5):1385–92. https://doi.org/10.1016/j.ijrobp.2004.05.035.
[90] Kraus-Tiefenbacher U, Bauer L, Scheda A, Schoeber C, Schaefer J, Steil V, et al. Intraoperative radiotherapy (IORT) is an option for patients with localized breast recurrences after previous external-beam radiotherapy. BMC Canc 2007;7:178. https://doi.org/10.1186/1471-2407-7-178.
[91] Trombetta M, Julian TB, Werts ED, Colonias A, Betler J, Kotinsley K, et al. Comparison of conservative management techniques in the re-treatment of ipsilateral breast tumor recurrence. Brachytherapy 2011;10(1):74–80. https://doi.org/10.1016/j.brachy.2010.01.005.
[92] Chadha M, Feldman S, Boolbol S, Wang L, Harrison LB. The feasibility of a second lumpectomy and breast brachytherapy for localized cancer in a breast previously treated with lumpectomy and radiation therapy for breast cancer. Brachytherapy 2008;7(1):22–8. https://doi.org/10.1016/j.brachy.2007.10.006.
[93] Hannoun-Levi J-M, Resch A, Gal J, Kauer-Dorner D, Strnad V, Niehoff P, et al. Accelerated partial breast irradiation with interstitial brachytherapy as second conservative treatment for ipsilateral breast tumour recurrence: multicentric study of the GEC-ESTRO Breast Cancer Working Group. Radiother Oncol 2013;108(2):226–31. https://doi.org/10.1016/j.radonc.2013.03.026.
[94] Merino T, Tran WT, Czarnota GJ. Re-irradiation for locally recurrent refractory breast cancer. Oncotarget 2015;6(33):35051–62. https://doi.org/10.18632/oncotarget.6036.
[95] Smanyko V, Meszaros N, Ujhelyi M, Fröhlich G, Stelczer G, Major T, et al. Second breast conserving surgery and interstitial radiotherapy for the treatment of breast tumor local recurrences. Five-year results. Orv Hetil 2018;159(11):430–8. https://doi.org/10.1556/650.2018.30984.