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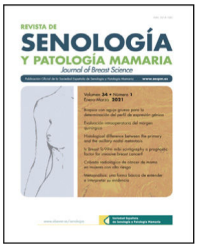

SPECIAL ARTICLE

Can breast cancer be reirradiated?

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Abstract Salvage mastectomy is still the standard procedure for ipsilateral breast tumor recurrence. A second breast-conserving approach with re-irradiation is considered nowadays feasible in selected patients, with good results in terms of local control and tolerance. In this work we summarize the different radiation techniques and their results in order to define recommendations to help groups starting to consider this approach in their institutions. Although the difficulty due to the low rate of breast cancer recurrences after first breast conserving therapy, further clinical trials are needed to confirm these results.

PALABRAS CLAVE
Cáncer de mama;
recidiva;
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¿Se puede reirradiar en cáncer de mama?

Resumen La mastectomía de rescate continúa siendo el tratamiento de elección en las recidivas locales en cáncer de mama. Actualmente, se puede considerar la posibilidad de realizar un segundo tratamiento conservador con re-irradiación en pacientes seleccionadas, con buenos resultados clínicos y de tolerancia. En este trabajo, hemos realizado un resumen de las diferentes técnicas de re-irradiación y de sus resultados, para definir unas recomendaciones que ayuden a los grupos que consideren iniciar un protocolo similar en sus centros de trabajo. A pesar de la dificultad intrínseca debido a la baja tasa de recidivas tras un primer tratamiento conservador, serían necesarios ensayos clínicos randomizados para confirmar estos resultados.

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Background

Early-stage breast cancer standard of care comprises conserving surgery and radiation therapy. Whole or partial breast irradiation based on external-beam radiotherapy or multi-catheter interstitial brachytherapy (MIB) can be used, based on tumor and patients' features.

Due to the improvement in survival after breast conserving therapy (BCT) patients are at increased risk for developing an ipsilateral breast tumor recurrence (IBTR), with a 20-year cumulative incidence rate around 15%.[1]

Salvage mastectomy (SM) is considered the gold standard treatment in IBTR. However, also salvage mastectomy does not eliminate the risk of (second) locoregional recurrence (10%), metastatic disease (20%) or breast-cancer related death, with overall survival rates of 80% at 5 years.[2] More and more treatment strategies are suggested in order to perform a repeat BCT in patients with IBRT after initial BCT, so this second conserving treatment (SCT) could be a good approach in selected patients. 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.[2]

So it seems clear that this SCT must comprise conserving surgery and re-irradiation to obtain comparable results to SM.[3]

Second conserving treatment

In the early 21st century, the local recurrence rates after completion of adjuvant therapy are still about 10% and 20% at 10 and 15 years, respectively.[4] By definition, IBTR was considered as a local recurrence occurring within the breast which was initially conservatively treated with post-operative RT.[5]

For IBTR after BCS, SM is the current standard surgical procedure recommended, but there is a 5–10% rate of third local recurrence. Previous voluminous nodal disease (pN2 or higher) seems to be associated with a high rate of third local recurrences.[6]

SCT could consist in a second breast conserving surgery alone (without re-irradiation) or a second breast-conserving surgery with re-irradiation. Nevertheless, in the SEER-database analysis performed by Wang, SCT with reirradiation have comparable results to SM in terms of local control and survival. Larger tumor (>2 cm), more nodal involvement (N2–3), higher grade (III), older age (>70 years), time interval < 10 years, and negative ER/PR status were prognostic factors associated with a worse breast cancer specific survival (BCSS). Those patients treated with BCS without reirradiation duplicate the risk of breast cancer related death, comparing with SM (Hazard ratio 2.20 and 1 respectively). However, those patients treated with BCS and reirradiation have a better BCSS compared with SM and BCS without irradiation (Hazard ratio 2.20, 1 and 0.67 respectively).[3]

Re-irradiation techniques

Breast re-irradiation with MIB

MIB Brachytherapy has been the most reported reirradiation technique in case of SCT (Table 1). Due to the possibility of delivering high doses to small volumes also with high conformity, it can be considered an optimal partial re-irradiation procedure. However, it requires an expert team and a specific technical facility.

Most of the published studies are retrospective series, probably related to the low rate of recurrences in patients previously treated with a first BCP. Reported third ipsilateral breast tumor event (IBTE) free survival ranges in the different studies from 77.4% to 100%. Regarding the series with longer follow-up, Guix et al.[17] reported the results in a homogeneous group of patients with excellent results in terms of local control (89,4% at 10 years), survival (96,7% at 10 years) and tolerance (0% G3 late toxicity), similar to those reported in smaller series by Vavassori et al. and Chatzikonstantinou et al.[19,20]

GEC-ESTRO multicentric study represents the wider international study, that analyzed 217 patients treated with surgical resection followed by re-irradiation of the tumor bed using low (LDR), pulsed (PDR) or high-dose rate (HDR) MIB.[14] With a median follow-up (MFU) of 3.9 years [range: 1.1–10.3] from the IBTR, 9 patients (4.1%) presented a third IBTE, leading to a 5- and 10-year actuarial rates of freedom from 2nd LR of 94.4% and 92.8%, respectively. Age > 55 years, grade 3 and negative hormonal receptor status were prognostic factors for third IBTE.

Reported grade 3 late toxicity ranges from 0% to 17%. The most frequent late side effects after breast MIB re-irradiation were cutaneous and sub cutaneous fibrosis, telangiectasia, hyperpigmentation, breast pain while ulceration was rare. Cumulative radiation doses (adding previous radiation and re-irradiation doses) higher than 100 Gy seems to be a prognosis factor for grade 2 late toxicity.[8]

Breast re-irradiation with external beam radiotherapy (EBRT)

Partial breast irradiation (PBI) has emerged as an alternative to whole breast irradiation (WBI) in selected patients undergoing second breast-conserving surgery (SBCS) limiting the risk of toxic effects by reducing the volume of tissue receiving reirradiation. The use of EBRT remains interesting in terms of accessibility, allowing many hospitals to give an alternative to the patients who decline a salvage mastectomy in case of IBRT.

There are many studies (Table 2) investigating the feasibility of external beam re-irradiation that showed encouraging results. In 2018, Janssen et al. evaluated 83 patients with local recurrence of breast cancer who underwent partial external beam re-irradiation (re-RT) either as part of a SCT or following mastectomy.[21] The re-RT schedules were 45 Gy (1.8 Gy per fraction) administered either to the partial breast (n = 42) or mastectomy scar (n = 41). With a MFU of 35 months (range 3–143 months), the

Table 1 MIB re-irradiation results.

Authors (year)	N patients	MFU (months)	MIB techniques	Dose (Gy)	3rdIBTE-FS (%)	OS		G3 toxicity (%)
						Years	%	
Maulard et al. (1995)[7]	38	48	LDR	30	79	5	55	8
Hannoun-Levi et al. (2004)[8]	69	50	LDR	30–50	77.4	5	91.8	10.2
Niehoff et al. (2006)[9]	19	19	HDR	28	62.5	1.5	68.7	3
Chadha et al. (2008)[10]	15	36	LDR	30–45	89	3	100	0
Guix et al. (2009)[11]	36	89	HDR	30	89.4	10	96.7	0
Hannoun-Levi et al. (2011)[12]	42	21	HDR	34	97			3
Kauer-Dorner et al. (2012)[13]	39	57	PDR	50.1	93	5	87	17
GEC-ESTRO (2013)[14]	217	47	LDR	46	94.4	5	88.7	11
			PDR	50.4		10	76.4	
			HDR	32				
Smanykó et al. (2019)[15]	39	59	HDR	22	94.5	5	81	8
Montagne et al. (2019)[16]	159	71	HDR	28–34	97.4	6	91.2	–
			LDR	30–55				
Forster et al. (2019)[17]	19	65	PDR	49.8–50.4	100	5	100	0
			HDR	34.2–32				
Cozzi et al. (2019)[18]	40	61.5	HDR	32 (19)	96.6	5	85.6	7.5
				34 (20)				
				16 (1)				
Vavassori et al. (2020)[19]	31	73.7	HDR	34	90.3	5	87.1	3.2
Chatzikonstantinou et al. (2021)[20]	20	69.6	HDR	32	86.8	5	92.3	0

MFU: median follow-up, MIB techniques: multi-catheter interstitial brachytherapy techniques, LDR: Low dose rate, HDR: High dose rate, PDR: Pulsed dose rate, 3rdIBTE-FS: third ipsilateral breast tumor event free survival rate; OS: overall survival.

authors reported a 3rdIBTE rate of 14.5% and acute and late skin toxicity were low (< grade 3), since grade 3 or 4 toxicity were not reported. The prognostic factors for favorable overall survival rates were younger age (p = 0.045), lower T stage (p = 0.019), and N0 stage (p = 0.005). The use of Intensity Modulated Radiation Therapy/Volumetric Modulated Arc Radiotherapy (IMRT/VMAT) was investigated by Bazan et al. in a cohort of 28 patients (18 isolated locoregional recurrences (LRR), 10 LRR with simultaneous distant disease) that received reirradiation with a median dose to the breast/chest wall of 50,4 Gy (50,4-61,8).[22] The most commom dose/fractionation was 45 Gy in 1,5 Gy/fraction twice daily. With a MFU of 12 months, the authors reported a 3rdIBTE-free survival rate of 91.7% and reported 2 patients (7%) with grade 3 toxicity (esophagitis and wound dehiscence). The patient with esophagitis received 45 Gy in 1,5 Gy/ fraction, twice daily with a boost of 15 Gy with the same fractionation schedule that included mediastinal disease.

The results of the NRG Oncology/RTOG 1014 phase 2 clinical trial have been published (Arthur DW et al.) in 2020 in JAMA Oncology with a MFU of 5.5 years.[23] Eligible patients (58 evaluable for analysis) with breast tumor recurrence less than 3 cm, without evidence of skin involvement, unifocal, 0 to 3 positive axillary lymph nodes, excision with negative margins and more than 1 year after first breast conservative surgery. Adjuvant partial breast reirradiation,1,5 Gy twice daily separated 6 h, during 15 days (45 Gy), using a 3D

Table 2 Reirradiation studies with external beam radiotherapy.

Authors (year)	N patients	MFU (months)	EBRT Technique	Total dose (Gy)/ fF	3rdIBTE (%) or 3rdIBTE-FSR	5-y OS (%)	>G3 toxicity (%)
Janssen et al. (2018)[21]	83	35	3D-CRT	45 /1,8	14,5 (at 21 months)	76	0
Bazan et al. (2018)[22]	28	12	IMRT/VMAT	45 /1,5 twice daily	91,7 at 1 year	NR	–
Thorpe et al. (2019)[25]	50	12,7	Proton therapy	45–76	93 at 1 year	97	16
Arthur et al. (2020)[23]	58	66	3D-CRT	45 /1,5 twice daily	5,2	95	7
LaRiviere et al. (2021)[26]	27	16,6	Proton therapy	51 /1,5 twice daily	95 at 1 year	NR	3

MFU: median follow-up; f: dose per fraction; 3rdIBTE: third ipsilateral breast tumor event rate; OS: overall survival; >G3: grade 3 and higuer toxicity rate; 3D-CRT: 3D conformal radiation therapy; IMRT: intensity modulated radiation therapy. VMAT: volumetric arc radiotherapy.

conformal technique. With 4 patients out of 58 who developed a 3rdIBTE, the authors reported a 3rdIBTE 5-year cumulative incidence of 5% with an overall survival (OS) rate of 95%. There were acceptable late grade 3 treatment-related adverse effects (AEs) (7%) and no grade 4 events after a second lumpectomy and PBI with 3D-CRT.

Proton therapy is recommended by the American Society for Radiation Oncology in cases where reirrradiation is needed; however, data are limited. The primary rationale is that protons have unique dose deposition characteristics that can deliver the prescribed target dose while giving a lower dose to normal tissues compared with photon-based forms of external beam radiation therapy. This could be particularly important in minimizing the risk from reirradiation for breast cancer, but there is little published data.[24]

Thorpe et al. investigated the feasibility of breast re-irradiation, based on proton therapy for 50 patients from 2011 to 2016 (including post mastectomy) with a 3rdIBTE-free survival rate at one year of 93%. MFU was 12.7 months (0–41.8). Median reRT dose was 55.1 Gy (45.1–76.3). Median cumulative dose was 110.6 Gy (70.6–156.8). Median interval between RT courses was 103.8 months (5.5–430.8). ReRT included regional nodes in 84% (66% internal mammary node [IMN]) Grade 3 AEs were experienced by 16% of patients (10% acute, 8% late) and were associated with body mass index (BMI) > 30 kg/m^2 (p = 0.04), bilateral recurrence (p = 0.02), and bilateral reRT (p = 0.004). All grade 3 AEs (CTCAE v4.0) occurred in patients receiving IMN reRT (p = 0.08). At 1 year, LRFS was 93%, and OS was 97%.[25]

LaRiviere et al. published a single-institution retrospective review of 27 patients with LRR of breast cancer and a history of prior radiation, treated with proton therapy between 2012 and 2019.[26] The median interval between courses was 9.7 years. Proton reirradiation regimens included whole breast/chest wall (WB/ CW) with regional nodal RT (22/27), nodal RT alone (2/27), or WB/CW alone (3/27). The median dose was 51 Gy, and the most common fractionation was 1.5 Gy twice daily. Median follow-up after reirradiation was 16.6 months. Acute grade 3 toxicities included dermatitis in 2 patients and breast pain in 2 patients. Grade 2 or higher late toxicities included 6 G2 rib fractures and 1 G2 brachial plexopathy, 1 G3 dermatitis, 1 G3 breast pain, and 1 G4 dermatitis. Twelve patients had new documented recurrences of which one was a second in-field LRR, and there were 7 deaths. Proton salvage appears to be safe with acceptable acute and late toxicity, and effective with >95% local-regional control.

In all these studies, no heart or lung toxicity was described.

Breast re-irradiation with intraoperative radiation therapy (IORT)

IORT has emerged as a popular alternative to brachytherapy for re-irradiation in the last decade. This technique allows for salvage lumpectomy and re-RT to be performed simultaneously, making it a "single shot" procedure. The IORT system is based on a miniaturized low power X-ray source, with a fluctuation between 50 and 100 kV or an electron beam.

In recent years, there are few series that report the use of IORT in cases of SCT. Between 2007 and 2020, five studies have shown that IORT has an average rate of 3rdIBTE-free survival of about 94%, with a range between 89% and 100%. Four of them with the Intrabeam device, which is a 50 kV photon beam mobile X-ray unit. Other use an electron beam delivered by a mobile lineal accelerator (Table 3).

Early studies by Kraus-Tienfenbacher et al. and Chin et al. include a small cohort of patients (17 and 12 respectively) using ORT with Intrabeam system. Their results showed no local recurrence in 26 and 14 months.[27,28] On the other hand, Blandino et al. explored the use of IORT using an electron beam, in 30 women who refused SM. The 5-year local control rate was 92.3%.[29] In the same year, Tangarajah et al., retrospectively analyzed the outcome of 39 patients treated with IORT using the Intrabeam device. The MFU was 58 months, with a 3rdIBTE-FS rate of 89.9%.[30]

More recently, Boehm et al. performed the largest study to date with a total of 57 patients also treated with the Intrabeam system. At a median follow-up of 24.3 months, the locoregional control rate was 89%.[31]

In terms of disease-free survival, Elfgen et al. found no significant difference in 26 patients treated with BCS and IORT in recurrence breast cancer compared to standard treatment.[32]

As described by Thangarajah et al. and Kraus-Tienfenbacher et al., acute toxicity rate was very low, with no grade 3 or 4 [30,].[27] Kraus-Tienfenbacher et al. reported excellent/good patient satisfaction rates.[27]

Recommendations

It is prioritary to personalize therapy options according to patients' preferences. In the St. Gallen International

Table 3 IORT re-irradiation studies.

Authors (year)	N pts	MFU (months)	Irradiation techniques	Dose (Gy)	3rdIBTE-FS (%)	5-y OS (%)	> G3 tox (%)
Kraus-Tiefenbacher et al. (2007)[27]	17	26	50 kV X-rays	20	100	_	_
Chin et al. (2017)[28]	12	14	50 kV X-rays	20	100	_	0
Blandino et al. (2017)[29]	30	47	Electron beam	18	92.3	91.2	21
Thangarajah et al. (2018)[30]	41	58	50 kV X-rays	20	89.7	82	0
Boehm et al. (2019)[31]	57	24.5	50 kV X-rays	20	89	_	2

N pts.: number of patients, MFU: median follow-up, 3rdIBTE-FS: third ipsilateral breast tumor event free survival rate; OS: overall survival; > G3 tox: grade 3 and higher toxicity rate.

Consensus Guidelines in 2021, repeat attempts at breast conservation were particularly favored by the Panel in the setting of low-risk (small, luminal A-type) breast cancers, presumably when additional radiation therapy might not be required.[33]

The Panel acknowledged that breast conservation with re-irradiation could be an option instead of mastectomy for some women with ipsilateral recurrence or second breast cancer arising >5 years after initial breast conservation and radiation. However, the Panel was split 50/50 on offering second attempts at breast conservation when reirradiation was not a clinical option. In any case, mastectomy need no longer be considered absolutely 'obligatory' for ipsilateral breast recurrence.

SCT can safely be proposed, as an alternative to SM, to carefully selected and well-informed patients, leading to a personalized treatment for saving patients from breast mutilation. MIB BT is the most evaluated technique. EBRT and IORT have only been tested in small series, so should be delivered under clinical trials.[1]

GEC-ESTRO APBI recommendations could be used as a potential decision making and prognosis tool for s SCT. Proper patient information is priority for high-risk patients that refuse SM.[16]

A second conservative approach can be safety perform to patients with the following characteristics:

- Age $\geq$ 50 years.
- Tumors $\leq$2 cm.
- Infiltrating ductal carcinomas.
- Low differentiation grade.
- Without nodal involvement.
- Time interval between first BCT and recurrence $\geq$4 years.
- Unifocal.
- Negative margins after repeated BCS.
- SCT feasibility.

Conclusions

Re-irradiation improves clinical results comparing with second BCS without re-irradiation. Re-irradiation after a second BCS is a feasible procedure, overall after the great technical improvements that allow a better dose conformity with good tolerance in terms of toxicity. SCT with re-irradiation could be considered an alternative to SM. Careful patients' selection following GEC-ESTRO recommendations could be a good approach. It is imperative to provide proper information in those high-risk patients that prefer to avoid breast mutilation. Interstitial brachytherapy is the most evaluated re-irradiation option, but EBRT and IORT should be considered under clinical trials with promising preliminary results. Collaborative groups trials with higher number of patients included are needed due to the low rate of breast cancer recurrences after the first BCT.

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Ethical comittee aproval

The characteristics of the review exempt it from ethics committee approval.

Conflict of interest

The authors declare no conflict of interest.

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