The Breast 49 (2020) 274–280

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Review

Second conservative treatment for second ipsilateral breast tumor event: A systematic review of the different re-irradiation techniques

Lucile Montagne [a], Arthur Hannoun [b], Jean-Michel Hannoun-Levi [a, *]

[a] Department of Radiation Oncology, Antoine Lacassagne Cancer Center, University of Cote D'Azur, Nice, France
[b] University of Lyon 2, Lyon, France

ARTICLE INFO

Article history:
Received 18 November 2019
Received in revised form
29 December 2019
Accepted 7 January 2020
Available online 9 January 2020

ABSTRACT

Aim: To address the different partial breast re-irradiation techniques available in the context of second conservative treatment (SCT), as an alternative to salvage mastectomy, for 2nd ipsilateral breast tumor event (IBTE) and summarize their respective oncological and toxicity outcomes.
Material and methods: A literature search was made based on MeSH/PubMed, including papers from 1995 to 2019. Each article was described according to the main irradiation technique, fractionation, oncological results and grade 3 toxicities related to the salvage conservative treatment.
Results: Twenty-two articles were identified, reporting the outcomes of over 1 000 patients. MIB Brachytherapy was the most used re-irradiation technique in case of SCT, with a median 3rdIBTE-FS rate of 88% and summed up grade 3 toxicities of 6%. As for IORT, the average rate of 3rdIBTE-FS was about Finally, external beam partial re-irradiation was recently tested in this indication with encouraging results in terms of tolerance.
Conclusion: When presenting a 2ndIBTE, a SCT can safely be proposed to carefully selected and well-informed patients, as an alternative to salvage mastectomy. MIB appears to be the first intention and most robust choice. IORT, external beam radiotherapy and balloon brachytherapy are interesting alternatives but have only been tested in small series. Further investigations are required and their use should be limited to clinical trial only.

Contents

* Corresponding author. Radiation Oncology Department, Antoine Lacassagne Cancer Center, University of Cote d'Azur, 33 Avenue Valombrose, 06107, Nice, CEDEX, France.
E-mail address: jean-michel.hannoun-levi@nice.unicancer.fr (J.-M. Hannoun-Levi).

https://doi.org/10.1016/j.breast.2020.01.003

1. Introduction

Breast cancer has been a matter of public health for the past decades, being the most common cancer among all (13.4%) [1]. Standard of care regarding early stages has evolved from mutilating mastectomy towards conservative radio-surgical treatment. Adjuvant breast irradiation is an essential tool in reducing the occurrence of local relapse. Whole or partial breast irradiation based on external beam radiotherapy or multi-catheter interstitial brachytherapy (MIB) can be used in this indication based on tumor and patient's features [2–4]. However, despite an optimal therapeutic approach, few patients may experience a second local ipsilateral breast tumor event (IBTE), with a 20-year cumulative incidence rate of 15% [2].

For 2ndIBTE, salvage mastectomy (SM) was historically considered as the gold standard treatment, with no other alternative of care. However, the concept of second conservative treatment (SCT) progressively rose, freeing the patient from a mutilating therapeutic management [5]. At this time, there has been no phase III trial directly comparing these two therapeutic approaches and therefore no clear guidelines to lead the treatment decision. Nevertheless, encouraging results in terms of oncological and cosmetic outcomes after SCT have been provided [6]. Recently, the Breast cancer working group of the GEC-ESTRO reported the results of a matched-pair analysis between SM and SCT with no significant differences regarding disease-free, specific and overall survival as well as 3rdIBTE-free survival rates [7].

If the role of adjuvant irradiation for primary breast cancer is clearly recognized, concerning 2ndIBTE, re-irradiation of the tumor bed is warranted. Indeed, regarding 2ndIBTE, Kurtz et al. showed that the 3rdIBTE rate was doubling with breast conservation surgery alone (23%) versus mastectomy (12%). More recent publications confirmed these results [8,9]. Currently, SCT with partial breast re-irradiation leads to an equivalent 3rdIBTE rate compared to SM (about 10%) while lumpectomy alone increases the risk of new local event (about 20%) [10]. It is known that accelerated partial breast irradiation (APBI) for low-risk breast cancer is validated as an alternative solution to whole breast irradiation [11]. But if APBI focuses on comfort and patient convenience, SCT with accelerated partial breast re-irradiation (APBrI) aimed to avoid a mutilating surgery [3]. Historically, the most used APBrI technique was multi-catheter interstitial brachytherapy (MIB) and its efficiency has been tested in multiple retrospective series. Recently, other re-irradiation techniques have emerged in combination with salvage lumpectomy, mimicking the process of a first breast conservative treatment, such as 3D-external radiotherapy, balloon-based brachytherapy and Intra-Operative Radiation Therapy (IORT).

The aim of this review was to address the different partial breast re-irradiation techniques available in the context of second conservative treatment for 2ndIBTE and summarize their respective oncological and toxicity outcomes.

2. Material and methods

A literature search was made based on MeSH/PubMed, for papers between 1995 and 2019. Two searches with MeSH terms when available were performed: 1) Breast Neoplasms/radiotherapy and Neoplasm Recurrence, Local/radiotherapy restricted to major topics, 2) Breast Neoplasms and intraoperative radiotherapy. The selected studies needed to address: one of the re-irradiation techniques in a cohort of more than 10 patients (pts); with consistent statistical results of toxicity and/or oncological outcomes; written in a full-length article in English language.

Each article was described according to the main irradiation technique, fractionation (total dose, dose/fraction), oncological results (3rdIBTE or 3rdIBTE-free survival - 3rdIBTE-FS - rates, OS) and grade 3 and over toxicities related to the salvage conservative treatment. For each re-irradiation technique, a brief description of principles and technical modalities was presented followed by the description of oncological outcome, toxicity profile and cosmetic results (if available). All the results were summarized in a table related to a specific breast re-irradiation technique.

3. Results

From January 1995 to September 2019, based on the 2 researches with the previously described MeSH terms (1: Breast Neoplasms/radiotherapy and Neoplasm Recurrence, Local/radiotherapy restricted to major topics and 2: Breast Neoplasms and intraoperative radiotherapy), 231 and 692 articles were retrieved for the first and second query respectively (Fig. 1). Among these 923 articles, 894 were initially removed from the analysis for the following reasons: no relation with SCT (891), no full text paper (1) and no English language (2). Among the 29 remaining articles, 7 were definitively removed because of: patient's cohort <10 pts (3), unpublished abstract (3) and no statistical results (1). Finally, a total of 22 articles related to 18 studies were selected for the analysis. Brachytherapy (13 studies), Intra-operative radiation therapy (IORT - 4 studies) and external beam radiation therapy (EBRT - 5 studies) were the 3 breast re-irradiation techniques reported in the literature.

3.1. Breast re-irradiation with brachytherapy

3.1.1. Principles and technical modalities

MIB Brachytherapy has been the most used and well-known re-irradiation technique in case of SCT. Given its ability to deliver a high dose to a small volume and its conformity, it can be considered as the optimal partial re-irradiation procedure. However, it requires a dedicated technical facility and a skilled team, with a significant experience in order to properly handle this procedure. Indeed, the dose distribution's optimization starts in the operative room (i.e. at the time of the implant), with some experience needed to fully master the technique. Many retrospective papers have been

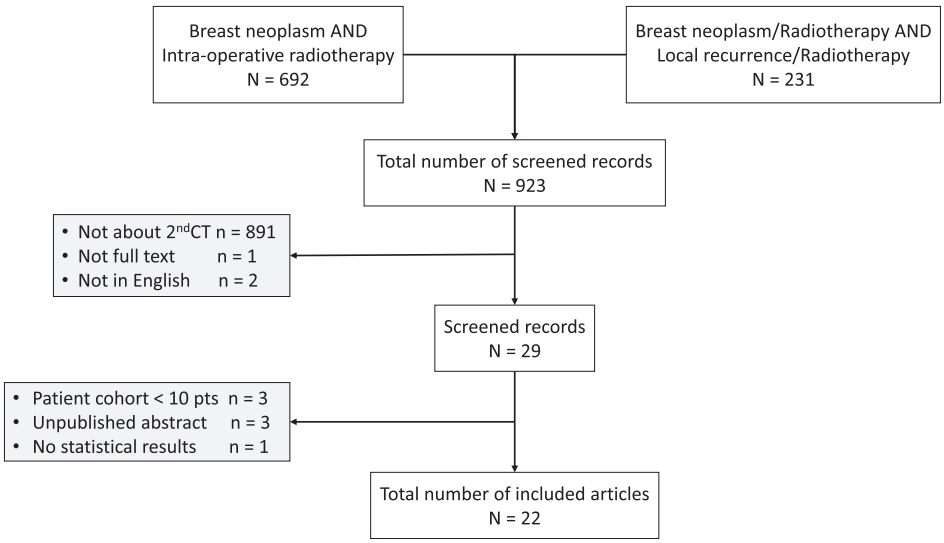

Fig. 1. Flow-chart of total number of screened records and included articles.

published on the subject, exploring the tolerance and impact on oncological outcomes.

Balloon based brachytherapy is a different device which can be used in case of re irradiation. The device is spherical, filled with a liquid content, inserted into the surgical cavity at the time of salvage lumpectomy. A high-dose rate radioactive source is passing through the device by a silicone catheter, into the balloon, to treat the tumor bed with one cm margins. Balloon based brachytherapy uses either a single catheter (Mammosite™ - (Hologic company - Marlborough, Massachusetts, USA) or multichannel systems (SAVI™- Cianna Medical, powered by Merit Medical - Aliso Viejo, California, USA; Contura™ - Hologic company - Marlborough, Massachusetts, USA).

3.1.2. Oncological outcomes

The average rate of 3rdIBTE-free survival for patients treated with brachytherapy is about 88%, ranged between 62.5 and 97.4% [6,12–22] (Table 1).

Back in 1995, Maulard et al. described this method treating local recurrence with a localized re-excision plus low-dose rate (LDR) peri-operative brachytherapy, with no evidence of 3rdIBTE rate for about three quarters of the patients (4 out of 15) [12]. Most of the first conducted studies used LDR or pulsed-dose rate (PDR) brachytherapy, in contrast with the homogeneous use of high-dose rate (HDR) brachytherapy currently observes. Guix et al. proposed a SCT for patients who refused salvage mastectomy and with a median follow-up (MFU) of 89 months, confirmed the safety of HDR brachytherapy procedure with a local control rate of 89.4% [17]. The largest study to date was conducted by the GEC-ESTRO breast cancer group, using LDR, PDR and HDR in combination with salvage lumpectomy, for 217 patients. Five and 10-year 3rdIBTE rates were 5.6 and 7.2% respectively [6]. Smanyko et al. reported the outcome of 39 patients treated by re-excision and peri-operative HDR interstitial brachytherapy [20]. With a MFU of 59 months, the authors reported a 5-year actuarial 3rdIBTE rate of 6%. In adequacy with the previous studies, we recently reported the results of a retrospective study using LDR and HDR MIB for 159 patients. With a MFU of 71 months, the 6-year 3rdIBTE-free survival rate was 97.4% [21].

For balloon brachytherapy, the only study in this particular indication was conducted by Trombetta et al. who tested this device on 18 patients with a MFU of almost 40 months. Two patients out of 18 (11%) presented a 3rdIBTE, treated by salvage mastectomy [23].

3.1.3. Toxicity profile and cosmetic results

Summed up toxicity was acceptable. On average, the rate of grade (G) 3 (and over) complications was 6% (Table 1). The most frequent late side effects after breast re-irradiation technique using MIB were cutaneous and sub cutaneous fibrosis, telangiectasia, hyperpigmentation, breast pain while ulceration was rare. The GEC-ESTRO study, reported 67% of G1, 16% of G2, 9% of G3 and 1% of G4 with a rate of excellent/good cosmetic results of 85% [6]. In their study, Guix et al. did not observed any grade 3 or 4 complications, while cosmetic results were considered acceptable for the vast majority of the patient (96%) [17]. A cumulative radiation dose (breast irradiation for the primary + re-irradiation) superior to 100 Gy was considered as prognosis factor in univariate analysis for grade ≥ 2 complications, leading to more severe cutaneous reaction [14].

For balloon-based brachytherapy, Trombetta et al. reported two patients out of 18 (11%) who developed infectious complication including one patient who had to undergo salvage mastectomy [23]. However, only 2 patients expressed cosmetic downgrading after SCT. Regarding the Harvard scale, 50% of the patients found no substantial difference before and after treatment.

3.2. Breast re-irradiation with intra-operative radiation therapy (IORT)

3.2.1. Principles and technical modalities

Intra operative Radiation therapy (IORT) has grown through the last decade as an attractive alternative to brachytherapy, because of its conceptual ease of use resulting in a “single shot” procedure allowing to perform, at the same time, salvage lumpectomy combined with re-irradiation of the tumor bed. The device system is based on a miniaturized low power X-ray source, fluctuating between 50 and 100 kV (Intrabeam Carl Zeiss Meditec, Jenna, Germany, Xoft® Axxent® Electronic Brachytherapy San Jose, USA) or Electron beam (Mobetron IntraOp Medical Corporation, Sunnyvale, USA; Novac, S·I.T. Sordina IORT Technologies S. p.A, Aprilla, Italy). The concept of IORT is quite similar to brachytherapy, in theory: delivering high (single) dose to a small volume but without radio-

Table 1
Partial breast re-irradiation with brachytherapy.

Authors	Year of publication	# pts	MFU (months)	Irradiation techniques	Dose (Gy)		3rdIBTE-FS (%)	OS		≥ G3 tox. (%)
					Total (Gy)	Dose/f Dose rate		@	(%)	
Maulard C et al. [12]	1995	38	48	MIB LDR	30	–	a)	5 y	55	8
Resch A et al. [13]	2002	17	59	MIB PDR EBRT	12.5 30	0.5–1	b)	4 y	70	0
Hannoun-Levi JM et al. [14]	2004	69	50	MIB LDR	30–50	–	77.4	5 y	91.8	10.2
Niehoff P et al. [15]	2006	19	19	MIB HDR	28	2.5 BID	62.5	1.5 y	68.7	3
				PDR	30	–				
Chadha M et al. [16]	2008	15	36	MIB LDR	30–45	–	89	3 y	100	0
Guix B et al. [17]	2009	36	89	MIB HDR	30	2.5 BID	89.4	10 y	96.7	0
Hannoun-Levi JM et al. [18]	2011	42	21	MIB HDR	34	3.4 BID	c)	–	3	
Kauer-Dorner D et al. [19]	2012	39	57	MIB PDR	50.1	0.6–1	93	5 y	87	17
GEC-ESTRO [6]	2013	217	47	MIB LDR	46	4 BID	94.4	5 y	88.7	11
				PDR	50.4			10 y	76.4	
				HDR	32					
Trombetta M et al. [23].	2014	18	39.6	Balloon HDR	34	3.4 BID	d)	–	–	
Smanyko V et al. [20]	2019	39	59	MIB HDR	22	4.4 BID	94	5 y	81	8
Montagne L et al. [21]	2019	159	71	MIB HDR	28–34	–	97.4	6 y	91.2	–
				LDR	30–55					
Forster T et al. [22]	2019	19	65	MIB PDR	49.8–50.4	0.5–0.7	100	5 y	100	0
				HDR	34.2–32	3.4–3.8				

pts: number of patients; MFU: median follow-up; Dose/f: dose per fraction; Dose rate in Gy per hour; BID: dose given twice a day; 3rdIBTE-FS: third ipsilateral breast tumor event free survival rate; 3rdIBTE: third ipsilateral breast tumor event rate; OS: overall survival; ≥ G3 tox.: grade 3 and higher toxicity rate; MIB: Mutlicatheter interstitial brachytherapy; LDR: low-dose rate; PDR: pulsed-dose rate; HDR: High-dose rate; EBRT: external beam radiation therapy.
a 21% of 3rdIBTE rate.
b 24% of 3rdIBTE rate.
c 3% of 3rdIBTE rate.
d 11% of 3rdIBTE rate.

protection issues (except for electron beam technique which needs a dedicated bunker).

3.2.2. Oncological outcomes

The average rate of 3rdIBTE-free survival for patients treated with IORT is about 95%, ranged between 89.7% and 100%, for recent but low-powered studies [24–27] (Table 2). Four small series (published between 2007 and 2017) reported the use of IORT in case of SCT. The most powered study was presented by Tangarajah et al. [24]. The authors retrospectively analyzed the outcome of 39 patients treated with IORT, using the Intrabeam™ device (Carl Zeiss company - Oberkochen, Germany). For most patients, a single dose of 20 Gy was delivered. With a MFU of 58 months, the 3rdIBTE-FS rate was 89.9%. Kraus-Tienfenbacher et al. reported IORT (Intrabeam™) results from a small cohort of 17 patients with no local recurrence at 26 months [26]. More recently, Blandino et al. explored the use of IORT using an electron beam delivered by a mobile linear accelerator [27]. Thirty women who refused salvage mastectomy were intra-operatively re-irradiated with a 5-y local control rate of 92.3% (MFU: 48 months) (Table 2).

3.2.3. Toxicity profile and cosmetic outcome

As described by Thangarajah et al. and Kraus-Tienfenbacher et al., acute toxicity rate was very low, with no grade 3 or 4 [24,26]. Kraus-Tienfenbacher et al. reported excellent/good patient satisfaction rates (82%) [26]. In the Chin et al. study, the rate of acute toxicity was low (only grade 1 to 2) while for late toxicity, the authors observed persistent G2 seromas for 4 patients (33%), G2 infection for 4 patients (17%) and one G3 infection (abscess drain) [25]. Blandino et al., observed a rate of 51% of excellent/good aesthetic results, but described a rate of 21% of G3 late fibrosis in the meantime [27].

3.3. Breast re-irradiation with external beam radiation therapy

3.3.1. Principles and technical modalities

The use of external beam radiotherapy remains interesting in terms of accessibility, allowing radiotherapy centers to propose an alternative to salvage mastectomy in case of 2ndIBTE. However, the potential side effects induced by the re-irradiation of the mammary gland need to be carefully monitored, as well as skin, lung and cardiac toxicities.

Partial re-irradiation of the breast is mainly conducted through 3D conformal techniques with two opposite fields only including the tumor bed with adapted margins, using photon and eventually electron energy in combination. Conventional dose-fractionation is proposed with 1.5 (BID) to 2 Gy/f, to achieve a total delivered dose ranged between 45 and 50 Gy (Table 3).

3.3.2. Oncological outcomes

The first two studies which investigated the feasibility of external beam re-irradiation showed encouraging results [28,29]. Indeed, in the Mullen et al. study, 20% of patients (4 out of 16) presented a 3rdIBTE at 2 years [28]. Deutsch et al. conducted a study

Table 2
Partial breast re-irradiation with IORT.

Authors	Year of publication	# pts	MFU (months)	Irradiation technique	Median Dose (Gy)	3rdIBTE-FS (%)	5-y OS (%)	≥ G3 tox. (%)
Kraus-Tiefenbacher U et al. [26]	2007	17	26	50 kV X-rays	20	100	–	–
Chin C et al. [27]	2017	12	14	50 kV X-rays	20	100	–	0
Blandino G et al. [27]	2017	30	47	Electron beam	18	92.3	91.2	21
Thangarajah F et al. [24]	2018	41	58	50 kV X-rays	20	89.7	82	0

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.

Table 3
Partial breast re-irradiation with external beam radiotherapy.

Authors	Year of publication	# pts	MFU (months)	Irradiation techniques	Dose (Gy)		3rdIBTE rate (%)	5-y OS (%)	≥ G3 tox. (%)
					Total (Gy)	Dose/f			
Mullen E et al. [28]	1997	17	75	Cobalt + Electron	50	2	–	–	–
Deutsch M et al. [29]	2002	39	51.5	Electron	50	2	–	–	–
Janssen S et al. [30]	2018	83	35	3D CRT	45	1.8	14.5[a]	76	0
Thorpe CS et al. [32]	2019	50	12.7	Proton	45–76	–	–	97	16
Arthur DW et al. [33]	2019	58	66	3D CRT	45	1.5 BID	5.2	95	7

pts: number of patients; MFU: median follow-up; Dose/f: dose per fraction; 3rdIBTE: third ipsilateral breast tumor event rate; OS: overall survival; ≥ G3 tox.: grade 3 and higher toxicity rate; 3DCRT: 3D conformal radiation therapy.
[a] At 21 months.

on 39 patients. and reported, with a MFU of 51 months, a 3rdIBTE-FS rate of 76.9% [29]. More recently, Janssen et al. evaluated the role of partial re-irradiation using 3D Conformal Therapy, delivering a total dose of 45 Gy in 25 fractions (1.8 Gy/f) for 83 patients [30]. With a MFU of 35 months, the authors reported a 3rdIBTE rate of 14.5%. The use of Intensity Modulated Radiation Therapy was investigated by Bazan et al. in a cohort of 28 pts [31]. With a MFU of 12 months, the authors reported a 3rdIBTE-free survival rate of 91.7%. Breast re-irradiation using proton therapy is also under investigation, thanks to its ability to reduce organ at risk toxicity. Thorpe et al. investigated the feasibility of breast re-irradiation, based on proton therapy for 50 patients (including post mastectomy) with a 3rdIBTE-free survival rate at one year of 93%. Re-irradiation of the regional nodes was done in 84% of the cases [32]. The results of the RTOG 10–14 phase 2 trial have been recently published with a MFU of 5.5 years [33]. With 4 pts out of 58 who developed a 3rdIBTE, the authors reported a 3rdIBTE 5-year cumulative incidence of 5% with an OS rate of 95%.

3.3.3. *Toxicity profile and cosmetic outcome*

Janssen et al., reported no grade 3 or 4 toxicity while they assumed an acceptable cosmetic profile [30]. However, Bazan et al. reported 2 patients (7%) with grade 3 toxicity (esophagitis and wound dehiscence) [31]. Thorpe et al. presented 16% of G3 toxicities, 10% of acute and 8% of late toxicities [32]. In the RTOG 10–14 phase 2 trial, the reported profile of tolerance was fairly acceptable with 7% of grade 3 late toxicity and no grade 4 [33]. In these studies, no heart or lung toxicity was described.

4. Discussion

In case of 2ndIBTE, second conservative treatment is nowadays accepted as an alternative to salvage mastectomy even in the absence of prospective trial. The latter is unlikely to happen given the need of randomization and the current availability of conservative procedures [34]. The role of partial breast re-irradiation in case of SCT is fundamental to achieve optimal local control, with the adjuvant treatment's benefit counteracting the risks of a second irradiation of the mammary gland and eventual long-term associated toxicities. Indeed, as shown by Vila et al., the rate of 3rdIBTE varies from 7 to 29% after lumpectomy alone, versus 2–24%, and largely under 10% in most recent series for lumpectomy plus re-irradiation of the tumor bed [35]. Presented at the 2018 ASTRO meeting, the Breast-cancer working group of the GEC-ESTRO displayed the results of a propensity-score matched analysis which compared salvage mastectomy versus second conservative treatment using HDR brachytherapy, for 430 patients (Salvage mastectomy: 215 pts vs. SCT: 215 pts) [7]. With a MFU of 65 months, no difference was found between the two salvage treatments regarding neither OS nor 3rdIBTE.

Patient selection for the most appropriate therapeutic option represents another issue regarding 2ndIBTE. The *Deutschen Gesellschaft für Radioonkologie* (DEGRO) recommendations identified the following selection criteria for SCT candidates: limited size, unifocal disease, age over 50, technical feasibility of SCT and patient preference [36]. The authors pointed out the importance of a long-time interval between 1st and 2ndIBTE. Indeed, if a new cancer occurs within an over 4-year period, it will be considered as a new primary and thus be treated as a 1stIBTE, whereas a shorter one would be apprehended as a true recurrence, coming along with a poorer prognostic [36]. Another study aimed to identify independent prognostic factors for 3rdIBTE in case of SCT [21]. With a MFU of 71 months, the authors analyzed the 3rdIBTE rate in 156 pts who underwent lumpectomy plus MIB (LDR and HDR) according to the GEC-ESTRO APBI classification: patients belonging to the high-risk group had about 10 higher-risk to develop a 3rdIBTE (GEC-ESTRO APBI classification was considered as an independent prognostic factor in multivariate analysis) [21]. Positive margins were also established as an independent risk factor for 3rdIBTE [21]. It is important to notice that, in most of these SCT studies, the primary endpoint was the rate of 3rdIBTE. However, in analogy with anal cancer and colostomy-free survival rate, which represent a composite factor considering both the impact of disease local control and treatment side effects, it would be interesting to evaluate the efficacy of re-irradiation techniques by using the mastectomy-free survival rate. Indeed, this endpoint could reflect both the oncological outcome (mainly 3rdIBTE) and induced-SCT toxicity.

MIB is the oldest and well-known breast re-irradiation technique, with long term results and safe toxicity profile [6,12–22]. Nevertheless, its use requires a well-trained team of radiation oncologists, medical physicists and radiology technicians. The alternative of IORT and balloon brachytherapy might then be appealing regarding their user-friendly aspect. However, the size of the source and its maneuverability cannot embrace every anatomical situation, in contrast with interstitial brachytherapy. A recent prospective study conducted by Lyons J. et al. from the University Hospitals Cleveland Medical Center, Ohio (NCT00945061 - completed with awaiting results), compared the use of balloon brachytherapy (Mammosite™/10 fractions over 5 days) versus IORT (50 kv, single fraction) in case of re-irradiation of the mammary gland [37]. A prospective phase II trial is ongoing, coordinated by Lemanski C. et al. from the Cancer Institute of Montpellier, France (NCT02386371) [38]. The main goal of this study is to evaluate the feasibility and tolerability of IORT in case of second conservative breast surgery. The use of 50Kv-IORT as monotherapy for adjuvant irradiation in breast cancer should be carefully considered due to the fact that, at this time, the two published randomized trials failed to demonstrate the non-inferiority between IORT and whole breast irradiation [39,40]. In case of SCT, IORT appears feasible, but due to the lack of consistent data, this technique should be cautiously used with patients enrolled in controlled clinical trials.

Hyperthermia (with or without re-irradiation) has not been

discussed in this research, because of its confidential procedure only performed in centers with high experience in this area. But we still acknowledge its efficacy improving local control [41]. The expected complications of MIB are now well-known and assert their safety of use. IORT seems to have the same toxicity outline but needs to be confirmed in larger series. The early experience of external beam re-irradiation (IMRT or 3DCRT) reported acceptable level of toxicity and promising oncological outcomes. The results of RTOG 1014 phase 2 trial confirmed this hypothesis with low grade 3 side effect rates [33].

Cosmetic outcomes should be considered with caution because of two potential biases. First, the cosmetic evaluation before SCT, after a first conservative treatment, is rarely evaluated, leading to potentially overestimate the damages caused by the second salvage therapy. Second, skin and breast tissue damages must be balanced by the fact that re-irradiation is a full part of the process. Consequently, cosmetic outcomes should not be considered as a primary endpoint because patients are mainly worried about keeping their breast, rather than the final aesthetic result. Immediate or differed breast reconstruction after salvage mastectomy could represent another option. However, due to the trophic toxicity potentially induced by the whole breast irradiation for the primary disease, more complex surgical techniques such as reconstructive flaps should be considered [42].

5. Conclusion

In case of 2ndIBTE, a SCT can safely be proposed, as an alternative to salvage mastectomy, to carefully selected and well-informed patients. At this time, MIB appears to be the most robust choice. IORT, external beam radiotherapy and balloon brachytherapy represent interesting alternatives and may be more accessible nowadays and easier to handle. However, they have only been tested in small series and their use should be limited to clinical prospective trial.

In the future, radiation oncologists will have to progressively master the new re-irradiation techniques (IORT, balloon brachytherapy or external beam radiotherapy) in order to offer the best possible personalized treatment for achieving a SCT and save the patient from breast mutilation.

Funding

None.

Ethics approval

This review was approved by the local ethic committee of the Antoine Lacassagne Cancer Center.

Authors' contributions

LM: acquisition of data and analysis, manuscript writing and final approval. AH: manuscript writing and final approval. JMHL: study concept, design, manuscript writing and final approval.

Declaration of competing interest

LM: no conflict of interests regarding this review. AH: no conflict of interests regarding this review. JMHL: no conflict of interests regarding this review

References

[1] Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Reprint of: cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2015;51:1201–2.
[2] Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total for the treatment of invasive breast cancer. N Engl J Med 2002;347:1233–41.
[3] Strnad V, Major T, Polgar C, et al. ESTRO-ACROP guideline : interstitial multicatheter breast brachytherapy as accelerated partial breast irradiation alone or as boost – GEC-ESTRO breast cancer working group practical recommendations. Radiother Oncol 2018;128:411–20.
[4] Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 2002;347:1227–32.
[5] Kurtz JM, Amalric R, Brandone H, et al. Results of wide excision for mammary recurrence after breast-conserving therapy. Cancer 1988;61:1969–72.
[6] Hannoun-Levi JM, Resch A, Gal J, 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;108:226–31.
[7] Hannoun Levi JM, van Limbergen E, Gal J, et al. Salvage mastectomy versus second conservative treatment for second ipsilateral breast tumor event: a propensity-score matched cohort analysis. Int J Radiat Oncol 2018;102:S80.
[8] Gentilini O, Botteri E, Veronesi P, et al. Repeating conservative surgery after ipsilateral breast tumor reappearance: criteria for selecting the best candidates. Ann Surg Oncol 2012;19:3771–6.
[9] Walstra CJEF, Schipper R, Poodt IGM, et al. European Journal of Surgical Oncology Repeat breast-conserving therapy for ipsilateral breast cancer recurrence : a systematic review. Eur J Surg Oncol 2019;45:1317–27.
[10] Hannoun-Levi J-M, Ihrai T, Courdi A. Local treatment options for ipsilateral breast tumour recurrence. Cancer Treat Rev 2013;39:737–41.
[11] Strnad V, Ott OJ, Hildebrandt G, et al. Groupe Européen de Curiethérapie of European Society for Radiotherapy and Oncology (GEC-ESTRO). 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. Lancet 2016;387(10015):229–38.
[12] Maulard C, Housset M, Brunel P, et al. Use of perioperative or split-course interstitial brachytherapy techniques for salvage irradiation of isolated local recurrences after conservative management of breast cancer. Am J Clin Oncol 1995;18:348–52.
[13] Resch A, Fellner C, Mock U, 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.
[14] Hannoun-Levi JM, Houvenaeghel G, Ellis S, 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.
[15] Niehoff P, Dietrich J, Ostertag H, et al. High-dose-rate (HDR) or pulsed-dose-rate (PDR) perioperative interstitial intensity-modulated brachytherapy (IMBT) for local recurrences of previously irradiated breast or thoracic wall following breast cancer. Strahlenther Onkol 2006;182:102–7.
[16] Chadha M, Feldman S, Boolbol S, et al. 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;7:22–8.
[17] Guix B, Lejárcegui JA, Tello JI, et al. Exeresis and brachytherapy as salvage treatment for local recurrence after conservative treatment for breast cancer: results of a ten-year pilot study. Int J Radiat Oncol Biol Phys 2010;78:804–10.
[18] Hannoun-Levi JM, Castelli J, Plesu A, et al. Second conservative treatment for ipsilateral breast cancer recurrence using high-dose rate interstitial brachytherapy: preliminary clinical results and evaluation of patient satisfaction. Brachytherapy 2011;10:171–7.
[19] Kauer-dorner D, Pötter R, Resch A, et al. Partial breast irradiation for locally recurrent breast cancer within a second breast conserving treatment : alternative to mastectomy ? Results from a prospective trial. Radiother Oncol 2018;102:96–101.
[20] Smanykó V, Mészáros N, Újhelyi M, et al. Second breast-conserving surgery and interstitial brachytherapy vs. salvage mastectomy for the treatment of local recurrences: 5-year results. Brachytherapy 2019;18:411–9.
[21] Montagne L, Gal J, Renaud MC, et al. GEC-ESTRO APBI classi fi cation as a decision-making tool for the management of 2nd ipsilateral breast tumor event. Breast Canc Res Treat 2019;176:149–57.
[22] Forster T, Akbaba S, Schmitt D, et al. Second breast conserving therapy after ipsilateral breast tumor recurrence - a 10-year experience of re-irradiation. J Contemp Brachytherapy 2019;11:312–9.
[23] 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;13:488–92.
[24] Thangarajah F, Heilmann J, Malter W, et al. Breast conserving surgery in combination with intraoperative radiotherapy after previous external beam therapy: an option to avoid mastectomy. Breast Canc Res Treat 2018;168:739–44.
[25] Chin C, Jadeja P, Taback B, et al. Evaluation of partial breast reirradiation with intraoperative radiotherapy after prior thoracic radiation: a single-institution report of outcomes and toxicity. Front Oncol 2017;7:175.
[26] Kraus-Tiefenbacher U, Bauer L, Scheda A, et al. Intraoperative radiotherapy

(IORT) is an option for patients with localized breast recurrences after previous external-beam radiotherapy. BMC Canc 2007;7:178.
[27] Blandino G, Guenzi M, Belgioia L, et al. Adjuvant intraoperative radiotherapy for selected breast cancers in previously irradiated women: evidence for excellent feasibility and favorable outcomes. Rep Pract Oncol Radiother 2017;22:277–83.
[28] Mullen EE, Deutsch M, Bloomer WD. Salvage radiotherapy for local failures oflumpectomy and breast irradiation. Radiother Oncol 1997;42:25–9.
[29] 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.
[30] Janssen S, Rades D, Meyer A, et al. Local recurrence of breast cancer: conventionally fractionated partial external beam re-irradiation with curative intention. Strahlenther Onkol 2018;194:806–14.
[31] Bazan JG, Wobb JL, Dicostanzo DJ, et al. Re-irradiation of local-regional disease in breast cancer using modern radiation techniques: preliminary results of tolerability and efficacy. Int J Radiat Oncol Biol 2018;102:597–8.
[32] Thorpe CS, Niska JR, Girardo ME, et al. Proton beam therapy reirradiation for breast cancer: multi-institutional prospective PCG registry analysis. Breast J 2019;25:1160–70.
[33] Arthur DW, Winter KA, Kuerer HM, et al. Effectiveness of breast-conserving surgery and 3-dimensional conformal partial breast reirradiation for recurrence of breast cancer in the ipsilateral breast: the NRG oncology/RTOG 1014 phase 2 clinical trial. JAMA Oncol 2019 Nov 21. https://doi.org/10.1001/jamaoncol.2019.4320. in press, [Epub ahead of print] PubMed PMID: 31750868; PubMed Central PMCID: PMC6902101.
[34] Trombetta M, Hannoun-Levi JM. Treatment of second ipsilateral breast tumor event: a need for a new type of evidence for avoiding mastectomy. Eur J Surg Oncol 2017;43:849–50.
[35] Vila J, Garcia-Etienne CA, Vavassori A, et al. Conservative surgery for ipsilateral breast tumor recurrence. J Surg Oncol 2014;110:62–7.
[36] Harms W, Budach W, Dunst J, et al. Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). DEGRO practical guidelines for radiotherapy of breast cancer VI: therapy of locoregional breast cancer recurrences. Strahlenther Onkol 2016;192:199–208.
[37] Lyons J, et al. Radiation therapy in treating patients with recurrent breast cancer - full text view - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT00945061. [Accessed 3 November 2019].
[38] Lemanski C, et al. Intraoperative radiotherapy after local recurrence in breast cancer - full text view - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02386371?term=NCT02386371&draw=2&rank=1. [Accessed 3 November 2019].
[39] Vaidya JS, Wenz F, Bulsara M, et al. TARGIT trialists' group. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. Lancet 2014;383(9917):603–13.
[40] Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomized controlled equivalence trial. Lancet Oncol 2013;14(13):1269–77.
[41] Marta GN, Hijal T, Carvalho HAD. Reirradiation for locally recurrent breast cancer. Breast 2018;33:159–65.
[42] Yun JH, Diaz R, Orman AG. Breast reconstruction and radiation therapy. Cancer Control 2018;25. 1073274818795489.