Original Article

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Salvage Mastectomy Is not the Treatment of Choice for Aggressive Subtypes of Ipsilateral Breast Cancer Recurrence: A Single-Institution Retrospective Study

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ABSTRACT

Objective: Patients with triple-negative (TN) or human epidermal growth factor 2 (HER2)-enriched ipsilateral breast cancer recurrence (IBCR) seem to be excluded from a second breast-conserving surgery (BCS) under the assumption that salvage mastectomy would provide better oncological outcomes. The objective of this study was to describe the clinical features of these patients, to compare the two surgical alternatives (salvage mastectomy *versus* second BCS) in terms of oncological results, and to identify independent factors influencing prognosis and surgical treatment.

Materials and Methods: We retrospectively reviewed all the consecutive patients with histologically confirmed TN or HER2-enriched IBCR. Disease-free survival (DFS), distant disease-free survival (DDFS), overall survival (OS), and breast cancer-specific survival (BCSS) were analyzed and compared between the two groups.

Results: Eighty-five patients were affected by TN or HER2-enriched IBCR. The majority of patients (72.9%) were treated with salvage mastectomy. There was no significant difference in terms of DFS between patients receiving a second BCS or mastectomy (p = 0.596). However, patients undergoing a second BCS had significantly better DDFS, OS and BCSS compared to mastectomy (p = 0.009; p = 0.002; p = 0.001, respectively). Tumor dimension <16 mm was found to significantly increase the probability of receiving a second BCS and positively affects recurrence and survival outcomes. Salvage mastectomy represents an independent poor prognostic factor for OS and BCSS.

Conclusion: Salvage mastectomy is not always necessary and it does not seem to increase survival compared to a second BCS. In patients with small aggressive subtypes of IBCR, a second conservative approach can still be evaluated and offered, presenting acceptable loco-regional control and survival.

Keywords: Breast cancer; triple-negative breast cancer; HER2; recurrence; breast-conserving surgery

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Key Points

- Up to 10% of women with breast cancer (BC) treated with breast-conserving surgery (BCS) and subsequent radiation can experience ipsilateral breast cancer recurrence (IBCR), within 10 years.
- Triple-negative and human epidermal growth factor 2-enriched BC subtypes have a higher risk of IBCR. The aggressive nature of these subtypes may appear to exclude such patients from receiving a second BCS, based on the notion that salvage mastectomy would result in improved oncological results.
- Tumor dimension <16 mm was found to significantly increase the probability of receiving a second BCS for aggressive subtypes of IBCR.
- In patients with aggressive subtypes of IBCR, salvage mastectomy should not be considered the treatment of choice, and it does not seem to increase survival compared to a second BCS.
- A second conservative approach can still be evaluated and should be offered, when technically feasible, presenting acceptable loco-regional control and survival.

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Introduction

The developments of breast cancer (BC) treatments have reflected the growing body of knowledge about BC biology (1). Different types of BC show substantial heterogeneity in spite of a common tissue of origin (2). Extensive research has taken place for subtyping BC at a molecular and genetic level, and indeed, gene expression profiling of BC has confirmed that it does not represent a single entity but a group of biologically distinct diseases (3). Triple-negative (TN) BC accounts for 10-20% of invasive breast neoplasms (2, 4), carrying a poorer prognosis than luminal-like tumors and with heterogeneous clinical presentation, behavior, and pathology (3, 4). Human epidermal growth factor receptor 2 (HER2) is a membrane tyrosine kinase and when activated affects cell proliferation and survival (5). HER2 is overexpressed in about 15–20% of BCs, representing a major driver for tumor development, progression, and poor prognosis (6). The conventional treatment for early-stage BC is breast-conserving surgery (BCS) followed by adjuvant radiotherapy (7). Even in patients affected by aggressive phenotypes, such as TN and HER2-enriched BC, when compared to mastectomy, BCS did not produce worse oncological results (8). However, roughly 5–10% of women treated with BCS and subsequent radiation can experience ipsilateral breast cancer recurrence (IBCR), within 10 years (7, 9). Previous studies have reported a higher risk of IBCR in TN and HER2-enriched BC subtypes (8, 10-13). The aggressive nature of TN and HER2-enriched BC subtypes may appear to exclude such patients from receiving a second BCS in the event of IBCR, based on the notion that salvage mastectomy would result in improved oncological results. Salvage mastectomy, despite this, may not totally eliminate the risk of a second loco-regional recurrence, metastatic disease, or cancer–related mortality (14). Up to now, there have been no prospective randomized studies to show that salvage mastectomy is preferable to a second BCS in terms of oncological safety for patients with aggressive subtypes of IBCR. The prognostic difference between repeat conserving therapy and salvage mastectomy for IBCR has been studied extensively (15-20). Salvage mastectomy should not be considered the optimal treatment for IBCR, according to two retrospective analyses conducted at our institution, and it does not appear to improve prognosis when compared to repeat BCS (21, 22) but specific long-term oncological outcomes of patients with aggressive subtypes of IBCR have not been evaluated. The objective of this study was to describe the clinical features of patients with aggressive subtypes of IBCR, to compare the two surgical alternatives (either salvage mastectomy or second BCS) in terms of oncological results, and to identify independent factors influencing prognosis and surgical treatment.

Materials and Methods

Design of the Study and Patient Management

Between January 2008 and December 2018, we analyzed all the consecutive patients with histologically confirmed TN or HER2-enriched IBCR who were treated at the Breast Unit of IRCCS Humanitas Research Hospital (Milan, Italy). The clinical characteristics of these patients were reported and the two treatment methods (second BCS or salvage mastectomy) were examined and compared. The following exclusion criteria were used: luminal-like IBCR; new ipsilateral primary tumor; disease-free interval (DFI) ≤6 months; and follow-up <36 months. The indication for re-irradiation was given based on particular clinical and pathological risk factors; patients did not receive routine adjuvant radiotherapy. Patients undergoing re-irradiation received either a hypofractionated radiation dose regimen of 40.5 Gy on the whole breast and 48 Gy on the tumor bed in 15 fractions overall or conventionally–fractionated whole breast irradiation of 50 Gy in 25 fractions with a tumor bed boost of 10 Gy in 5 fractions. Each patient gave informed consent for the operation and collection of clinical data.

Definitions

There are two types of IBCR. True recurrence is defined as the reappearance of malignant cells that were not eliminated by the initial BCS or adjuvant radiation, whereas, a new ipsilateral primary tumor is defined as a *de novo* malignancy originating from mammary epithelial cells of the remaining breast tissue (23). Although there are no conventional classification guidelines, we categorized IBCR as either true recurrence or a new primary based on biology, histology, and tumor site (21, 22). If the biology and histology of an IBCR matched that of the primary BC and it was within 3 cm of the primary tumor bed or in the surgical scar, it was considered true recurrence. If the IBCR had a change in biology or histology, or changed from infiltrating carcinoma to carcinoma *in situ*, or was more than 3 cm from the previous BC site, it was considered a new primary. TN BC was defined as absence of estrogen and progesterone receptors and negativity for HER2. HER2 status was assessed by immunohistochemistry and defined as negative if the score was 0/1+, equivocal if the score was 2+, or positive if the score was 3+. Equivocal cases were further assessed by fluorescent *in situ* hybridization. HER2-enriched and TN BCs were defined as aggressive subtypes. All the patients with IBCR who were analyzed were affected by aggressive subtypes of true recurrences.

DFI was defined as the time between the first BCS for primary BC and the onset of IBCR. Disease-free survival (DFS) was defined as the period from the date of IBCR surgery (either salvage mastectomy or second BCS) until the date of any tumor development including loco-regional recurrence or distant metastasis. Distant disease-free survival (DDFS) was defined as the duration between the date of IBCR surgery and the date of distant metastasis identification. Overall survival (OS) was defined as the time interval from IBCR treatment to death from any cause or to the date of last contact. Breast cancer-specific survival (BCSS) was calculated by choosing BC as the cause of death and recording the follow-up time after censoring deaths from other causes.

Statistical Analysis

Patients were chosen from our prospectively maintained institutional database and retrospectively analyzed. Categorical variables were compared using the chi-square test or Fisher's Exact test, as appropriate. The recurrence and survival curves were generated using the Kaplan–Meier method. The log-rank test was performed to compare the oncological outcomes of the two treatment groups (salvage mastectomy *versus* second BCS) considering demographic and tumor features. Last follow-up was updated up to February 16, 2022. Follow-up was ≥36 months in all patients with aggressive subtypes of IBCR and no patient was lost to follow-up. A logistic regression model was used in the multivariate analysis to find independent predictors of surgical therapy for aggressive subtypes of IBCR. Any variable associated with the result at the univariate analysis was included in the multivariate analysis (inclusion cut-off value $p<0.05$). Using the Cox proportional hazards model, a multivariate analysis was performed to identify independent factors influencing the prognosis of patients with aggressive subtypes of IBCR. Statistical significance was set at $p<0.05$. IBM SPSS, version 25.0 was used for data analyses and figures (IBM Inc., Armonk, NY, USA).

Results

Characteristics of Patients

A total of 309 patients with IBCR underwent surgical treatment at our institution. Of these, 85 patients were affected by aggressive biological subtypes of IBCR. Overall, 56 (65.9%) and 29 (34.1%) patients had TN and HER2-enriched IBCR, respectively, after a median DFI of 44 months (range, 8–160 months). The median age was 60 years (range, 32–87 years), and 48 (56.5%) patients were post-menopausal. One patient was affected by *BRCA1*-associated TN IBCR. The median diameter of IBCR was 16 mm (range, 3–46 mm). The majority of patients (72.9%) with aggressive subtypes of IBCR were treated with salvage mastectomy. Twenty-three (27.1%) patients underwent a second BCS and of these, 9 (39.1%) patients underwent re-irradiation. Regarding adjuvant treatment, 49 (57.7%) and 14 (16.5%) patients underwent post-operative chemotherapy and Trastuzumab, respectively. Table 1 details demographic, tumor, and post-operative characteristics of patients with aggressive subtypes of IBCR.

Oncological Outcomes and Independent Factors for Treatment and Prognosis

The median follow-up was 77 months (range, 36–224 months). At the time of the last follow-up, 32 patients (/85, 37.7%) had re-recurrence. In the BCS group, 7 (/23, 30.4%) and 3 patients (/23, 13.0%) had loco-regional recurrence and distant metastases, respectively. In the mastectomy group, 22 (/62, 35.5%) patients developed distant recurrence and of these, 13 patients developed metastatic disease associated with loco-regional recurrence. In the BCS group, all patients with loco-regional recurrence were surgically treated with mastectomy. In the mastectomy group, all patients who developed distant metastases were treated with chemotherapy and in addition 5 patients underwent excision of isolated skin metastasis. Overall, 25 patients (/85, 29.4%) died; 6 (/23, 26.1%) and 19 patients (/62, 30.7%) in the BCS and mastectomy groups, respectively. The 1-, 3-, and 5-year DFS rates were 95.8%, 69.1%, 43.2% and 78.4%, 63.3%, 49.4% in patients receiving a second BCS or salvage mastectomy, respectively. The 1-, 3-, and 5-year DDFS rates were 95.8%, 95.8%, 88.5% and 78.4%, 63.3%, 49.4% in patients receiving a second BCS or salvage mastectomy, respectively. The 1-, 3-, and 5-year OS rates were 95.8%, 87.5%, 87.5% and 93.5%, 76.6%, 55.7% in patients receiving a second BCS or salvage mastectomy, respectively. The 1-, 3-, and 5-year BCSS rates were 95.8%, 95.8%, 95.8% and 96.7%, 79.1%, 57.5% in patients receiving a second BCS or salvage mastectomy, respectively. There was no significant difference in terms of DFS between patients with aggressive subtypes of IBCR receiving a second BCS or salvage mastectomy ($p = 0.596$). However, patients with aggressive subtypes of IBCR undergoing a second BCS had significantly better DDFS, OS, and BCSS compared to salvage mastectomy ($p = 0.009$, $p = 0.002$, and $p = 0.001$, respectively). Figures 1-4 show the Kaplan–Meier recurrence and survival curves of patients with aggressive subtypes of IBCR. Comparison of oncological outcomes is summarized in Table 2. Table 3 details and compares demographic and tumor characteristics of patients with aggressive subtypes of IBCR, according to the surgical method used (second BCS *versus* salvage mastectomy). At univariate analysis, histotype, dimension, Ki67, and vascular invasion were significantly different between the two groups ($p = 0.021$, $p = 0.001$, $p = 0.040$, and $p = 0.022$, respectively). However, in multivariate analysis, only one independent predictive factor of treatment for patients with aggressive subtypes of IBCR was identified. Tumor dimension <16 mm [78.3% *versus* 38.7%, odds ratio (OR) = 3.602, 95% confidence interval (CI) = 1.534–8.459, $p = 0.003$] was found to significantly increase the probability of receiving a second BCS for aggressive

Table 1. Characteristics of 85 patients with aggressive biological subtypes of ipsilateral breast cancer recurrence

Characteristics	Number (%)/Median (range)
Patients	
Age (years)	60.0 (32.2–87.4)
Post-menopausal	48 (56.5%)
BRCA1-mutation carrier	1 (1.1%)
Tumor	
Histotype	
- Ductal	79 (92.9%)
- Lobular	6 (7.1%)
Grading	
- 1	4 (4.7%)
- 2	17 (20.0%)
- 3	64 (75.3%)
Stage	
- pT1a	4 (4.7%)
- pT1b	15 (17.7%)
- pT1c	49 (57.7%)
- pT2	16 (18.8%)
- pT3-4	1 (1.1%)
- Nx	36 (42.4%)
- pN0	44 (51.8%)
- pN1	3 (3.5%)
- pN2	2 (2.3%)
Dimension (mm)	16 (3–46)
Biological subtypes	
- HER2-enriched	29 (34.1%)
- Triple negative	56 (65.9%)
Ki67 (%)	45 (7-90)
Vascular invasion	22 (25.9%)
Treatment	
- BCS	23 (27.1%)
- Mastectomy	62 (72.9%)
- Neo-adjuvant chemotherapy	3 (3.5%)
- Radiotherapy	9 (10.6%)
- Endocrine therapy	4 (4.7%)
- Adjuvant chemotherapy	49 (57.7%)
- Trastuzumab	14 (16.5%)

BCS: breast-conserving surgery; HER2: HER2 evaluated either on immunohistochemistry or on *in situ* hybridization; according to the ASCO CAP guidelines; HER2: human epidermal growth factor receptor 2

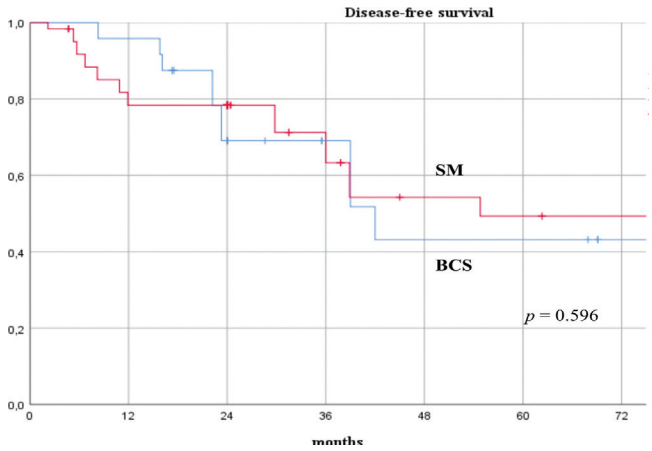

Figure 1. Disease-free survival curves (breast-conserving surgery *versus* salvage mastectomy)

SM: salvage mastectomy; BCS: breast-conserving surgery

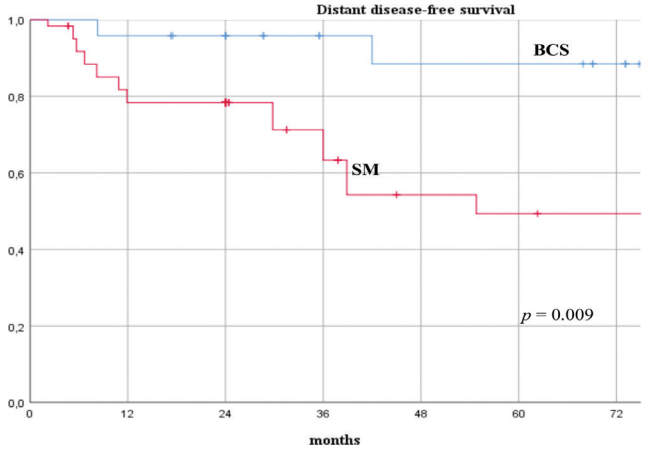

Figure 2. Distant disease-free survival curves (breast-conserving surgery *versus* salvage mastectomy)

SM: salvage mastectomy; BCS: breast-conserving surgery

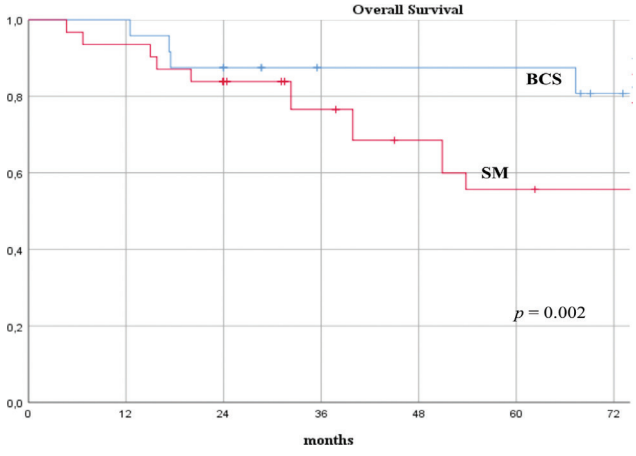

Figure 3. Overall survival curves (breast-conserving surgery *versus* salvage mastectomy)

SM: salvage mastectomy; BCS: breast-conserving surgery

subtypes of IBCR. Additionally, dimension of the recurrent tumor <16 mm, DFI ≥44 months, and absence of vascular invasion were found to significantly increase both recurrence and survival outcomes. On the contrary, salvage mastectomy was significantly associated with a decreased OS and BCSS (p = 0.002 and p = 0.002, respectively). The univariate and multivariate analyses are summarized in Tables 3 and 4.

Table 2. Oncological outcomes after second breast cancer surgery (breast-conserving surgery versus mastectomy) of patients with aggressive biological subtypes of ipsilateral recurrence

Outcomes	BCS	Mastectomy	*p*-value
DFS rate			
- 1-year	95.8%	78.4%	
- 3-year	69.1%	63.3%	0.596
- 5-year	43.2%	49.4%	
DDFS rate			
- 1-year	95.8%	78.4%	
- 3-year	95.8%	63.3%	0.009[a]
- 5-year	88.5%	49.4%	
OS rate			
- 1-year	95.8%	93.5%	
- 3-year	87.5%	76.6%	0.002[a]
- 5-year	87.5%	55.7%	
BCSS rate			
- 1-year	95.8%	96.7%	
- 3-year	95.8%	79.1%	0.001[a]
- 5-year	95.8%	57.5%	

BCS: breast-conserving surgery; DFS: disease-free survival; DDFS: distant disease-free survival; OS: overall survival; BCSS: breast cancer-specific survival; [a]: statistically significant

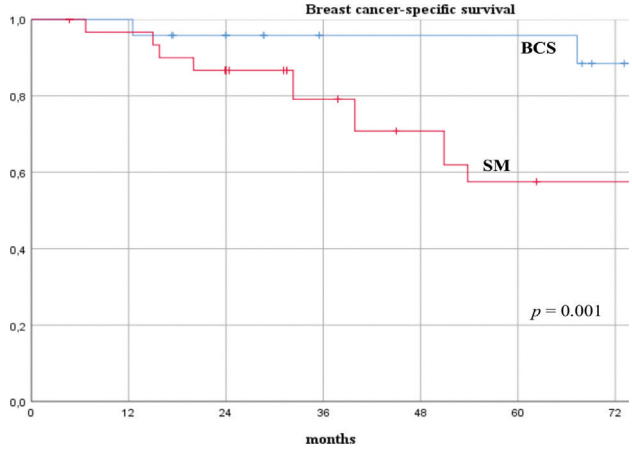

Figure 4. Breast cancer-specific survival curves (breast-conserving surgery *versus* salvage mastectomy)

SM: salvage mastectomy; BCS: breast-conserving surgery

Discussion and Conclusion

To begin with, a higher risk of IBCR in HER2-enriched and TN biological subtypes has been reported. Therefore, the surgical management of this category of aggressive recurrence remains a matter of debate. In the review performed by Wang et al. (8), the authors analyzed the results of 15,312 BC patients and reported that the TN biological subtype presented an increased risk of both IBCR and distant metastasis compared with non-TN subtypes (OR = 1.88, 95% CI = 1.58–2.22; OR = 2.12, 95% CI = 1.72–2.62, respectively). Corso et al. (10) reported that TN and HER2-enriched breast neoplasms were significantly associated with an increased risk of IBCR (p = 0.008 and p = 0.020, respectively). Lowery et al. (12) analyzed a total of 12,592 patients and reported that luminal-like tumors had a lower risk of IBCR than both TN (OR = 0.38, 95% CI = 0.23–0.61) and HER2-

Table 3 Comparison of clinicopathological characteristics of patients with aggressive biological subtypes of ipsilateral breast cancer recurrence undergoing either breast-conserving surgery or mastectomy

Characteristics	BCS (No. 23) Tot. (%)/ median (range)	Mastectomy (No. 62) Tot. (%)/ median (range)	Univariate analysis	Multivariate analysis
			p-value	*p*-value OR (95% CI)
Demographic				
Age (years)	57.1 (38.3–87.4)	61.1 (32.2–86.3)		
- <60	13 (56.5%)	29 (46.8%)	0.223	-
- ≥60	10 (43.5%)	33 (53.2%)	-	
Menopausal status				
- Pre-menopausal	5 (21.7%)	32 (51.6%)	0.749	-
- Post-menopausal	18 (78.3%)	30 (48.4%)	-	
DFI (months)	46.4 (16.1–126.8)	41.5 (7.9–160.7)		
- <44	9 (39.1%)	32 (51.6%)	0.323	-
- ≥44	14 (60.9%)	30 (48.4%)	-	
Tumor				
Histotype				
- Ductal	21 (91.3%)	58 (93.6%)	0.021[a]	1.873 (0.657–5.338) 0.240
- Lobular	2 (8.7%)	4 (6.4%)	-	-
Grading				
- 1	1 (4.3%)	3 (4.8%)	0.089	-
- 2	2 (8.7%)	15 (24.2%)	-	
- 3	20 (87.0%)	44 (71.0%)	-	
Dimension (mm)	12 (4–28)	17 (3–46)		
- <16	18 (78.3%)	24 (38.7%)	0.001[a]	3.602 (1.534–8.459) 0.003[a]
- ≥16	5 (21.7%)	38 (61.3%)	-	-
Biological subtypes				
- HER2-enriched	5 (21.7%)	24 (38.7%)	0.219	-
- Triple negative	18 (78.3%)	38 (61.3%)	-	
Ki67 (%)	38 (15–80)	45 (7–90)		
- <45	15 (65.2%)	26 (41.9%)	0.040[a]	0.724 (0.238–2.208) 0.571
- ≥45	8 (34.8%)	36 (58.1%)	-	-
Vascular invasion				
- Yes	2 (8.7%)	20 (32.3%)	0.022[a]	1.763 (0.674–4.611) 0.248
- No	21 (91.3%)	42 (67.7%)	-	.

BCS: breast-conserving surgery; OR: odds ratio; CI: confidence interval; DFI: disease-free interval; HER2: human epidermal growth factor 2; HER2: HER2 evaluated either on immunohistochemistry or on *in situ* hybridization, according to the ASCO CAP guidelines, [a]: statistically significant

enriched BCs (OR = 0.34, 95% CI = 0.26–0.45) following BCS. Kim et al. (13) evaluated 2,102 consecutive BC patients who underwent BCS followed by adjuvant radiotherapy, reporting an increased risk of IBCR in the HER2-enriched subtype (OR = 12.24, 95% CI = 2.54–57.96).

Nonetheless, whereas conservative therapy is the gold standard for primary BC (7), there is no strong evidence to support the use a second BCS, as well as salvage mastectomy, as the standard of care in case of aggressive subtypes of ipsilateral recurrence. In general, the prognostic significance of surgery (either salvage mastectomy or second BCS) for IBCR is unknown, and past studies reported conflicting outcomes (17, 18). Recent studies, however, have found that patients with IBCR who were treated with a second BCS had no significantly worse outcomes than those who underwent salvage mastectomy. The meta-analysis performed by Mo et al. (15) included 2,532 patients with IBCR undergoing either salvage mastectomy or a second BCS and showed that the DFS rate after a second conserving treatment was higher than that after mastectomy (OR = 1.87, 95% CI = 1.22–2.86, p = 0.004). Wu et al. (16) reported the results of 475 patients who underwent a second BCS and 1,600 patients who underwent salvage mastectomy for IBCR. During a median follow-up of 130 months, no significant differences were observed in the OS and BCSS rates between the two treatment groups before and after a propensity score matching analysis. The latest studies seem to indicate that a second BCS is a safe and feasible alternative for patients with IBCR. Similarly, our analysis also shows the superiority of the DDFS, OS, and BCSS rates in aggressive biological subtypes of IBCR treated with a second BCS compared to salvage mastectomy.

In patients with IBCR, there is no unanimity on the feasibility and oncological safety of a second course of re-irradiation. The need for a second course of radiation often represents the reason for not offering repeat BCS to patients with IBCR. Although it is often assumed that a second course of adjuvant radiotherapy is not well tolerated by the tissues, resulting in intolerable toxicity, several authors have

Table 4. Multivariate analyses of independent factors influencing the oncological outcomes of patients with aggressive biological subtypes of ipsilateral breast cancer recurrence

Independent factors	DFS HR (95% CI)	*p*-value	DDFS HR (95% CI)	*p*-value	OS HR (95% CI)	*p*-value	BCSS HR (95% CI)	*p*-value
Patient								
Age (years)								
- <60	Reference		Reference		Reference		Reference	
- ≥60	1.800 (0.388–8.354)	0.453	1.600 (0.268–9.570)	0.606	1.231 (0.206–7.348)	0.819	0.583 (0.074–4.584)	0.608
DFI (months)								
- <44	Reference		Reference		Reference		Reference	
- ≥44	0.348 (0.146–0.830)	0.017[a]	0.212 (0.081–0.558)	0.002[a]	0.230 (0.081–0.655)	0.006[a]	0.168 (0.046–0.611)	0.006[a]
Tumor								
Dimension (mm)								
- <16	Reference		Reference		Reference		Reference	
- ≥16	8.065 (2.320–28.034)	0.001[a]	17.011 (3.853–75.099)	0.001[a]	13.881 (2.730–70.579)	0.002[a]	36.773 (4.579–295.322)	0.001[a]
Ki67 (%)								
- <45	Reference		Reference		Reference		Reference	
- ≥45	0.459 (0.165–1.272)	0.134	0.226 (0.067–0.758)	0.016[a]	0.235 (0.057–1.121)	0.070	0.221 (0.040–1.212)	0.082
Vascular invasion								
- Yes	Reference		Reference		Reference		Reference	
- No	7.320 (2.918–18.364)	0.001[a]	13.699 (4.592–40.865)	0.001[a]	9.258 (3.038–28.213)	0.001[a]	12.722 (3.231–50.094)	0.001[a]
Surgery								
- BCS	Reference		Reference		Reference		Reference	
- Mastectomy	0.494 (0.179–1.362)	0.173	0.526 (0.170–1.634)	0.267	0.246 (0.027–0.697)	0.002[a]	0.313 (0.092–0.511)	0.002[a]

DFS: disease-free survival; DDFS: distant disease-free survival; OS: overall survival; BCSS: breast cancer-specific survival; HR: hazard ratio; CI: confidence interval; DFI: disease-free interval; BCS: breast conserving surgery, [a]: statistically significant

found that re-irradiation represents a feasible and safe treatment with promising oncological outcomes. Deutsch (24) reported 5-year OS and DFS rates of 77.9% and 68.5%, respectively, in 39 patients with IBCR treated with a second BCS and a repeat course of external beam radiotherapy. The NRG Oncology/RTOG 1014 phase II clinical trial (25), evaluated the results of 58 patients with IBCR who underwent a second lumpectomy and external beam partial breast re-irradiation. After a median follow-up of 5.5 years, four patients had BC re-recurrence, with a 5-year cumulative incidence of 5% (95% CI = 1–13%). Both the DDFS and OS rates were 95% (95% CI = 85–98%). In our analysis, only nine (39.1%) patients treated with a second BCS underwent a second course of adjuvant radiotherapy. However, no significant difference in terms of DFS between patients receiving repeat BCS or mastectomy was observed.

Oncoplastic breast surgery and prosthetic reconstruction in previously irradiated breasts represent additional matters of controversy in IBCR treatment. Oncoplastic techniques do not delay adjuvant therapies but a second course of radiotherapy may lead to a higher incidence of fat necrosis, volumetric depression, and deformity (26). To reduce the complication rate, there is a frequent tendency to perform oncoplastic techniques, seeking the reconstruction of the breast cone and mobilizing the smallest possible volume of parenchyma (27). Regarding salvage mastectomy followed by prosthetic breast reconstruction, very little literature has evaluated the short-term morbidity and complication rates in previously irradiated breast but patients with IBCR have been discouraged from implant placement. Prior irradiation, according to Lee and Mun (28) increases the risk of reconstructive failure (13.9% *versus* 7.2% not irradiated), total complications (36.6% *versus* 18.8% not irradiated), capsular contracture (15.4% *versus* 4.8% not irradiated), infection (16.1% *versus* 7.9% not irradiated), and seroma (7.5% *versus* 2.9% not irradiated). According to Reish et al. (29) nipple-sparing mastectomy and immediate reconstruction in patients who had radiation is associated with a greater rate of complications and operative revisions. Chen et al. (30) found that patients who previously received radiation, had a higher risk of complications, with a reconstructive failure occurring in 50% of breasts. Given these considerations, we assume that, when technically feasible in terms of cosmetic results, a second BCS with oncoplastic breast reconstruction should be considered the preferred surgical option for aggressive subtypes of IBCR.

Study Limitations

It is important to note that this study has some limitations. To begin with, this is a single-center study subject to limitations due to its retrospective design using observational data. Secondly, the majority of patients with aggressive subtypes of IBCR treated with a second BCS did not undergo repeat radiotherapy. Therefore, the prognostic value of this adjuvant treatment could not be fully evaluated. However, this study also presents some strong points, including the classification method and inclusion criteria which were used enabled the identification of a homogeneous group of patients and no patient was lost to follow-up.

In conclusion, our outcomes corroborate the oncological results of previous studies on IBCR and provide additional evidence in support of a second conserving surgery for the treatment of aggressive biological subtypes. Salvage mastectomy is not always necessary and it does not seem to increase survival compared to a second BCS. This reinforces the concept that the prognosis of TN and HER2-enriched BC recurrence is mainly driven by the biology of the disease, rather than by the extent of surgery. In patients with small (<16 mm) aggressive subtypes of IBCR, a second conservative approach can still be evaluated and offered, presenting acceptable loco-regional control and survival.

Ethics Committee Approval: This study was approved by The Humanitas University Research Ethics Committee (approval number: H22-04-IBCR, date: 04.04.2022).

Informed Consent: Each patient provided informed consent for operation and clinical data acquisition.

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Authorship Contributions

Surgical and Medical Practices: D.G., A.S., R.S., D.F., S.V., V.V., E.B., L.S., C.T.; Concept: D.G., A.S., R.S., D.F., S.V., V.V., C.T.; Design: D.G., A.S., R.S., D.F., S.V., V.V., C.T.; Data Collection and/or Processing: D.G., A.S., E.B., L.S., C.T.; Analysis and/or Interpretation: D.G., A.S., E.B., L.S., C.T.; Literature Search: D.G., A.S., R.S., D.F., S.V., V.V., E.B., L.S., C.T.; Writing: D.G., A.S., R.S., D.F., S.V., V.V., E.B., L.S., C.T.

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