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Repeating Conservative Surgery after Ipsilateral Breast Tumor Reappearance: Criteria for Selecting the Best Candidates

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ABSTRACT

Background. Mastectomy is still considered the treatment of first choice in patients with ipsilateral breast tumor recurrence (IBTR) after breast-conserving surgery (BCS) and whole-breast radiotherapy.

Methods. We retrospectively evaluated 161 patients with invasive IBTR who underwent a second BCS in order to describe prognosis, determine predictive factors of outcome, and select the subset of patients with the best local control. Median follow-up after IBTR was 81 months.

Results. Median age at IBTR was 53 years. Five-year overall survival after IBTR was 84 % (95 % confidence interval [CI] 78–89). Five-year cumulative incidence of a second local event after IBTR was 29 % (95 % CI 22–37). At the multivariate analysis, IBTR size >2 cm and time to relapse ≤48 months significantly increased the risk of local reappearance (hazard ratio [HR] 3.3, 95 % CI 1.6–7.0; and HR 1.9, 95 % CI 1.1–3.5). The 5-year cumulative incidence of a further local reappearance of the tumor after repeating BCS was 15.2 % in the patients with IBTR ≤2 cm and time to IBTR >48 months, 31.2 % in the patients with IBTR ≤2 cm and time to IBTR ≤48 months, and 71.2 % in patients with IBTR >2 cm ($P < 0.001$).

Conclusions. The best candidates for a second BCS are those with small (≤2 cm) and late (>48 months) IBTR. The information about the risk of a further local reappearance after repeating BCS should be shared with the patients in the decision making process.

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A small portion of patients with primary breast cancer who receive breast-conserving surgery (BCS) will develop ipsilateral breast tumor recurrence (IBTR).[1,2] In these patients, mastectomy is still considered the treatment of choice even when a further wide local excision would be technically feasible. We previously reported the outcome of a cohort of patients presenting with IBTR after BCS and whole-breast radiotherapy who received a second conservative procedure, with a median follow-up of 44 months.[3] The objective of the present study was to update the previous analysis with a median follow-up of 81 months in order to establish the criteria for selecting the best candidates to receive a second BCS after IBTR.

PATIENTS AND METHODS

The present cohort of patients has already been the subject of a previous publication by our group.[3] The analysis was based on a median follow-up of 44 months after the IBTR. We now describe the outcome of the same patients after a median follow-up of 81 (range 4–164) months.

Between April 1997 and December 2004, a total of 12,357 patients were operated on and prospectively entered into the database of the European Institute of Oncology of Milan. Three hundred fourteen consecutive patients with invasive operable IBTR as a first event and no evidence of synchronous metastatic disease were identified. For the

treatment of primary cancer, all patients received BCS followed by conventional external radiotherapy over the breast and locoregional radiotherapy whenever appropriate. One hundred four patients were also operated on in our institute for their primary cancer, whereas 210 were initially operated on at a different hospital and then referred to our institute for the treatment of IBTR.

One hundred sixty-one patients received a second conservative surgery and are the cohort considered in this analysis. The remaining 153 patients underwent total mastectomy and were the subject of another study by our group.[4]

At occurrence of IBTR, all patients underwent a physical examination, mammography, and breast ultrasonography to exclude multicentricity. Only a small minority underwent MRI of the breast. After the surgical treatment of IBTR, all the patients were discussed within the multidisciplinary meeting attended by surgeons, medical oncologists, radiation oncologists, and pathologists and received adjuvant treatment according to staging and biological features. None of the patients received further radiotherapy after the treatment of IBTR. Patients were usually followed up according to standard clinical practice by physical examination every 6 months and mammography with or without breast ultrasonography every year. In cases of symptoms or when clinically indicated, bone scan, chest X-ray, liver ultrasonography, or CT scan were performed.

Survival end points were local recurrence, any event, and death. The cumulative incidence of local recurrences was estimated in a competing risk framework.[5] Local events were defined as second IBTR or breast skin recurrence. All events other than local recurrence were treated as competing events, and the Gray test was used to assess the significance of differences in local events across subgroups. The log-rank test was used for all events and deaths. Differences with $P < 0.05$ were considered statistically significant. Multivariable Cox proportional hazard models were used to evaluate the independent prognostic value of the clinicopathological features.

Analyses were performed with the SAS software version 9.2 (SAS Institute, Cary, NC) and R software, version 2.12.2 (http://www.r-project.org). All tests were two-sided.

TABLE 1 Patient characteristics

Characteristic	Classification	*n* (%)
Presentation at primary cancer		
Age	<35 years	19 (11.7)
	35–50 years	80 (49.7)
	51–60 years	34 (21.1)
	>60 years	28 (17.4)
Size of tumor	≤2 cm	107 (72.3)
	>2 cm	41 (27.7)
Regional lymph nodes involved	0	88 (63.8)
	1–3	34 (24.6)
	4–9	11 (8.0)
	10+	5 (3.6)
Histotype	Ductal	129 (81.2)
	Lobular	19 (11.9)
	Other	11 (6.9)
Presentation at first IBTR		
Age	<35 y	7 (4.3)
	35–50 y	61 (37.9)
	51–60 y	51 (31.7)
	>60 y	42 (26.1)
Time to IBTR	≤24 mo	36 (22.4)
	25–48 mo	55 (34.2)
	>48 mo	70 (43.5)
Size of IBTR	≤0.5 cm	16 (10.6)
	0.6–1.0 cm	45 (29.8)
	1.1–1.5 cm	54 (35.8)
	1.6–2.0 cm	20 (13.2)
	>2.0 cm	16 (10.6)
Histotype	Ductal	128 (79.5)
	Lobular	13 (8.1)
	Other	20 (12.4)
Estrogen receptor	Positive	125 (78.1)
Progesterone receptor	Positive	101 (63.5)
Her2/neu	Overexpressed	19 (12.2)
Ki-67	<20 %	64 (41.6)
Vascular invasion	Present	26 (17.6)
Multifocality	Present	16 (10.5)

Information is missing for a few patients

IBTR ipsilateral breast tumor recurrence

RESULTS

Table 1 represents patient characteristics at presentation of primary breast cancer and at the occurrence of IBTR. Median age at IBTR was 53 years. Thirty-three patients (20.5 %) had received both chemotherapy and hormone therapy for the first breast cancer, 37 (23.0 %) hormone therapy, 40 (24.8 %) chemotherapy, and 51 (31.7 %) no systemic therapy. Additionally, 15 patients (9.3 %) received both chemotherapy and hormone therapy for their IBTR, 32 (19.9 %) hormone therapy, 103 (64.0 %) chemotherapy, and 11 (6.8 %) no systemic therapy. Forty-eight patients died, with a 5-year overall survival of 84 % (95 % confidence interval [CI] 78–89) (Fig. 1). Table 2 lists the events after the surgical treatment of IBTR. Cumulative 5-year incidence of a further local event after repeating BCS was 29 % (95 % CI 22–37). Table 3 represents the univariate analysis assessing clinical and pathologic features of IBTR associated with

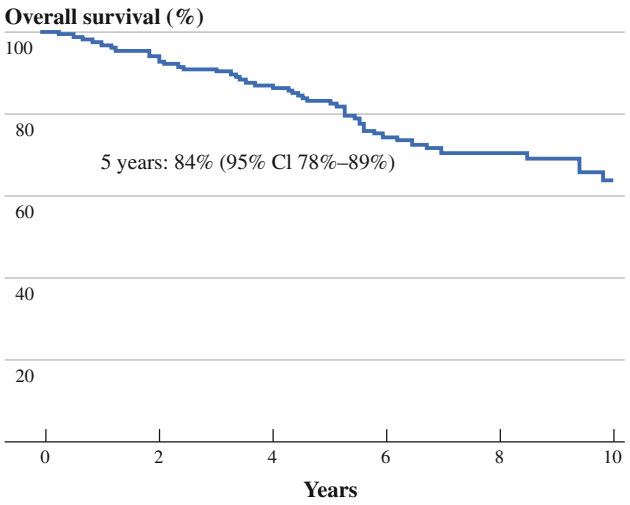

FIG. 1 Overall survival (%) after first IBTR

TABLE 2 Description of second events

First event	*n* (%)
IBTR	44 (27.3)
Skin recurrence	3 (1.9)
Regional nodes	5 (3.1)
Locoregional	3 (1.9)
Metastases	24 (14.9)
Local and distant	3 (1.9)
CBTR	2 (1.2)
Other primary tumor	4 (2.5)
Death as first event	9 (5.6)
Deaths overall	48 (29.8)

IBTR ipsilateral breast tumor recurrence, *CBTR* contralateral breast tumor recurrence

survival. No variables besides IBTR size and time to IBTR were found to be significantly associated with the risk of local reappearance.

At the multivariate analysis (Table 4), recurrent IBTR size >2 cm and time to relapse ≤48 months significantly increased the risk of local reappearance (HR 3.3, 95 % CI 1.6–7.0; and HR 1.9, 95 % CI 1.1–3.5). Moreover, patients with early IBTR (≤48 months) had an increased risk of further events and death (HR 2.0, CI 1.3–2.1; and HR 3.1, 95 % CI 1.5–6.2, respectively). In Fig. 2, we report the subgroup analysis of local events based on IBTR size and time to IBTR. The 5-year cumulative incidence of a further local reappearance of the tumor after repeating BCS was 15.2 % in the patients with tumor ≤2 cm and time to IBTR >48 months, 31.2 % in the patients with tumor ≤2 cm and time to IBTR ≤48 months, and 71.2 % in patients with tumor >2 cm ($P < 0.001$, Gray test).

Finally, in our attempt to evaluate the impact of adjuvant treatment on the risk of local relapse, we observed no effect of adjuvant systemic treatment for IBTR after adjusting for estrogen receptor status, IBTR size, and time to IBTR.

DISCUSSION

Some women with IBTR after BCS and radiation are interested in breast preservation and are opposed to mastectomy, which still represents the standard of care. This work addressed the issue of which patients may be reasonably considered for a second conservative treatment.

We found that the subset of patients with a recurrent tumor <2 cm which occurred after 48 months from the primary cancer treatment experienced a 15.2 % five-year cumulative incidence of a further local event after repeating BCS. Women with those characteristics represent the best candidates for repeating conservative surgery. On the other hand, when the recurrent tumor is larger than 2 cm, the probability of having a third malignancy in the same breast is so high that mastectomy is virtually unavoidable. These results and the subsequent conclusions logically follow; we might consider that the best candidates for repeating breast conservation are the ones with an early detection of a new primary cancer. In our series, many patients were operated elsewhere for the first time, and therefore we did not have complete data on the location and histology of the primary cancer so that we could distinguish between a true recurrence and a new primary cancer.[6] Nevertheless, the IBTRs that occurred late after treatment of the primary cancer are in general likely to be considered as new primary cancers. These patients, as recently pointed out by Yi et al.,[7] have a better overall and disease-free survival than do patients with true recurrence. This statement again follows logically: a rapidly recurrent tumor mirrors a high aggressiveness of cancer cells that do not respond to radiotherapy and medical treatments. Conversely, it is well known that patients with a true recurrence in the same breast have an increased likelihood of developing distant metastases, which represents a marker of aggressiveness.[8]

The present analysis strengthens our previously published data and strongly suggests that mastectomy should not be considered the only option in all patients with IBTR.[3] We acknowledge that many patients presenting with intrabreast disease recurrence would in fact undergo mastectomy, for technical or cosmetic reasons, or because the patient prefers it. However, it is important to let the patients know that, under some selected circumstances, breast conservation can still be considered, with acceptable medium to long-term local control.

TABLE 3 Univariate survival analysis

Characteristic	Classification	No. at risk	Local recurrence[a] No. of events (5-years cum inc %)	P^b	All events[c] No. of events (5-years cum inc %)	P^d	Death No. of events (5-years cum inc %)	P^d
All patients		161	47 (29.0)		97 (49.5)		48 (16.3)	
Age	≤50 years	68	22 (34.1)	0.455	40 (51.6)	0.918	21 (22.1)	0.874
	>50 years	93	25 (25.4)		57 (47.1)		27 (11.9)	
Size of IBTR	≤2 cm	135	34 (23.2)	0.001	76 (47.1)	0.030	35 (15.7)	0.030
	>2 cm	16	10 (71.2)		13 (75.0)		9 (25.0)	
Time to IBTR	≤48 months	87	31 (38.4)	0.022	64 (62.1)	<0.001	37 (23.0)	<0.001
	>48 months	74	16 (19.2)		33 (33.8)		11 (8.2)	
Histotype	Ductal	128	36 (27.3)	0.560	74 (49.4)	0.432	39 (18.8)	0.520
	Lobular	13	5 (42.9)		9 (57.7)		5 (8.3)	
Estrogen receptor	Positive	125	36 (26.7)	0.578	71 (45.1)	0.059	31 (12.9)	0.023
	Negative	35	10 (29.8)		25 (63.7)		16 (28.6)	
Progesterone receptor	Positive	101	33 (30.6)	0.460	60 (45.5)	0.358	26 (13.0)	0.163
	Negative	58	13 (24.3)		36 (56.6)		21 (22.4)	
Her2/neu	Not overexpressed	134	38 (26.9)	0.914	78 (45.4)	0.138	36 (14.3)	0.184
	Overexpressed	19	4 (26.0)		12 (62.7)		7 (26.3)	
Ki-67	<20 %	64	17 (22.5)	0.223	34 (38.0)	0.043	14 (9.5)	0.078
	≥20 %	90	28 (33.9)		58 (57.1)		31 (20.0)	
Vascular invasion	Present	26	7 (31.8)	0.892	16 (53.9)	0.506	8 (23.1)	0.867
	Absent	121	36 (28.4)		72 (50.1)		36 (15.9)	
Multifocality	Present	16	4 (33.8)	0.951	14 (75.0)	0.014	6 (25.0)	0.389
	Absent	136	41 (29.0)		76 (47.5)		38 (15.6)	

cum inc cumulative incidence, *IBTR* ipsilateral breast tumor recurrence

[a] Events: IBTR or skin recurrence

[b] Differences in survival between strata were tested by the Gray test

[c] Events: any recurrence or death as first event

[d] Differences in survival between strata are tested by the log-rank test

TABLE 4 Multivariate survival analysis

Characteristic	Local recurrence HR (95 % CI)	All events HR (95 % CI)	Death HR (95 % CI)
Size of tumor >2 cm	3.3 (1.6–7.0)	1.7 (0.9–3.1)	1.8 (0.9–3.8)
Time to IBTR ≤48 mo	1.9 (1.1–3.5)	2.0 (1.3–2.1)	3.1 (1.5–6.2)
Estrogen receptor negative	0.8 (0.4–1.8)	1.1 (0.7–1.9)	1.5 (0.8–2.8)
Ki-67 ≥20 %	1.3 (0.7–2.5)	1.4 (0.9–2.2)	1.4 (0.7–2.8)

HR hazard ratio, *CI* confidence interval, *IBTR* ipsilateral breast tumor recurrence

Nevertheless, it is necessary to underline that this study has several limitations as a result of its retrospective design. An important limitation is the selection of patients. In fact, of the 314 consecutive patients with IBTR managed in the study period, 161 received a second BCS mainly because of more favorable presentation, therefore representing a subgroup of patients with the theoretically best-estimated prognosis.

The selection of patients suitable for undergoing repeat BCS might be further improved by preoperative imaging. Only a few patients included in this analysis received MRI because most of the IBTRs were diagnosed in the pre-MRI era. Nevertheless, currently at our institute, all patients who have an IBTR who are potentially suitable for breast conservation after clinical examination and conventional imaging (mammogram, ultrasound) undergo breast MRI in order to rule out multifocality and multicentricity.[9,10]

In the whole cohort of patients, the 5-year cumulative incidence of local relapse was 29 %. This figure is similar to that which has been previously reported.[11–15] It is worth remembering that these patients underwent a second BCS

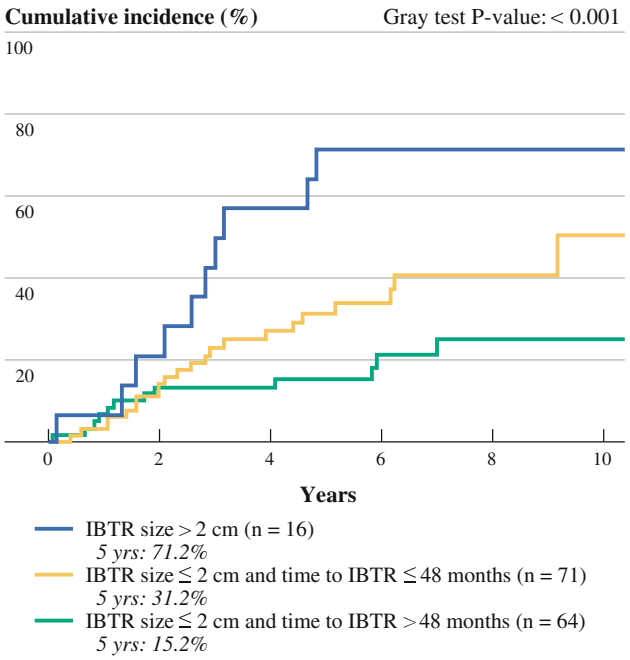

FIG. 2 Cumulative incidence (%) of local events after first IBTR by IBTR size and time to IBTR

without receiving postoperative radiotherapy, which significantly reduces IBTR in the treatment of primary breast cancer.[2,16] In fact, in patients with primary breast cancer who receive BCS without radiotherapy, the local recurrence rate is 30–40 %.[2,15]

The issue of repeat irradiation is clearly one of the research interests in this special clinical scenario. The Radiation Therapy Oncology Group (RTOG) has launched a phase II study of repeating BCS and 3D-conformal partial breast reirradiation for local recurrence of breast carcinoma. This study has the primary objective of evaluating skin, breast, and chest wall adverse events occurring within 1 year from the completion of reirradiation. The trial started in 2010 and is still open to accrual.[17] Another intriguing investigational option is the application of electron intraoperative therapy (ELIOT) in patients who already received BCS and whole-breast irradiation. ELIOT is a partial breast irradiation technique in which a single dose of radiotherapy is delivered directly to the tumor bed under the visual control of the surgeon, thus allowing the skin to be spared.[18] At the moment, we are offering patients the possibility of receiving ELIOT after repeating BCS for IBTR within a prospective study evaluating both toxicity and outcome.

When deciding on the most suitable type of surgery to offer, surgeons should give their patients thorough and complete information on benefits and risks, then take into account patient preference. In addition, cosmetic outcome should be discussed. It is likely that after two wide local excisions, considerable asymmetry may arise. In this case, bilateral reshaping should be discussed.

Another issue to be considered is the limitation of reconstructive options in the case of mastectomy after BCS and whole-breast radiotherapy. In this context, reconstruction with implants has a high risk of contracture, and therefore reconstruction using autologous flaps seems preferable in most cases, even though the time and risks of surgery are increased.[19,20]

In conclusion, the best candidates for a second BCS are those with small (≤2 cm) and late (>48 months) IBTR. Patients with these characteristics are likely to be affected by a new primary cancer rather than a true recurrence. This information about the risk of a further local reappearance after repeating BCS should be shared with patients during the decision-making process. Also, appropriate preoperative imaging with MRI is recommended during preoperative assessment before repeating BCS.

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