



ORIGINAL ARTICLE

Long-term oncological results of breast conservative treatment with oncoplastic surgery

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Summary Oncoplastic surgery combining breast conservative treatment (BCT) and plastic surgery techniques may allow more extensive breast resections and improve aesthetic outcomes, but no long-term oncological results have been published.

Long-term oncologic results of 148 consecutive BCT with concomitant bilateral plastic surgery have been analysed and were compared to historical data of BCT trials.

Median follow-up was 74 months. Complete excision was obtained in 135 patients (91%); focally involved margins in 8 (5%); and close (<2 mm) margins in 5 (3%). Five patients developed ipsilateral recurrence (3%), 19 (13%) developed distant metastasis and 11 patients died (7.53%). Patients with tumours larger than 2 cm were at greater risk of local recurrences and distant metastasis.

Long-term oncologic results of BCT with oncoplastic surgery are comparable with the results of BCT randomized trials.

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Introduction

Long-term results of randomized trials have shown that breast-conserving therapy (BCT) provide same

oncologic results as the mastectomy in small breast cancer.^{1,2} Good final cosmetic results is one of the main objective of the BCT. Criteria for breast conservation have been recently expanded to include larger tumours which traditionally were treated by mastectomy. Moreover, small breast or tumour located in the inferior quadrants usually give unfavourable aesthetic results after wide tumourectomy.

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Oncoplastic surgery is an emerging approach which combines BCT and plastic surgery techniques. It involves appropriate oncologic surgery, immediate omolateral reconstruction using plastic surgery techniques, and correction of the contralateral breast, whenever a symmetry procedure is required.³ Combined plastic surgery procedure may allow a wider resection together with a better aesthetic outcome but there are few data on its impact on local recurrences, distant metastasis and overall survival. The aim of this study is to report the long-term oncological results of this procedure in a series of 148 patients treated at the European Institute of Oncology and to compare these results with the historical data of BCT trials.

Materials and methods

From September 1994 through December 1999, 3210 patients were submitted to BCT for early breast cancer at the European Institute of Oncology, in Milan (EIO). Of them, 148 patients (5%) underwent a BCT associated with concomitant bilateral plastic remodeling. Tumour characteristics, oncological and plastic surgery techniques, adjuvant radiotherapy and systemic treatment, complications and oncological follow-up of the patients, were registered. Neoadjuvant chemotherapy, previous treatment for other breast cancer, breast cancer recurrences, bilateral breast cancer, pregnancy or breast-feeding at diagnosis, inflammatory cancer, surgery performed outside our institute, were excluded from this study. All the patients were re-classified according to the Revision of the American Joint Committee on Cancer Staging System for Breast Cancer.⁴

Surgical techniques

Preoperative drawings were done the day before surgery, with the patient in upright position. These preoperative markings were helpful in providing guidance to the oncologic surgeon to avoid unnecessary skin or glandular removal, visible scarring or nipple-areola pedicle damage during the oncologic procedure. All the patients underwent breast cancer surgery and plastic procedure during the same operation thanks to a double team approach. The tumour was removed with at least 1 cm of macroscopically free margin, en-bloc with the tumour. After removal of the specimen, the remaining breast tissue was bimanually explored in its deep and superficial surfaces, in order to individualize eventual occult lesions.⁵ The techniques used to reshape the involved breast were: the superior pedicle technique^{6,7} when

the tumour was located in the inferior part of the breast, the inferior pedicle when the tumour was in the upper part of the breast, the round block when the tumour was located at a distance from the central pedicle.⁸ In case of large defects the latissimus dorsi or a definitive silicone implant were used. The contralateral mammaplasty was performed concomitantly in all cases of this series, with a technique similar to the one used on the treated breast. A reductive contralateral mammaplasty was usually indicated to get the symmetry. All the specimens removed on the contralateral breast were submitted to definitive pathological analysis.⁹ A complete axillary dissection or sentinel node biopsy was performed in all clinically indicated cases, independently of oncoplastic technique. When sentinel node was positive, a complete axillary dissection was performed, according to EIO protocol previously described.¹⁰

Histopathological examination

All the specimens were weighted and oriented in the operating room to allow the pathologist a better evaluation of the margins for eventual indications of further reexcisions. The volume of each specimen was calculated by multiplying measurements of length, width and height.¹¹ The specimens were inked before cutting; formalin-fixed and paraffin-embedded sections were stained with haematoxylin-eosin for routine examination. The tissue sections included neoplasm and edge of resection. In our Institute we routinely adopt an uniform guideline for surgical margins: a negative margin is defined as containing no tumour cells within a distance of 1 cm to the cut edge of the surgical specimen. However, in the literature, most of the groups have used >2 mm as the cut-off point for negative margins.¹² In order to make the results of our study comparable with other studies, we also used a 2 mm surgical margin as the cut-off point for negative margins. Positive margins were defined as having tumour cells directly at the cut edge of the specimen. Close margins were defined as having tumour cells between the cut edge of the specimen and the boundary defined as negative (≥ 2 mm).

Adjuvant treatment

The decision to use adjuvant systemic therapy (hormonotherapy or chemotherapy) was based on clinical and pathological status¹³ and carried out without modification of our standard protocols. All chemotherapy regimens begun 15–45 days after surgery. We used 4 chemotherapy protocols in this series of patients: cyclophosphamide, fluorouracil

and methotrexate (CMF), anthracycline plus cyclophosphamidex (AC), AC+CMF (4 cycles of anthracycline plus cyclophosphamide and 3 cycles of cyclophosphamide, fluorouracil and methotrexate), or high-dose chemotherapy with autologous stem cell transplantation. Anthracycline regimens or high-dose chemotherapy with autologous stem cell transplantation were indicated for more aggressive diseases (premenopausal patients, ER and PgR negative, and more than 3 positive lymph nodes).

Radiotherapy was delivered to the breast at a dose of 50 Gy plus a boost of 10 Gy, after the end of the chemotherapy, or at least 30 days after surgery, when the chemotherapy was not indicated.

Follow-up

Along the first 5 year follow-up after the surgery, the patients were seen every 6 months by clinical oncologist, breast surgeon and/or plastic surgeon. They underwent a complete clinical examination, blood exams, chest radiography, liver ultrasound, gynecologic ultrasound (only in patients undergoing adjuvant therapy with tamoxifen), and mammography every year. Bone scans were indicated only in case of suspicious blood exams or clinical symptoms. After 5 years patients were seen every year with a mammography and ultra sound.

Statistical analysis

The estimated crude cumulative incidence of tumour recurrence, contralateral breast carcinomas, regional or distant metastasis, and other primary tumour, was calculated according to a framework described by Marubini and Valsecchi.¹⁴ Time to occurrence of these events was computed from the date of surgery. The overall survival curves were obtained with use of Kaplan–Meier method,¹⁵ whilst competing risk methods were assessing the cumulative incidence of local recurrence and distant metastasis, considering which event occurred first. Finally, multivariate COX proportional regression was used to assess the independent prognostic value of selected tumour and patient's characteristics on the development of local recurrence, distant metastasis or death. Statistical analysis was performed with the SAS software. All tests were two-sided.

Results

Patients and tumour characteristics are shown in Table 1. Average patient's age was 50 years (range

31–71). Ninety-one patients were premenopausal (61.5%), and 28 (18.9%) had positive first and second grade familiarly history for breast cancer.

Table 1 Characteristics of the women who underwent oncoplastic surgery.

	Cases (<i>n</i> = 148)
Age (years)	
< 40	18
40–49	57
50–59	50
60–69	21
≥ 70	2
Tumour size (mm)	
1–10	18
11–20	65
21–30	42
> 30	19
Grading	
I	34
II	60
III	48
Unknown	6
Vascular invasion	
Yes	54
No	94
Multifocal tumours	
Yes	31
No	117
Surgical margins	
Negative	135
Positive	8
Closed (< 2 mm)	5
Ki-67	
≤ 16	57
> 16	81
Unknown	10
Axilla	
NX	12
N0	60
N1mi	8
N1a	44
N2a	13
N3a	11
Adjuvant chemotherapy	
Yes	89
No	58
Adjuvant hormonotherapy	
Yes	108
No	39
Complementary radiotherapy	
Yes	141
No	6
Hormone receptor status	
ER or PgR positive	106
ER and PgR negative	35
ER and PgR Missing	7

Table 2 Rates of local recurrences and distant metastasis among women who underwent oncoplastic surgery of the breast according to base-line characteristics.

Characteristic	Local recurrence		Distant metastasis	
	No. of patients	<i>p</i>	No. of patients	<i>p</i>
Overall	5		19	
Menopausal status		0.388		0.731
Pre	4		11	
Post	1		8	
Diameter of primary tumour		0.009		0.00003
1–20 mm	0		3	
> 21 mm	5		16	
Histological grading		0.248		0.029
G1	0		1	
G2 and G3	5		18	
ER/PgR (hormone receptors)		0.363		0.060
+	3		11	
–	2		8	
Ki67				
≤ 16	0	0.066	2	0.007
> 16	5		17	
Vascular invasion		0.401		0.292
Present	1		9	
Absent	4		10	
Plurifocality		0.303		0.188
Yes	0		2	
No	5		17	
Margins		0.372		0.480
Closed or positive	1		1	
Negative	4		18	
Axillary nodes		0.265		0.237
Involved	4		6	
Not involved	1		13	

Table 3 Long-term oncological results in oncoplastic surgery of the breast.

Stage	Patients	Relapse	Metastases	Death
<i>p</i> Tis	11	0	0	0
<i>p</i> T1a–1b	15	0	0	0
<i>p</i> T1c	60	0	3	1
<i>p</i> T2–3	59	5	16	10

Table 4 Characteristics of the patients who had local relapse.

	<i>p</i> T	<i>p</i> N	Age	ER/PgR	Ki67	Others
1st patient	2	1a	41	+	60	
2nd patient	2	3a	56	–	33	
3rd patient	2	1a	39	–	18	IVP+
4th patient	2	0	35	–	70	Margin+
5th patient	2	1a	33	–	40	

In 71 patients (48%) the tumour was in the right breast. Superior-external quadrant were involved in 47 patients (33%), superior-internal quadrant in 22 (15%), union of superior quadrants in 17 (11%), inferior-external quadrant in 17 (11%), inferior-internal quadrant in 16 (11%), union of inferior quadrants in 14 (9%), central quadrant in 15 (10%). In 4 patients (3%) we found tumours in 2 different quadrants. There were 137 (93%) patients with invasive tumours and 11 with DCIS. Average size of the tumour determined in the pathology analysis was 22 mm (range 3–100), and 31 (21%) tumours were multifocal.

Mean weight of breast tissue removed 198 g (range 20–2100 g). Assessment of excision margins showed complete excision of the tumour in 135 patients (91%); focally involved margins with DCIS in 8 patients (5%); and closed (<2 mm) margins in 5 patients (3%). One patient with focally involved margins with DCIS underwent a total mastectomy.

Table 5 Prognostic factors for the development of local recurrence, distant metastasis and for death in 55 pT2–pT3 oncoplastic breast cancer patients.

	Local recurrence (5 events)	Distant metastases (16 events)	Death (10 events)
Age <45	22.5 (1.37–370) $p = 0.0294$	6.35 (1.77–22.8) $p = 0.0047$	12.5 (1.72–90.9) $p = 0.0126$
ER-/PgR (hormone receptors)	0.21 (0.02–2.45) ns	0.21 (0.06–0.76) $p = 0.0182$	0.11 (0.01–0.94) $p = 0.0431$
2 or more positive nodes	5.04 (0.26–97.6) ns	9.59 (2.62–35.1) $p = 0.0047$	20.7 (2.74–156) $p = 0.0033$

Hazards ratio (HR), 95% confidence intervals (CI) and p -value obtained from multivariate Cox proportional hazards regression model.

No association was found with tumour grade, pluri-focality, peritumoural vascular invasion (PVI) or Ki67.

Table 6 Oncoplastic remodeling and histological findings of the contralateral breast.

Oncoplastic remodeling of the contralateral breast	Cases ($n = 148$)
Reductive mammaplasty	135
Mastopessi	9
Definitive silicone implant	4
Histological findings in reduction specimen	Cases ($n = 135$)
Normal breast tissue	40
Fibrocystic disease	31
Proliferative fibrocystic disease	53
Proliferative disease with atypia	2
Ductal carcinoma in situ (DCIS)	6
Lobular carcinoma in situ (LCIS)	2
Invasive ductal carcinoma	1

She developed a local recurrence and a distant metastasis and died after 48 months from the first surgery. The second patient with focally involved margins received a boost on the tumour bed, similar to the patients with negative margins. The remaining 6 patients were not submitted to secondary surgery and did not develop any recurrence in a mean follow-up of 78.7 (± 19.9) months.

Complete axillary dissection was performed in 129 patients (87%); sentinel node biopsy in 7 (5%); and 12 did not received any kind of axillary treatment (8%). Axillary metastases were observed in 76 patients (56%). Sixteen patients (11%) presented early complications observed during the two first months after the operation: 7 wound infections (5%), 4 hematomas, 2 partial nipple-areola necrosis (1%), 1 breast lymphorrhea (0.7%), 1 hyperplasic wound (0.7%), 1 partial wound

dehiscence (0.7%). These complications did not delay the systemic and local adjuvant treatments.

All the patients received some kind of adjuvant systemic therapy. Seventy-one (48%) received CMF regimen, 47 (32%) AC regimen, 31 (21%) AC+CMF regimen, 2 (1%) were included in a high-dose chemotherapy protocol with autologous stem cell transplantation, and 58 (39%) did not receive any kind of chemotherapy. Adjuvant hormonotherapy with tamoxifen was indicated in 108 patients (73%). All except 6 patients (4%) of this series received adjuvant radiotherapy.

Local recurrences and distant metastasis

Median follow-up was 74 months (range 10–108), and only 2 patients (1%) were lost at follow-up. Five patients developed an ipsilateral breast cancer recurrence (3%), in an average time of 23 months (range 12–36) after the first surgery. Four patients had a recurrence in the tumour bed and one in the axilla. Two out of 5 recurrences were submitted to mastectomy and breast reconstruction and implant, one patient underwent mastectomy and TRAM flap reconstruction, two patients received chemotherapy alone due to metastatic disease concomitant with local relapse (LR). In the univariate analysis the probability of local recurrence was significantly higher in the group of patients with tumours larger than 2 cm ($p = 0.009$). We did not experience LR in pT1 patients.

Nineteen patients (13%) developed distant metastasis, in an average time of 33 months (range 1–65) after the first surgery. The metastases sites were: bone 13, liver 10, lung 7, brain 5, supraclavicular 5, internal mammary chain 2, skin 1. The risk of distant metastasis was significantly higher in the group of patients with tumours larger than 2 cm ($p = 0.00003$) and histological grading G2 and G3 ($p = 0.029$) (Table 2). Sequence of events in

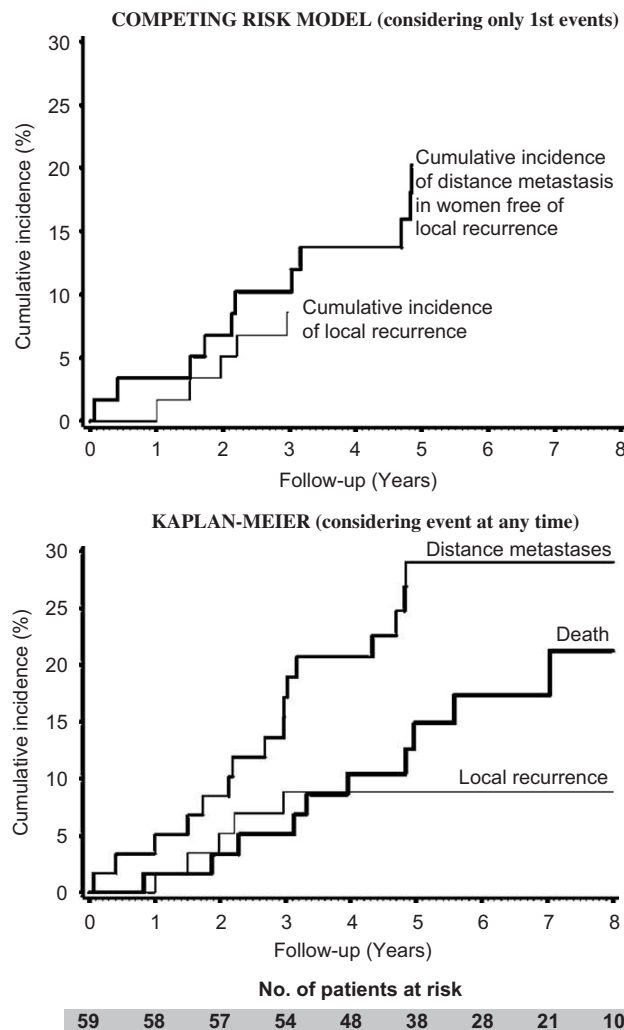


Figure. 1 cumulative incidence of local recurrence, distant metastases and death in patients with T2–T3 breast cancer who had oncoplastic surgery.

59 patients with *pT2* or *pT3* tumours showed that 43 remained alive free of disease (73%), 5 had LR (8%) with distant metastases (4 died from the disease), and 11 developed distant metastases (19%) without local recurrence (6 died successively) (Tables 3 and 4). Prognostic factors for local recurrences, distant metastasis and for death in 55 *pT2–pT3* oncoplastic breast cancer patients are shown in Table 5.

Other events in the contralateral breast

Four patients underwent a quadrantectomy, 4 a total mastectomy and 1 a modified radical mastectomy in the contralateral breast, due to a second breast cancer diagnosed during the follow-

up. The oncoplastic techniques used for remodeling the contralateral breast to improve the symmetry and the respective histological findings are shown in Table 6.

Mortality

Eleven patients (7.53%) died of breast cancer, in an average of 45 months after the first surgery. Most of them (10 patients) were T2 tumours, G3 (7 patients), ER/PgR negative (6 patients), and positive axillary's lymph nodes (7 patients).

The long-term oncological results are shown in Table 3. The cumulative incidence of local recurrence, distant metastases and deaths in patients

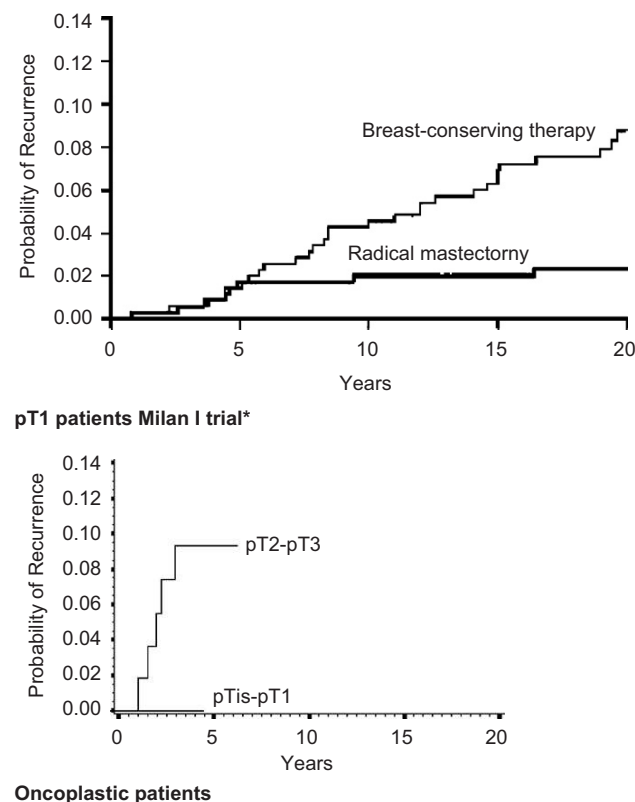


Figure. 2 Crude cumulative incidence of local recurrences in oncoplastic breast cancer patients in comparison with that observed after radical mastectomy and recurrences in the same breast after breast-conserving therapy in the Milan Trial I (*adapted from Veronesi et al. *New Engl J Med* 2002; 347:1227–1232).

with T2–3 are shown in Figs. 1 and 2. No events were registered in the DCIS group

Discussion

The aim of our study is to provide long-term oncological results after oncoplastic surgery. The lack of results in the literature is explained by the recent development of the oncoplastic surgery.^{1,16}

We try to compare our results with those of the Milan trial, of the NSABP B07 trial and the study of the Curie Institute on oncoplastic surgery results even if the populations are different, mainly in what concerns the maximum dimension of the tumour. The NSABP trial excluded tumours greater than 4 cm, and the Milan I trial excluded tumours greater than 2 cm, which in our series represent, respectively, 11% and 42% of cases.

The rate of LR is low in our series: 3% of patients have experienced a LR after 5 years. This is to compare with the 14.3% of cumulative incidence of LR in the NSABP trial, the 9.4% after 5 years in the Institut Curie study and the 0.5% after 5 years in the

Milan I trial (8.8% after 20 years). But if we consider only the tumours less than 2 cm (as in the Milan I) we don't have LR at all. And if we compare the crude cumulative incidence of local recurrences in our pT2 and pT3 patients with that observed after radical mastectomy and after breast-conserving surgery in the Milan I Trial we note that the probability of LR in pT2/pT3 in our series reaches a plateau as after mastectomy while after breast-conserving treatment in the Milan trial, the incidence of LR increases even after 20 years. (Fig. 2). Therefore, in terms of LR, the oncoplastic treatment can be considered as safe as mastectomy in tumours less than 2 cm and probably safer than the "classical" conservative surgery in tumours of more than 2 cm. We can explain this by the better control of margins. Free margins is one of the main recommendations of B. Fisher in the last review of the NSABP B-06 trial. However, we should balance such conclusion considering the differences of adjuvant treatment between our series and the Milan Trial.

Oncoplastic surgery allows a wider glandular resection as demonstrated in a previous publication³

and it is confirmed in this study where the average weight of glandular tissue that has been removed is 198 g.

The rate of positive or close margin involvement in our study is 8%, which is less than of the 10% observed in the NSABP B-06 trial, and much less than the 48% of the European Organization for Research and Treatment of Cancer (EORTC) trial.^{2,17–20}

The most established risk factors for local recurrence after BCT are young age, positive resection margins, multicentric disease and vascular invasion. These factors seem to have less prognostic value after oncoplastic surgery. In our study, the diameter of the tumour greater than 0.2 cm was the only statistically significant prognostic factor (Table 2). The oncoplastic approach modifies the location of the margin of the tumour bed. However, re-excision is always possible with accuracy provided that it is guided by the plastic surgeon who performed glandular shaping.

The symmetry procedure in the contralateral breast, as in our previous published data, allowed a good check-up of the glandular tissue at the time of the breast remodeling, especially when there is no evidence of tumour in the preoperative exams.⁵ In our current series, 07 clinically and radiological occult contra lateral cancers were found in the reduction specimen (5%). Moreover, in 2 patients (1%) we found fibrocystic disease with atypia, which is known as a risk factor^{21,22} (Table 6). Such results show that there is a subgroup of patients with high risk of occult contralateral cancer that should be closely followed. In case of occasional diagnosis of cancer in the contralateral breast, we still cannot evaluate the efficacy of performing secondary sentinel node biopsy after remodeling procedures. A study is currently in progress to answer this question.

Conclusions

The cosmetic improvement in case of extensive tumour resection has been proved but the safety of oncoplastic surgery until now was not tested in specific trials due to technical and ethical difficulties. Our results confirm the safety of the oncoplastic surgery especially in T2, T3 tumours.

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