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Conservative surgery in patients with multifocal/multicentric breast cancer

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Abstract *Purpose* Many physicians recommend mastectomy in case of multifocal (MF) or multicentric (MC) breast cancer due to a theoretical risk of poor local control with less extensive surgery. We retrospectively evaluate outcome of patients with MF/MC cancers who had breast conservation with specific attention on local control and predictive factors of recurrence. *Patients and methods* Four hundred and seventy six patients with either MF (n = 421) or MC (n = 55) breast cancer, underwent breast-conserving surgery between 1997 and 2002 in a single institution. Median follow up was 73 months (range 11–118). *Results* Median age was 53 years (range 23–86). Invasive lobular carcinoma was found in 88 patients (18.5%) and mixed ductal-lobular cancer in 27 (5.7%) patients. Two hundred and sixty-seven patients (76.7%) had two identified tumor

foci, 55 patients (15.3%) had three and 29 patients (8.0%) had four or more. Two hundred and sixty-one patients (55.3%) had nodal involvement. The 5-year cumulative incidence of local relapse was 5.1%. At the multivariate analysis, over-expression of HER2/neu and lack of both estrogen and progesterone receptors (HR: 3.2, 95% C.I. 1.01–10.0, and HR: 2.7, 95% C.I. 1.06–7.7, respectively) were associated with a higher ipsilateral breast cancer reappearance rate. Involvement of four or more lymph nodes and lack of estrogen and progesterone receptors (HR: 2.7, 95% C.I. 1.06–6.7, and HR: 4.7, 95% C.I. 2.1–10.4, respectively) were associated with poorer overall survival. *Conclusions* In selected patients with MF/MC breast cancer, wide conservative surgery is not associated with poor local disease control and can be considered whenever acceptable cosmetic results can be achieved.

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Introduction

With widespread use of mammographic screening and increased accuracy of diagnostic imaging, the surgical treatment of multifocal (MF) and multicentric (MC) breast cancer has come to represent a new challenge for the conservative approach [1]. The presence of multiple foci of cancer within the same breast has traditionally been considered a contraindication for conservative surgery. In fact, many surgeons continue to propose mastectomy for MF/MC because earlier series have demonstrated high rates of local recurrence following breast conserving surgery [2, 3]. Moreover, physicians often recommend mastectomy in order to complete local treatment when unexpected

multifocality is documented at the final pathologic report, even when surgical margins are disease-free. When two separate tumours are located in different quadrants, breast conservation is not usually considered even in patients with large breasts who might be suitable for a double wide excision. However, the difficulty of endorsing a conservative approach in these patients could be explained by limited available data.

The aim of this study was to retrospectively evaluate the outcome of patients with multiple invasive breast cancer who received conservative surgery with special attention being paid to local control, and to identify predictive factors for recurrence in these patients.

Patients and methods

Between March 1997 and December 2002, 8100 patients were operated on for invasive breast cancer at the European Institute of Oncology of Milan, Italy and were prospectively entered into our data base. We retrieved 476 patients who underwent conservative surgery for MF or MC breast cancer (at least two different pathologically confirmed invasive foci within the same breast). Diagnosis of multiple invasive breast cancer was performed either clinically by palpation, radiologically or at pathological examination. Multifocality was defined as the presence of different tumours within the same quadrant, and multicentricity as the presence of tumours in different quadrants of the breast, which were managed by a double incision.

All patients' cases were discussed after surgery at a multidisciplinary meeting attended by breast surgery, medical oncology, radiotherapy and pathology specialists. Sixty patients (12.6%) received adjuvant chemotherapy alone, 191 patients (40.1%) received hormonal therapy alone, and 217 (45.6%) patients received both chemotherapy and endocrine treatment. Eight patients (1.7%) did not receive any medical adjuvant treatment.

Four-hundred and fifty-four patients received standard postoperative external whole breast radiotherapy, 13 received intra-operative radiotherapy and nine did not receive any radiation treatment. The median age was 53 years (range 23–86). The median follow up was 73 months (range 11–118).

Two-hundred and seventy eight patients underwent upfront axillary dissection either due to the presence of clinically pathological nodes or because they had been treated before the sentinel node era. Eighty-eight underwent sentinel lymph node biopsy (SLNB) and axillary dissection because of the presence of metastases in the sentinel node, 106 received SLNB alone, and four did not have any axillary staging.

All those patients who were not seen in the last 6 months were contacted by telephone in order to update the follow up. No patients were lost to follow up.

Pathology

The distinction between the tumors was assessed both grossly, recording the distance between the foci and microscopically, routinely sampling the interposed tissue between the neoplastic foci. Multifocality and multicentricity were prospectively diagnosed on the pathology report only if the interposed tissue was free of neoplasia, both in situ or infiltrating.

HER-2/*neu* over-expression was investigated immunohistochemically, using a specific polyclonal antiserum (Dako A/S, Carpinteria, CA). The staining results were recorded in a four-tier scale, from 0 to 3+, according to the percentage of immunoreactive cells, and to the intensity and completeness of membrane staining as recommended by the Food and Drug Administration, USA [4]. Only an intense and complete membrane staining of the tumour cells (3+) was taken as evidence of Her2/*neu* over-expression.

Patients with distant metastases, bilateral cancer, clinical or pathological T4 or those who received primary medical treatment were excluded from the analysis. Table 1 summarizes the patients' and tumours' characteristics. The reported tumor size represents the largest tumor focus. Ten patients had focally positive margins at the final pathologic report and, after careful discussion of the available options, were not submitted to re-excision according to patient' preference.

Statistical considerations

Primary endpoints were cumulative incidence of local events, cumulative incidence of first events and cumulative mortality. Recurrences within the same breast, with or without involvement of regional nodes, were considered as local events. First events were any type of recurrence, second primary cancer, contralateral breast cancer recurrence or death, whichever occurred first. If patients had simultaneous local and distant recurrence they were considered as having a distant recurrence in the analysis. Cumulative mortality was calculated as the cumulative incidence of deaths from any cause.

Crude cumulative incidence of local events was computed in a competing risk framework as described by Marubini and Valsecchi [5], and compared across different subgroups by means of the Gray test [6]. The Log-rank test was used to assess survival differences between groups for cumulative incidence of first events and cumulative mortality. Multivariate Cox proportional hazards regression

Table 1 Patients' characteristics and stratification for multifocal/multicentric tumours

Variable	Classification	Total No. (%)	Multifocal No. (%)	Multicentric No. (%)	Chi-square <i>P</i> -value
All patients		476	421 (88.4)	55 (11.6)	
Age	<35 years	25 (5.3)	23 (5.5)	2 (3.6)	0.492
	35–49 years	178 (37.4)	159 (37.8)	19 (34.6)	
	50–64 years	200 (42.0)	172 (40.9)	28 (50.9)	
	≥65 years	73 (15.3)	67 (15.9)	6 (10.9)	
Menopause	Pre	193 (40.6)	171 (40.6)	22 (40.0)	0.930
	Peri/post	283 (59.4)	250 (59.4)	33 (60.0)	
Number of foci ^a	2	276 (76.7)	246 (79.4)	30 (60.0)	0.011
	3	55 (15.3)	42 (13.6)	13 (26.0)	
	≥4	29 (8.0)	22 (7.1)	7 (14.0)	
pT	pT1a-pT1b	84 (17.7)	77 (18.3)	7 (12.7)	0.529
	pT1c	257 (54.0)	227 (53.9)	30 (54.6)	
	pT2-pT3	135 (28.4)	117 (27.8)	18 (32.7)	
Extensive in situ component	Absent	297 (62.4)	262 (62.2)	35 (63.6)	0.840
	Present	179 (37.6)	159 (37.8)	20 (36.4)	
Margins	Negative (>1 mm)	421 (88.5)	372 (88.4)	49 (89.1)	0.983
	Close (≤1 mm)	45 (9.4)	40 (9.5)	5 (9.1)	
	Positive	10 (2.1)	9 (2.1)	1 (1.8)	
Number of positive lymph nodes ^a	0	211 (44.7)	186 (44.5)	25 (46.3)	0.795
	1–3	167 (35.4)	150 (35.9)	17 (31.5)	
	≥4	94 (19.9)	82 (19.6)	12 (22.2)	
Histotype	Ductal	333 (70.0)	294 (69.8)	39 (70.9)	0.928 ^b
	Lobular	88 (18.5)	78 (18.5)	10 (18.2)	
	Mixed Duct.-Lob.	27 (5.7)	22 (5.2)	5 (9.1)	
	Other	28 (5.9)	27 (6.4)	1 (1.8)	
Estrogen receptors	Positive	417 (87.6)	369 (87.6)	48 (87.3)	0.937
	Negative	59 (12.4)	52 (12.4)	7 (12.7)	
Progesterone receptors	Positive	372 (78.2)	329 (78.2)	43 (78.2)	0.995
	Negative	104 (21.8)	92 (21.8)	12 (21.8)	
Grading ^a	G1	65 (14.1)	59 (14.5)	6 (11.1)	0.777
	G2	250 (54.1)	219 (53.7)	31 (57.4)	
	G3	147 (31.8)	130 (31.9)	17 (31.5)	
HER2/neu ^a	Over-expressed	40 (13.3)	32 (12.5)	8 (18.6)	0.272
	Not over-expressed	260 (86.7)	225 (87.5)	35 (81.4)	
Ki-67 ^a	<20%	235 (49.7)	209 (50.0)	26 (47.3)	0.704
	≥20%	238 (50.3)	209 (50.0)	29 (52.7)	
Vascular invasion	Absent	327 (68.7)	292 (69.4)	35 (63.6)	0.584
	Present	81 (17.0)	69 (16.4)	12 (21.8)	
	Extensive	68 (14.3)	60 (14.3)	8 (14.3)	

^a Information is not available for all the patients

^b Lobular vs. ductal. The reported tumor size represents the largest tumor focus

Bolded entries indicate statistical significance (i.e. *P*-value < 0.05)

models were used to identify the prognostic independent clinico-pathological features associated with survival. For local events, Cox Proportional Hazard model was computed in a competing risk framework [7]. All analyses were

performed with the SAS software (SAS Institute, Cary, NC) and the R software (The R Development Core Team 2004; Free Software Foundation, Boston, MA). All tests were two-sided.

Table 2 Description of events

Description of events	No. (%)
First event	
Local ^a	24 (5.0)
Loco-regional ^a	2 (0.4)
Regional	7 (1.5)
Distant	51 (10.7)
Local and distant	1 (0.2)
Contralateral breast tumor	6 (1.3)
Other primary tumor	11 (2.3)
Death as first event (any cause)	9 (1.9)
Death (any cause)	36 (7.6)

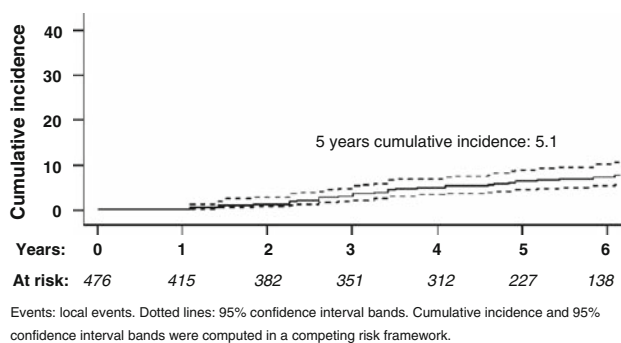
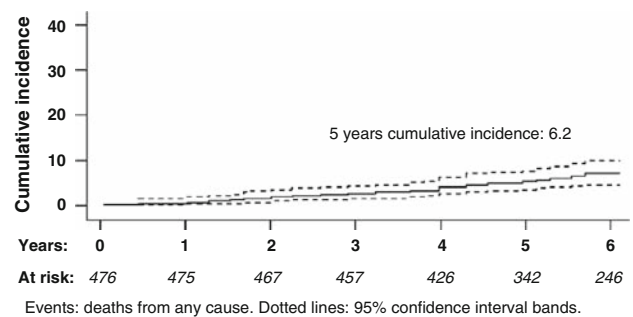
^a Considered as local events in the following analyses

Results

Median age was 53 years (range 23–86). Table 1 shows patients' and tumor characteristics with stratification for multifocal (MF) and multicentric (MC) tumours. Four hundred and twenty-one patients (88.4%) had MF and 55 (11.6%) had MC disease. The only difference between patients with MF and MC tumours was that the number of foci was significantly higher in patients with MC disease. Invasive lobular carcinoma was diagnosed in 88 patients (18.5%) and invasive mixed ductal-lobular cancer in 27 (5.7%). Two hundred and sixty-seven patients (76.7%) had 2, 55 patients (15.3%) had three and 29 patients (8.0%) had 4 or more tumor foci. Two hundred and sixty-one patients (55.3%) had nodal involvement.

Table 2 describes the events. Briefly, 24 patients (5.0%) developed ipsilateral breast recurrence, 2 (0.4%) had loco-regional recurrence, and 51 (10.7%) had distant metastases as first event.

Figures 1 and 2 represent cumulative incidence of local recurrence (5.1% at 5 years) and mortality (6.2% at 5 years), respectively.

**Fig. 1** Cumulative incidence of local events**Fig. 2** Cumulative mortality

Factors related to local and distant relapses, and to overall survival at the univariate and multivariate analyses are listed in Tables 3 and 4, respectively.

At the multivariate analysis, over-expression of HER2/neu and lack of both estrogen and progesterone receptors (HR: 3.2, 95% C.I. 1.01–10.0, and HR: 2.7, 95% C.I. 1.06–7.7, respectively) were associated with higher ipsilateral breast cancer reappearance rate. Involvement of 4 or more lymph nodes and lack of estrogen and progesterone receptors (HR: 2.7, 95% C.I. 1.06–6.7, and HR: 4.7, 95% C.I. 2.1–10.4, respectively) were associated with poorer overall survival.

Discussion

To our knowledge, few papers [2, 3, 8–13] have been published concerning conservative surgery in patients with MF/MC, and all have dealt with a limited number of patients. Former series reported a high risk of local recurrence in patients treated with conservative surgery. In fact, Kurtz et al. [2] in their experience with 61 patients with two or more macroscopic tumor nodules, concluded that patients with macroscopically multiple invasive breast cancer were at a higher risk of local failure if tumors were clinically or radiologically apparent (36% rate of local recurrence). Wilson and colleagues [3] reported that the local recurrence rate was greater in patients with synchronous ipsilateral breast cancer as compared to patients with single lesions (72-month actuarial breast recurrence rate of 25% and 12%, respectively). More recently, Cho et al. [11] reported that in selected cases the combination of conservative surgery and radiation therapy resulted in acceptable local-regional control, based on their experience with 15 patients affected by multiple ipsilateral invasive breast cancer. Kaplan et al. [12], after evaluating their experience with 36 patients, concluded that breast conservation is an effective treatment for patients with synchronous ipsilateral breast carcinoma. Okumura and colleagues [13] compared 34 patients with multiple invasive breast cancer to 594 patients with unifocal disease and

Table 3 Univariate analysis of prognostic factors

Variable	Classification	Local events		All first events		Deaths	
		Events (5 years Cum Inc)	<i>P</i> -value	Events (5 years Cum Inc)	<i>P</i> -value	Events (5 years Cum Inc)	<i>P</i> -value
All patients		26 (5.1)		111 (23.5)		36 (6.2)	
Age	<35 years	2 (8.5)	0.130	8 (25.9)	0.131	2 (8.0)	0.008
	35–49 years	11 (6.0)		38 (22.6)		6 (3.6)	
	50–64 years	6 (2.4)		42 (19.5)		17 (6.4)	
	≥65 years	7 (9.7)		23 (35.4)		11 (11.2)	
Multifocal/multicentric	Multifocal	23 (4.9)	0.829	97 (23.2)	0.393	31 (6.0)	0.515
	Multicentric	3 (8.0)		14 (26.2)		5 (7.6)	
Number of foci ^a	2	7 (2.4)	0.192	56 (22.5)	0.832	17 (5.0)	0.802
	3+	5 (5.7)		19 (19.8)		6 (5.4)	
pT	pT1a–pT1b	7 (10.6)	0.347	15 (22.5)	0.014	5 (4.9)	0.210
	pT1c	12 (4.9)		50 (20.6)		16 (5.8)	
	pT2–pT3	7 (5.1)		46 (29.1)		15 (7.7)	
Extensive in situ component	Absent	14 (5.0)	0.597	69 (25.1)	0.584	26 (7.1)	0.101
	Present	12 (6.0)		42 (20.9)		10 (4.7)	
Margins	Negative/close	25 (5.5)	0.313	108 (23.1)	0.286	35 (6.0)	0.793
	Positive	1 (25.0)		3 (50.0)		1 (12.5)	
Number of positive lymphnodes ^a	0	8 (3.7)	0.308 ^b	26 (12.5)	<0.001^b	9 (3.4)	<0.001^b
	1–3	12 (5.6)		41 (23.8)		13 (6.4)	
	≥4	5 (6.3)		43 (45.0)		13 (11.2)	
Histotype	Ductal	20 (6.1)	0.638	87 (26.9)	0.229	29 (8.0)	0.805
	Lobular	4 (4.4)		17 (17.6)		7 (3.4)	
Estrogen receptors	Positive	18 (4.1)	0.003	84 (19.8)	<0.001	22 (3.6)	<0.001
	Negative	8 (16.1)		27 (48.5)		14 (24.2)	
Progesterone receptors	Positive	13 (2.8)	<0.001	71 (17.7)	<0.001	17 (3.1)	<0.001
	Negative	13 (15.6)		40 (43.6)		19 (16.9)	
Grading ^a	G1	0 (0.0)	0.046^c	6 (9.0)	<0.001^c	2 (3.1)	<0.001^c
	G2	13 (5.3)		42 (16.0)		11 (2.7)	
	G3	10 (6.4)		59 (40.6)		22 (13.4)	
Her2/neu ^a	Overexpressed	7 (19.8)	<0.001	23 (56.9)	<0.001	10 (26.9)	<0.001
	Not overexpr.	9 (4.0)		49 (20.9)		16 (4.4)	
Ki-67 ^a	<20%	8 (3.5)	0.036	34 (14.4)	<0.001	11 (2.2)	0.013
	≥20%	18 (7.9)		77 (32.4)		25 (10.2)	
Vascular invasion	Absent	14 (3.8)	0.135 ^d	57 (17.3)	<0.001^d	19 (4.1)	0.033^d
	Present	5 (8.1)		23 (32.5)		8 (9.5)	
	Extensive	7 (8.3)		31 (40.3)		9 (12.1)	

Five-year cumulative incidences for *local events* were computed in a competing risk framework and compared by the Gray test. Five-year cumulative incidences for *first events* and *deaths* were compared by the log-rank test. Bolded entries indicate statistical significance (i.e. *P*-value < 0.05)

^a Information is not available for all patients

^b Positive vs. negative

^c G2–G3 vs. G1

^d Present/extensive vs. absent

did not find any difference in terms of local control, disease-free survival or cosmetic result.

Our attitude is strongly in favour of breast conservation, and we elect this surgical approach as the treatment of

choice, even for patients with multiple invasive cancer as long as it is technically and cosmetically feasible. Here, we re-evaluate the largest series of patients with pathologically confirmed multiple foci of breast cancer and treated with

Table 4 Multivariate analysis

	Comparisons	Local events HR (95% C.I.)	All first events HR (95% C.I.)	Deaths HR (95% C.I.)
pT	pT2/3 vs. pT1	–	1.17 (0.78; 1.75)	–
Number of positive lymphnodes	1–3 vs. 0	–	1.86 (1.12; 3.08)	1.68 (0.70; 4.00)
	4+ vs. 0	–	2.73 (1.58; 4.75)	2.65 (1.06; 6.66)
Er/Pgr receptors	Both absent vs. at least one positive	2.76 (1.06; 7.68)	2.40 (1.43; 4.05)	4.68 (2.10; 10.4)
Her2/neu	Overexpressed vs. not overexpressed	3.18 (1.01; 10.0)	1.64 (0.92; 2.93)	1.82 (0.71; 4.67)
Ki-67	≥20 vs. <20	1.45 (0.57; 3.68)	1.45 (0.92; 2.27)	1.31 (0.59; 2.92)
Vascular invasion	Present/extensive vs. absent	–	1.50 (0.98; 2.29)	1.86 (0.89; 3.88)

Hazard ratios and confidence intervals were calculated using the Cox Proportional Hazard model. For local events the Cox Proportional Hazard model was computed in a competing risk framework. The model for mortality was adjusted for age considered as a continuous variable. Bolded entries indicate statistical significance (i.e. *P*-value < 0.05)

breast conservation. Our cohort comprises patients with multiple palpable tumours located within the same quadrant or in different quadrants, or patients with an unexpected MF invasive disease found at the final pathological report. Multifocality and multicentricity in breast cancer are historically defined as the presence of two or more tumor foci within a single quadrant of the breast or within different quadrants of the same breast, respectively [14]. The only significant difference between patients with MF and MC tumours was the number of foci, which was higher in patients with MC disease. In our opinion, these definitions help to simply illustrate two different scenarios of multiple invasive breast cancer. As two separate tumors within the same quadrant could in fact be more distant from each other than two tumors located in different quadrants, it is important to point out that strict definitions run the risk of falling into discussions which are merely semantic. The distance between tumors should also be regarded with caution, as overall proportion with breast size should be also taken into account.

It is interesting to note that despite the high rate of node metastases (55% of the patients), as expected in MF/MC breast cancer [15, 16], distant metastases occurred in only 10.7% of the patients. One might speculate that the high rate of endocrine-responsive tumours in this series (87.6%), which is probably related to the high prevalence of invasive lobular carcinomas, might lead to a better outcome following adequate adjuvant treatment at least during the first 5 years. Furthermore, patients with lobular or ductal carcinoma had a similar outcome in terms of local recurrence (4.4 and 6.1%, respectively). This confirms that, despite the common multifocality and bilaterality of invasive lobular carcinoma, its occurrence does not by itself preclude breast conservation, as long as it is adequately excised.

The main finding of our study is that the 5 years cumulative incidence of local relapse was 5.1%, which is in our opinion quite acceptable and similar to that reported in patients with unifocal disease [17, 18]. Therefore, these data,

derived from a large series of patients, emphasize that breast conserving surgery is safe for patients with MF/MC breast cancer, as it provides acceptable local control when the disease is adequately excised. Furthermore, breast conservation achieved a good outcome even in patients with MC disease who were treated with separate wide local excisions (8% 5 years cumulative incidence of local relapse).

The multivariate analysis which showed that over-expression of HER2/neu and lack of estrogen and progesterone receptors worsened local disease free survival. Due to the availability of an effective therapy against cells over-expressing HER2/neu it is likely that outcome will be improved with the adjuvant administration of trastuzumab [19, 20].

This is a retrospective analysis and therefore some limitations have to be underlined. First, we were not able to collect reliable data on clinical and radiological presentation. It would be interesting to have this information in order to better characterize the patient cohort. Obviously, all patients with multicentric cancer had preoperative diagnosis since they underwent double incision but for the majority of the population we cannot say how many patients had either clinically palpable lumps or radiologically detected tumours or incidental finding at surgery or at pathologic evaluation. Secondly, this is a selected population of patients. In fact, all these women were considered suitable for breast conservation from both the oncologic and cosmetic point of view after careful discussion.

Despite the above mentioned limitations and critiques which might be raised, we think that these data are of important clinical interest since only a few papers with a limited number of patients have been reported so far on this topic. In specialized centers with high patient volume conservative surgery is usually performed in presence of multifocal cancer, but many surgeons or medical oncologists acting in community hospitals continue to recommend mastectomy for the presence of multifocality itself.

As stated earlier, patients were selected for the expected acceptable cosmetic outcome as well. In most cases of

multicentric cancer women had large breasts with tumors far each other and located at the periphery of the breast. In this clinical scenario it is not hard to imagine that satisfactory outcome could be achieved.

We believe that the data collected within this study are relevant to the discussion with motivated patients in order to decide upon the type of surgery to be conducted. Given the low rate of local recurrence, in selected patients breast conservation can be considered for patients with MF/MC breast cancer, whenever adequate surgery and acceptable cosmetic results can be achieved.

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