

## Original article

## Breast-conserving surgery in 201 very young patients (&lt;35 years)

Oreste Gentilini<sup>a,\*</sup>, Edoardo Botteri<sup>b</sup>, Nicole Rotmensz<sup>b</sup>, Antonio Toesca<sup>a</sup>, Helio De Oliveira<sup>a</sup>, Claudia Sangalli<sup>a</sup>, Marco Colleoni<sup>c</sup>, Mattia Intra<sup>a</sup>, Viviana Galimberti<sup>a</sup>, Paolo Veronesi<sup>a,d</sup>, Alberto Luini<sup>a</sup>, Umberto Veronesi<sup>a</sup>

<sup>a</sup> Division of Breast Surgery, European Institute of Oncology, Via Ripamonti 435, 20141, Milano, Italy

<sup>b</sup> Division of Epidemiology and Biostatistics, European Institute of Oncology, Milano, Italy

<sup>c</sup> Department of Medical Oncology, Unity of Clinical Research, European Institute of Oncology, Milano, Italy

<sup>d</sup> University of Milan School of Medicine, European Institute of Oncology, Milano, Italy

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## ABSTRACT

**Introduction:** Surgical treatment of breast cancer in very young patients (<35 years) is still a matter of debate, since age is a predictive factor of local recurrence after breast conservation.

**Patients and Methods:** We retrospectively evaluated outcome and prognostic factors of 201 consecutive patients treated with breast conservation followed by whole breast irradiation between 1997 and 2004 with special attention paid to local control. The average follow up was 72 months (range 13–133 months).

**Results:** The mean age was 32 years (Range 20–34). Invasive ductal carcinoma was found in 175 (87.1%) patients. Two (1%) patients had invasive lobular carcinoma. One-hundred and eighteen patients (58.7%) had tumors of 2 cm or smaller. Sentinel lymph node biopsy was performed in 105 (52.2%) patients. One-hundred and ten (54.7%) patients had node-negative disease, 68 (33.8%) patients had 1–3 positive nodes and 23 (11.4%) +4 positive nodes. Eighteen patients (9.0%) developed a local recurrence, 25 (12.5%) developed distant metastases and 23 patients (11.4%) died during follow up. The 5- and 10-year cumulative incidence of local events were 8.2% and 12.3% respectively. The univariate analysis did not identify any variables affecting local disease-free survival.

**Conclusions:** Breast conservation in very young patients achieves an acceptable local control rate. No prognostic factors were associated with local events.

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## Introduction

Very young patients are arbitrarily defined as those less than 35 years of age. This subset of patients has common features frequently showing a more aggressive pattern at presentation with respect to older pre-menopausal counterparts.<sup>1</sup> Furthermore, younger patients have an increased rate of recurrence after breast-conserving surgery.<sup>2,3</sup> For these reasons<sup>4</sup> some surgeons might be more prone to recommend a mastectomy in very young patients. At the European Institute of Oncology of Milan, Italy however, our attitude towards this subset of patients is very conservative and we decided to retrospectively evaluate our experience with breast conservation in very young patients, focusing special attention on local control and the identification of factors affecting local disease-free survival.

## Patients and methods

Between 1997 and 2004 we treated 12,163 patients with breast cancer who were prospectively entered into our data base. Five hundred and eighty-one (4.7%) patients were less than 35 years old. Patients with distant metastases at the time of surgery, bilateral breast cancer, other previous tumours and those who received neoadjuvant treatment were excluded from the analysis.

Seventy-two patients underwent mastectomy whereas 201 women received breast-conserving surgery and these latter represent the cohort of our study.

All patients included in the analysis had negative margins.

Preoperative work-up was performed with routine blood tests and tumour markers (CEA and CA15.3), mammography, breast ultrasound and chest X-ray. Magnetic resonance of the breast was performed only in a small minority of patients. Further staging exams were performed only when clinically indicated. In patients with pathologically confirmed axillary metastases or tumours larger than 2 cm a bone scan was recommended after surgery.

\* Corresponding author. Tel.: +39 0257489376; fax: +39 0257489780.

E-mail address: [oreste.gentilini@ieo.it](mailto:oreste.gentilini@ieo.it) (O. Gentilini).

**Table 1**  
Patients' characteristics.

Variable	Classification	Total No. (%)
All patients		201
Age in years	20–24	10 (5.0)
	25–29	45 (22.4)
	30–34	146 (72.6)
BC family history <sup>a</sup>	No	147 (75.0)
	1st degree	23 (11.7)
	2nd degree	26 (13.3)
pT	1a/1b	23 (11.4)
	1c	95 (47.3)
	2	79 (39.3)
	3	2 (1.0)
	x	2 (1.0)
Number of positive lymphnodes	0	110 (54.7)
	1–3	68 (33.8)
	≥4	23 (11.4)
Histotype	Ductal	175 (87.1)
	Lobular	2 (1.0)
	Other	24 (11.9)
Extensive in situ component	Absent	158 (78.6)
	Present	43 (21.4)
Estrogen Receptors <sup>a</sup>	Positive	139 (70.6)
	Negative	58 (29.4)
Progesteron Receptors <sup>a</sup>	Positive	121 (61.4)
	Negative	76 (38.6)
Grading	G1	24 (12.7)
	G2	57 (30.3)
	G3	107 (56.9)
Her2/neu <sup>a</sup>	Overexpressed	28 (19.3)
	Not overexpressed	117 (80.7)
Ki-67 <sup>a</sup>	<20%	51 (27.1)
	≥20%	137 (72.9)
Vascular invasion <sup>a</sup>	Absent	131 (65.8)
	Present	39 (19.6)
	Extensive	29 (14.6)

<sup>a</sup> Information is not available for some patients.

### Postoperative treatment

All the patients were discussed at our weekly multidisciplinary meeting attended by surgical, medical and radiation oncologists, pathologists, and experts in prevention and genetics and adjuvant treatment was proposed according to the stage and biology of the tumour.

One-hundred and nine patients received adjuvant chemotherapy plus hormonal treatment, 31 patients received endocrine therapy alone, 57 patients received chemotherapy alone and 4 patients did not receive any adjuvant systemic treatment.

All patients included in this analysis underwent standard whole breast irradiation after surgery.

Patients were followed up with physical examination every six months, annual mammography and breast ultrasound, blood tests every 6–12 months and further evaluations only in case of symptoms.

**Table 2**  
Description of events.

Description of Events	No. (%)
First event	
Local <sup>a</sup>	16 (8.0)
Loco-regional <sup>a</sup>	2 (1.0)
Regional	3 (1.5)
Distant	22 (11.0)
Local and distant	3 (1.5)
Contralateral breast tumor	7 (3.5)
Other primary tumor	3 (1.5)
Death as first event (any cause)	3 (1.5)
Death (any cause)	23 (11.4)

<sup>a</sup> Considered as local events in the following analyses.

Patient records were retrospectively reviewed with approval of the institutional review board.

### Statistical analysis

Cumulative incidence of local events, cumulative incidence of first events and cumulative mortality were the primary endpoints. Recurrences within the same breast, with or without involvement of regional nodes, were considered as local events. If patients had simultaneous local and distant recurrence they were considered as having a distant recurrence in the analysis.

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

### Results

Median follow up was 72 months (range 13–133 months).

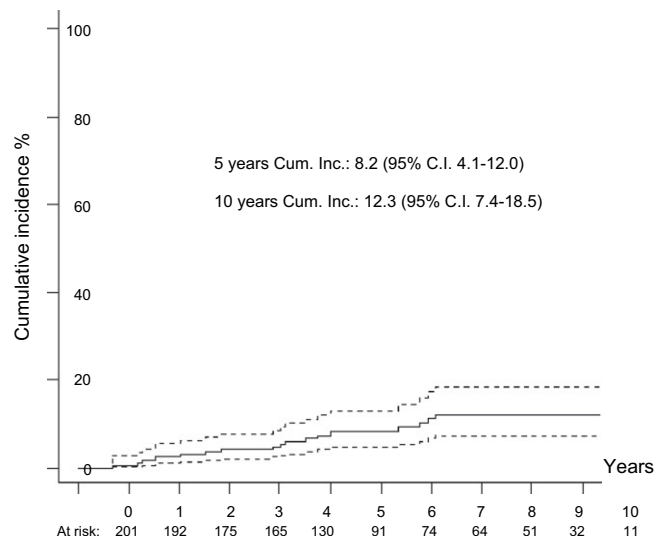
**Table 1** summarizes the features of the 201 patients included in the analysis.

Notably, 23 patients (11.7%) and 26 patients (13.3%) had a first and second degree family history for breast cancer, respectively. Ductal carcinoma was found in 175 (87.1%) patients. Two (1%) patients had lobular carcinoma. One-hundred and eighteen patients (58.7%) had tumor of 2 cm or smaller.

One-hundred and ten (54.7%) patients had node-negative disease, 68 (33.8%) patients had 1–3 positive nodes and 23 (11.4%) had 4 or more positive nodes. Sentinel lymph node biopsy was performed in 105 (52.2%) patients which was positive in 29 and negative in 76 patients.

Non-endocrine responsive tumours were found in 29.4% of the patients.

**Table 2** describes the events. Eighteen patients (9.0%) developed an intra-breast tumour reappearance. The median time to second local events was 47 months. The vast majority of these local events were considered a true recurrence, and only two of 18 were deemed second ipsilateral breast tumours. Distant metastases occurred in 25 patients (12.5%) and 23 patients (11.4%) died during

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

**Table 3**  
Univariate analysis of prognostic factors.

Variable	Classification	Local Events		All first Events		Deaths	
		Events (5 years Cum Inc)	p-value	Events (5 years Cum Inc)	p-value	Events (5 years Cum Inc)	p-value
All patients		18 (8.2)		59 (28.1)		23 (9.8)	
Age	20–24	0 (0.0)	0.594	1 (20.0)	0.535	1 (0.0)	0.926
	25–29	5 (7.1)		14 (25.4)		6 (9.8)	
	30–34	13 (9.1)		44 (27.3)		16 (10.4)	
pT	pT1	12 (9.1)	0.494	32 (24.5)	0.407	12 (10.6)	0.566
	pT2–pT3	6 (7.3)		26 (32.4)		10 (7.5)	
Number of positive lymphnodes	0	12 (10.3)	0.378	32 (26.1)	0.165	14 (12.5)	0.279
	1–3	4 (5.0)		17 (26.6)		5 (3.0)	
	≥4	2 (9.4)		10 (41.3)		4 (17.4)	
Extensive in situ component	Absent	13 (8.4)	0.685	50 (29.5)	0.145	19 (11.2)	0.537
	Present	5 (11.8)		9 (22.1)		4 (4.7)	
Estrogen Receptors <sup>a</sup>	Positive	14 (9.5)	0.368	40 (29.3)	0.668	12 (6.0)	0.040
	Negative	4 (5.8)		19 (27.9)		11 (19.6)	
Progesteron Receptors <sup>a</sup>	Positive	13 (11.1)	0.432	36 (29.9)	0.744	11 (6.9)	0.141
	Negative	5 (7.0)		23 (26.7)		12 (15.0)	
Grading <sup>a</sup>	G1	1 (0.0)	0.728	4 (4.3)	0.136	0 (0.0)	0.003
	G2	5 (6.0)		14 (22.0)		2 (2.2)	
	G3	10 (9.2)		37 (34.7)		19 (15.4)	
Her2/neu <sup>a</sup>	Overexpressed	2 (3.8)	0.995	8 (27.9)	0.671	2 (3.4)	0.618
	Not overexpressed	9 (7.9)		31 (26.7)		12 (9.3)	
Ki-67 <sup>a</sup>	<20%	4 (5.2)	0.689	10 (14.2)	0.062	2 (2.5)	0.043
	≥20%	13 (9.4)		44 (33.7)		19 (12.1)	
		13 (9.4)		35 (24.0)		11 (8.3)	
Vascular invasion <sup>a</sup>	Absent	13 (9.4)	0.627	35 (24.0)	0.029	11 (8.3)	0.285
	Present	2 (5.3)		8 (22.2)		6 (13.6)	
	Extensive	3 (7.3)		14 (52.3)		5 (8.5)	

Cumulative incidences for local events were computed in a competing risk framework and compared by the Gray test. Cumulative incidences for first events and deaths were compared by the log-rank test.

<sup>a</sup> Information is not available for some patients.

<sup>b</sup> ≥4 vs. <4.

<sup>c</sup> G3 vs. G1–G2.

follow up. The 5- and 10-year cumulative incidence of local events were 8.2% and 12.3% respectively (Fig. 1). The univariate analysis, as shown in Table 3, did not identify any variables affecting local disease-free survival. Absence of ER, poor differentiation and high proliferation index were associated with significantly ( $p < 0.05$ ) worse overall survival, whereas nodal status was not.

## Discussion

Breast cancer in very young patients represents a rare but increasing clinical scenario.<sup>7</sup> This condition is emotionally demanding and sometimes leads to a more aggressive and possibly unnecessary radical approach.

It is well known that the younger the age the higher the risk of developing local relapse after breast conservation.<sup>2,3</sup> Therefore some authors are more prone to recommend mastectomy<sup>4</sup> in this cohort of patients.

This is a large and recent series, collected in a single center with a strict definition (<35 years) in which 201 patients received breast conservation followed by whole breast irradiation. The most important finding of this study is that the cumulative incidence of IBTR after conservative surgery appears to be acceptable (12.3% at 10 years). In our opinion, these data do not justify recommending mastectomy in very young patients solely for the risk of a local reappearance of the tumor. In our institute the choice of type of surgery in very young patients is not dependent on age. The recommendation on type of surgery is given according to the tumor/breast ratio and to the expected cosmetic outcome exactly as it happens in older premenopausal or postmenopausal patients. On the other hand, it must be underlined that patients need to be carefully investigated and selected for breast conservation. In this series all patients underwent mammography and breast ultrasound. Magnetic resonance imaging (MRI) was not routinely performed and it was recommended only in a small minority of patients when clinically requested.

Diagnosis of breast cancer in very young patients raises the suspicion of BRCA mutation. In our series 11.7% of the patients had a first-degree family history for breast cancer, which is consistent with previous reports.<sup>8</sup> At the moment, in our institute all patients under 35 years of age who are diagnosed with breast cancer are offered the opportunity to undergo genetic consultation.

The small number of local events might have limited the statistical analysis but in this series no prognostic factors for worse local control could be identified suggesting that further studies are warranted to improve our knowledge on this issue.

Staging and biology of tumors reported in this cohort are quite similar to the paper by Zhou et al. Despite this, an important difference has to be underlined: 67% underwent one or more re-excision in the Boston experience, whereas none of our patients was re-excised. This is probably due to a different surgical approach strategy. We usually perform a wider conservative surgery than lumpectomy which is the standard of care in the U.S. as the Milan 2 trial<sup>9</sup> demonstrated that wide local excision or quadrantectomy achieved a statistically significant better local control than a limited conservative procedure such as lumpectomy.

In conclusion, a wide conservative surgery achieves a good local control in very young patients (<35 years). No prognostic factors were associated with local events in this population.

## Conflict of interest statement

None declared.

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