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Original article

Conservative surgery with and without radiotherapy in elderly patients with early-stage breast cancer: A prospective randomised multicentre trial

C. Tinterri [a,*], W. Gatzemeier [a], V. Zanini [b], L. Regolo [b], C. Pedrazzoli [g], E. Rondini [g], C. Amanti [h], G. Gentile [k], M. Taffurelli [j], P. Fenaroli [e], C. Tondini [e], G. Sacchetto [d], P. Sismondi [l], R. Murgo [i], M. Orlandi [m], E. Cianchetti [f], C. Andreoli [c]

[a] Breast Unit, Istituto Clinico Humanitas, via Manzoni 56, 20089 Rozzano, Milano, Italy
[b] Division of Surgery and Senology, The Maugeri Foundation, Pavia, Italy
[c] Italian School of Senology, Milan, Italy
[d] Division of Surgery, General Hospital Alba, Italy
[e] Division of Surgery and Senology, General Hospital Bergamo, Italy
[f] Division of Senology, General Hospital Ortona, Italy
[g] Division of Surgery, Arcispedale Santa Maria Nuova Reggio Emilia, Italy
[h] Division of Surgical Science and Medical Technology, University La Sapienza, Roma, Italy
[i] Division of Surgery, Casa Sollievo della Sofferenza Hospital, S. Giovanni Rotondo, Italy
[j] Division of Surgery, S. Orsola Malpighi Hospital, Bologna, Italy
[k] Division of Surgery, S. Maria della Misericordia Hospital, Udine, Italy
[l] Division of Gynaecology, Cancer Research Centre Torino, Turin, Italy
[m] Division of Gynaecology, General Hospital Cirié, Italy

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ABSTRACT

Breast conserving therapy (BCT) including postoperative irradiation of the remaining breast tissue is generally accepted as the best treatment for the majority of patients with early-stage breast cancer. The question is whether there is a necessity for irradiating all patients. Between 2001 and 2005, 749 women aged 55–75 years with infiltrating breast carcinoma were randomly assigned to breast conservative surgery, with or without radiotherapy (RT), to evaluate the incidence of in-breast recurrence (IBR).

After 5 years of median follow-up, the cumulative incidence of IBR was 2.5% in the surgery-only arm and 0.7% in the surgery plus RT arm. There are no differences in terms of overall survival and distant disease-free survival. The preliminary evaluation suggests that breast irradiation after conservative surgery can be avoided without exposing these patients to an increased risk of distant-disease recurrence. Prolonged follow-up will further clarify the possible risks and late sequelae potentially induced by breast RT.

In the Western world, breast conserving therapy (BCT) is recommended as the standard treatment for most of those patients with early-stage breast cancer.[1]

Postoperative irradiation of the remaining breast tissue represents an integral part of BCT to decrease the risk of local recurrences. Nevertheless, the question as to whether postoperative radiotherapy (RT) is necessary for all patients to improve local control when conservative surgery is performed is still a matter of debate. Results of randomised trials comparing BCT with and without radiation therapy, in fact, showed a significant increase of ipsilateral breast tumour recurrence in the non-irradiated group. The rate at 5 years was between 2% and 20% with irradiation and between 27% and 42% without irradiation.[2–7] However, none of the studies have demonstrated a statistically significant difference in the overall survival between the two treatment groups. Furthermore, until now, none of the trials were able to define a uniform and reliable risk factor profile to determine a group of patients at 'low risk' for local recurrence in whom radiation therapy could be avoided.

The Milan randomised trials explored all the main approaches of locoregional control of breast cancer.[8,9] The Milan III was a randomised study comparing quadrantectomy, axillary dissection and radiotherapy (QUART) and quadrantectomy and axillary dissection without radiotherapy (QUAD).

After 12 years' medium-term follow-up, the following results were observed: there was no difference between the two treatment arms in terms of overall survival.

* Corresponding author. Breast Unit, Istituto Clinico Humanitas, via Manzoni 56, 20089 Rozzano, Milano, Italy.

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Patients treated with surgery alone experienced a significantly higher incidence of local relapse compared with the group which received postoperative RT (21.6% vs. 5.4%). However, stratified by age, it could be noticed that in patients over 55 years, the local relapse rate was markedly lower than in patients of younger age. Furthermore, patients older than 65 years showed a similar incidence of local relapse independently of whether they received RT or not. Consequently, a conclusion drawn from these results was that age probably represents an important risk factor for local relapse.

These findings taken together with several specific histopathological features of the tumour, which were also associated with a higher frequency of local recurrence in the Milan III and the trials mentioned above, formed the basis for the rationale of a new study, which is described in detail below.

Patients and methods

From January 2001 to December 2005, 749 patients with early breast cancer from 11 centres in Italy were randomly assigned to the RT arm (homogeneous breast irradiation 50 Gy + 10 boost) or the control arm. The study was approved by the Ethical Committee of the Maugeri Foundation (IRCCS). The main characteristics of the patients and tumours were fairly well balanced between the treatment groups, and treatment allocation was centralised and stratified per site; 373 patients were randomised to quadrantectomy, sentinel node biopsy/axillary dissection and RT and 376 to quadrantectomy, sentinel node biopsy/axillary dissection without RT. The main characteristics of the patients are reported in Table 1. In all the patients the surgical margins were clean.

Table 1
Baseline characteristics (intent-to-treat groups).

	Surgery only		Surgery + irradiation	
	$N = 376$		$N = 373$	
	N	%	*N*	%
Age (years)				
≤65	186	49.5	202	54.2
>65	190	50.5	171	87.7
pT				
pT1	322	85.6	327	45.8
pT2	45	12.0	39	10.4
Not reported	9	2.4	7	1.9
Histology				
Ductal infiltrating	273	72.6	279	74.8
Lobular infiltrating	57	15.2	53	14.2
Ductal plus lobular	10	2.6	6	1.6
Infiltrating	36	9.6	35	9.4
Axillary nodes				
Negative	305	81.1	314	84.2
Positive	60	16.0	51	13.7
Not reported	11	2.9	8	2.1
Oestrogen receptors				
Positive	330	87.8	328	87.9
Negative	32	8.5	36	9.7
Not assessed	14	3.7	9	2.4
Progesterone receptors				
Positive	280	74.5	282	75.6
Negative	82	21.8	82	22.0
Not assessed	14	3.7	9	2.4

Patients fulfilling the inclusion criteria and having signed the informed consent form were randomised between surgeries with or without complementary breast irradiation.

A total of 22 of the 376 patients (5.9%) allocated to surgery only were delivered breast irradiation and 27 of 373 women (7.2%) allocated to surgery followed by irradiation failed to receive postoperative RT.

Study design and eligibility of patients

The RT 55–75 trial represents a randomised controlled clinical trial to assess the role of radical breast irradiation in post-menopausal women with early breast cancer undergoing conserving surgery (Fig. 1). The main eligibility criteria included age 55–75 years, monofocal invasive carcinoma of the breast less than 2.5 cm in largest diameter at the histological evaluation, absence of extensive intraductal component and vascular invasion-like component of primary tumour and absence of multicentricity. Patients were eligible regardless of the status of hormonal receptors and tumour grading. Exclusion criteria included the presence of more than three involved axillary nodes, history of previous invasive cancer of any site and contraindications to irradiation.

The primary treatment

Surgery

Surgical treatment comprises the Veronesi quadrantectomy, which includes the 'en bloc removal' of the breast tumour, a radial healthy tissue around the lesion, the skin above and the underlying muscular fascia. According to the results of studies conducted by Holland on ductal cancer spread, in cases of lesions less than 1.5 cm in maximum diameter, a more conservative resection is performed. Tumour size, histological type and section edges were evaluated. Specimen X-rays were performed to confirm the presence and the eccentricity of non-palpable lesions. Frozen sections can be avoided if malignancy has been proven preoperatively with a cytological examination. In clinically negative axillary lymph nodes, sentinel node biopsies were performed, which were followed by a complete axillary dissection of the three levels, only in cases of metastatic involvement of the sentinel node. In clinically positive nodes, total axillary dissections encompassing levels I–III were immediately carried out.

Radiotherapy

The residual breasts were irradiated by opposite tangential fields. Use of high-energy radiation sources is mandatory (X photons of 4–6 MV linear accelerator). The application of wedge filters as compensation is suggested. A whole dose of 50 gray (Gy) was delivered in 2 Gy fractions per day (five fractions per week). At the end of this treatment, a boost of 10 Gy (electron field) was applied on the tumour bed (2 Gy per day per five fractions). RT technique (target volume, dose delivered, set-up and simulation) references are reported by the Standard Radiotherapy Treatment of Early Breast Cancer (AIRO, 1997).[10]

Adjuvant treatment

Patients received adjuvant treatment according to axillary nodal status and biological tumour parameters.

End points

The primary end point was the cumulative incidence of IBR (to include both local recurrence and second primary in the ipsilateral breast), defined as the time elapsed from the date of randomisation to the documented occurrence of the event.

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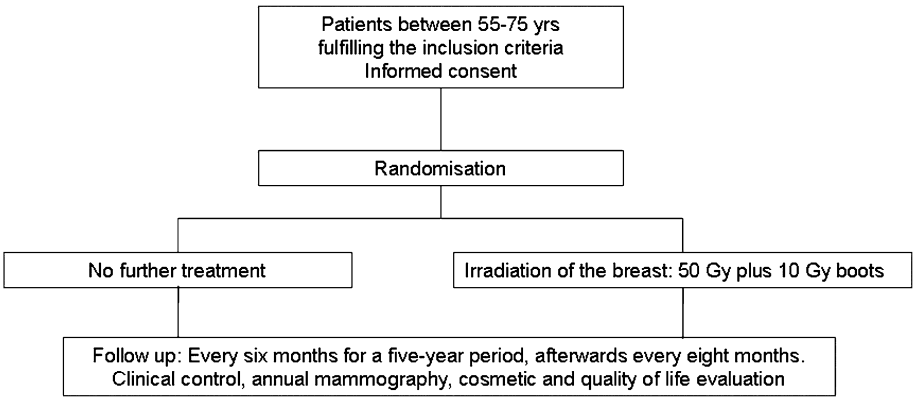

Fig. 1. Study design.

Secondary end points were distant disease-free survival (to include contralateral breast cancer, distant relapses, second primary cancer other than breast and death in the absence of any cancer) and overall survival (all causes of death).

Furthermore, advantages accessible to patients and the National Health Care (NHC) in avoiding postoperative RT were taken into consideration:

- More widespread distribution of BCT, in particular, in areas where radiotherapeutic treatment is not available, thereby avoiding unnecessary mastectomies,
- Avoiding side effects of RT,
- Rationalisation of RT division workload,
- Improvement of cosmetic results,
- Facilitating breast reconstruction in case of local relapse in the non-irradiated breast,
- Psychological advantages for the patient and
- Cost reduction for the NHC, the patients and society.

Treatment of local relapse

The treatment of relapse is performed by taking the following parameters into consideration.

- The location of local relapse,
- Type of lesion (nodular or lymphangitis) and
- Residual and contralateral breast volume.

If possible, a second conservative surgical operation is proposed to the patients. In cases of local relapse appearing in patients who were treated with surgery alone, conventional RT after second surgery is performed. If mastectomy cannot be avoided, immediate breast reconstruction is suggested to the patients. In patients who have had a sentinel node biopsy performed as the first treatment, complete axillary dissection is carried out. The adjuvant therapy takes into consideration the previous oncological treatment performed.

Follow-up

Periodical check-up: Patients were invited to return every 6 months during the following 5 years and subsequently every 8 months.

Clinical examination: Local control of the operated breast, regional lymph nodes and contralateral breast was performed by the physicians.

Annual X-ray mammography plus breast ultrasound control were performed where necessary.

The following unfavourable events were recorded:

- Local relapse,
- Second primary tumour (in the same breast),
- Contralateral breast tumour and
- Distant metastases.

Statistical analysis

All randomly assigned patients were included in efficacy analyses, which were conducted on an intention-to-treat basis.

All time events were computed from the date of randomisation and Kaplan–Meyer curves were used to estimate rates of events and their standard deviations (SDs). Cumulative incidence of IBRT was estimated as described by Marubini and Valsecchi.[11]

Due to the limited number of the primary end-point event (IBR), multivariate analyses of treatment effects in different patient subsets were deemed inappropriate.

Results

After a median follow-up of 53 months (lead 83 months), a total of 10 IBRs were documented, eight in the surgery-only group and two in the surgery plus irradiation arm. The 5-year cumulative risk of IBR is displayed in Fig. 2. The hazard ratio for the risk of events in the surgery-only group was 4.01 (95% confidence interval (CI): 0.85–18.89) and it failed to reach conventional statistical significance ($P = 0.07$). The site of local re-appearances is concentrated in the resection area, both in the patients treated with surgery alone and in patients treated with surgery plus RT.

Table 2 reports the actuarial risk of IBR in the two treatment groups, according to the main patient and tumour characteristics. In both the study arms, low risk rates were documented in small tumours and in oestrogen receptor-positive tumours.

Distant disease-free survival and overall survival (Figs. 3 and 4) were superimposable in both treatment groups. The 5-year probabilities of distant disease-free survival were $96.5\% \pm 1$ in the surgery-only group and $95\% \pm 1$ in the surgery plus irradiation arm. Distant events included contralateral breast cancer (two patients in each treatment group), distant disease relapse (nine and 11 patients), second primary cancer (three and nine patients) and death in the absence of cancer (three and four patients). The 5-year probability of overall survival was $96\% \pm 1$ in the surgery-only arm and $95\% \pm 1$ in the surgery plus irradiation group.

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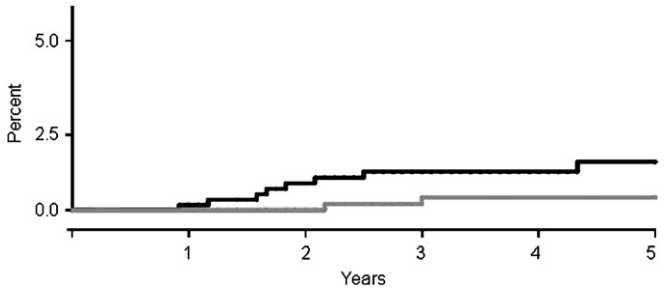

Fig. 2. Five-year cumulative incidence of in-breast recurrence. Key: black curve = surgery only; gray curve = surgery plus irradiation.

Discussion

In fairness, the origin of this study can be referred to a real dialogue between one surgeon of our group and a patient aged 72, just operated on with BCS, and who was told in detail about postoperative RT. Uncommonly enough, it has been the patient who took the lead in the conversation and who forced the doctor to think long and hard on how to find a solution to her problems: She lived in a small village on the mountains. There was only one bus a day to the city (and the nearest RT facility). She had neither money for a daily taxi for 6 weeks, nor did she have a son or a daughter who could bring her daily to have the treatment. It was winter season and, consequently, icy roads and fog… Conclusion: "To me, it is very clear that this treatment, in my specific situation, is overall more dangerous than the possible local recurrence.[12] So, sorry, but I will not do it." What should we answer to such a question?

Certainly not the simple and plain cancellation of postoperative RT after BCS, since the question was already answered by the Milan II study and several others, in which the local recurrence rate in the non-RT group was shown to be exceedingly higher. Could the answer be in looking for one or more subgroups of patients who could avoid RT? The key issue here is, according to us, that most if not all the studies proving the efficacy of postoperative RT are quite old and were designed before the advent of modern prognostic and predictive parameters. The recent publication of the Danish Breast Cancer cooperative Group (DBCG) makes excellent data available to the medical community but related to cases treated between 1977 and 2001[13] and, not surprisingly, including 23% of patients who received tamoxifen in addition to surgery, 23% chemotherapy and 35% RT. It is impossible to make any in-depth correlation and

Table 2
Cumulative incidence of IBR according to baseline characteristics.

	Surgery only			Surgery + irradiation		
	N	%	95% CI	*N*	%	95% CI
Total	8	2.5	0.7–4.4	2	0.7	0–1.7
Age						
≤65 years	3	1.7	0–3.5	2	1.3	(0–3.0)
>65 years	5	3.5	0.4–6.7	0	–	
pT						
pT1	6	2.2	0.4–4.1	1	0.5	0–1.3
pT2	2	5.4	0–12.7	1	2.4	0.8.6
pN						
Negative	7	2.8	0.7–4.9	2	0.8	0–2.0
Positive	1	2.0	0–6.0	0	–	
ER						
Positive	5	1.2	0.2–3.7	2	0.8	0–1.9
Negative	3	10.0	0–21.0	0	–	

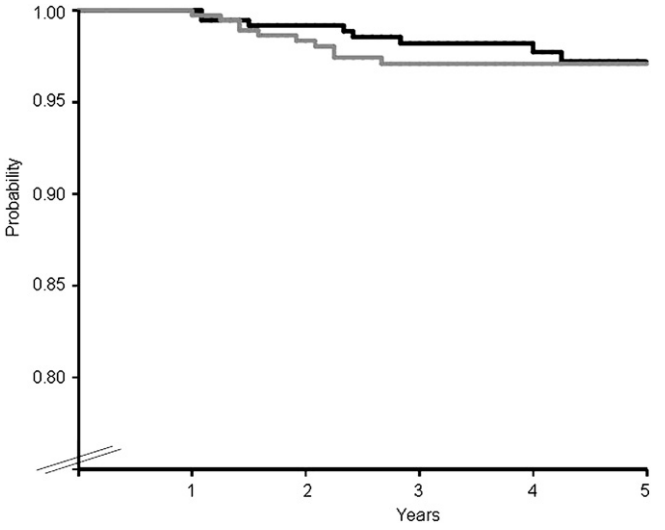

Fig. 3. Five-year probability of distant disease-free survival. Key: black curve = surgery only; gray curve = surgery plus irradiation.

analysis, however, with hormone receptor status, with grading, vascular invasion, proliferation index and, of course, HER2 expression. It seems extremely difficult to address these very complex and controversial issues, forgetting about the approach of the1970s – when post-BCS RT was conceived – which was essentially aimed at the physical destruction of the malignant cell, way before all the contemporary knowledge about biological concepts such as 'hormone responsiveness', 'receptor modulation' and apoptosis. Studies are more recently making the effort of trying to differentiate patients at least in high and low risk, particularly when comparing different technological approaches.[14,15]

Unfortunately, we have no hesitation to admit that our study looks now old from this point of view, because we have chosen age as a factor to define the level of risk, assuming that the risk of local relapse should be lower in the elderly patient, where there is still a lot to be understood about the management of early-stage breast cancer in elderly women.[16] Much additional evidence to support clinical practice in the elderly patient with breast cancer is still needed and physicians should encourage enrollment of these patients in clinical trials.[17,18] One should differentiate among the

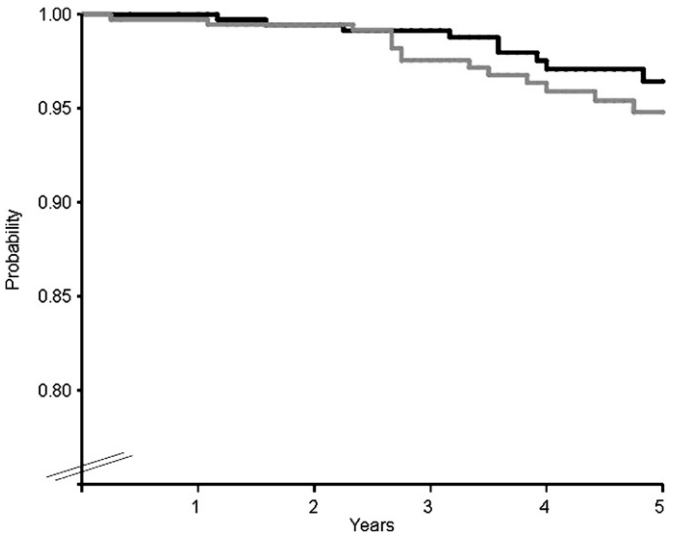

Fig. 4. Five-year probability of overall survival. Key: black curve = surgery only; gray curve = surgery plus irradiation.

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different issues, that is, age of the patient, biological profile of the disease and socioeconomic factors, although age and socioeconomic factors are often closely inter-related, since elderly patients may more frequently experience serious difficulties in having access to full and proper treatment. New approaches aiming at reducing the burden of after BCS RT are welcome in general, and of course, particularly for the elderly, such as a lower total dose in a smaller number of fractions,[19] or partial breast irradiation using high-dose-rate (HDR) implants to deliver radiation to the tumour bed alone.[20] Biological characteristics of the tumour are the other issue, since there is no doubt anymore that a 0.5-cm tubular carcinoma, G1, ER+ (90%) PgR+ (90%), Ki67 5%, non-vascular invasion, sentinel node negative, HER2 negative is a completely different disease from a 2.5-cm ductal carcinoma, G3, ER and PgR negative, Ki67 35%, vascular invasion, four metastatic lymph nodes and HER2+++. What we need to understand now is whether there is a difference in the need for postoperative RT in these two opposite extreme cases and in all those in between, adjusting for the age factor: some studies seem to confirm that RT is still needed to ensure a significant reduction in local and overall relapse even in women with favourable early breast cancer, simultaneously treated with tamoxifen/anastrazole.[21] Some others suggest that RT after BCS may not be a cost-effective treatment unless it results in a recurrent rate that is at least 5% lower in absolute terms than those treated without RT.[22] The study presented here wishes to contribute to the debate on this very important issue. Too many mastectomies are still performed in elderly patients 'only' because they cannot afford (in the broadest possible sense) post-operative RT. Too many social and psychological costs are paid to the dogma of post-breast-conserving surgery RT not to see the urgent need for innovative and more flexible solutions.

Conflict of interest statement

None declared.

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