Ann Surg Oncol
DOI 10.1245/s10434-013-3233-x

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

Breast-Conservative Surgery With and Without Radiotherapy in Patients Aged 55–75 Years With Early-Stage Breast Cancer: A Prospective, Randomized, Multicenter Trial Analysis After 108 Months of Median Follow-up

C. Tinterri, MD[1], W. Gatzemeier, MD[1], A. Costa, MD[2], M. A. Gentilini, PhD[3], V. Zanini, MD[4], L. Regolo, MD[4], C. Pedrazzoli, MD[5], E. Rondini, MD[5], C. Amanti, MD[6], G. Gentile, MD[7], M. Taffurelli, MD[8], P. Fenaroli, MD[9], C. Tondini, MD[9], G. Sacchetto, MD[10], P. Sismondi, MD[11], R. Murgo, MD[12], M. Orlandi, MD[13], E. Cianchetti, MD[14], and C. Andreoli, MD[1]

[1]Breast Unit, Istituto Clinico Humanitas, Rozzano, Milan, Italy; [2]European School of Oncology, Milan, Italy; [3]Center of Epidemiology and Clinical Evaluation, Trento, Italy; [4]Division of Surgery and Senology, The Maugeri Foundation, Pavia, Italy; [5]Division of Surgery, Arcispedale Santa Maria Nuova, Reggio Emilia, Italy; [6]Division of Surgery and Medical Technology, Sant' Andrea Hospital, Rome, Italy; [7]Division of Surgery, S. Maria della Misericordia Hospital, Udine, Italy; [8]Division of Surgery, S. Orsola Malpighi Hospital, Bologna, Italy; [9]Breast Unit, Ospedali Riuniti, Bergamo, Italy; [10]Division of Surgery, General Hospital Alba, Alba, Italy; [11]Division of Gynaecology, Cancer Research Centre Torino, Turin, Italy; [12]Breast Unit, Casa Sollievo della Sofferenza Hospital, San Giovanni Rotondo, Italy; [13]Division of Gynaecology, General Hospital Cirié, Cirié, Italy; [14]Breast Unit, G. Bernabeo Hospital, Ortona, Italy

ABSTRACT

Objectives. Breast-conserving therapy (BCT), including postoperative whole breast irradiation (WBI), is generally accepted as the treatment of choice for most patients with early-stage breast cancer. The question whether WBI is mandatory in all patients remains one of the most controversial issues in BCT. To answer this question, a randomized, prospective, multicentre study was launched in January 2001. Primary endpoints of the study were to assess the cumulative incidence of in-breast-recurrences (IBR) and overall survival (OAS) after conservative surgery (BCS) with or without WBI.

Methods. From January 2001 until December 2005, 749 patients with unifocal infiltrating breast cancer up to 25 mm, 0–3 positive axillary lymph nodes, no extensive intraductal component or lymphvascular invasion from 11 centres in Italy, were randomly assigned to BCS+WBI (arm 1:373 patients) or BCS alone (arm 2:376 patients). Treatment arms were well balanced in terms of baseline characteristics. Systemic adjuvant therapy was administered according to the institutional policies. Kaplan–Meier method was used for survival analysis and log-rank test to evaluate the difference between the two arms.

Results (Last Analysis 31.12.2012). After median follow-up of 108 months, 12 (3.4 %) IBR were observed in arm 1 and 16 (4.4 %) in arm 2. OAS was 81.4 % in arm 1 and 83.7 % in arm 2. There was no statistically significant difference regarding IBR and death in the two treatment groups.

Conclusions. These data are promising and suggest that WBI after BCS can be omitted in selected patients with early stage breast cancer without exposing them to an increased risk of local recurrence and death. Longer follow-up is needed to further consolidate these results.

Conservative management of breast cancer has become the routine method of choice. In prospective, randomized, clinical trials, breast-conserving therapy (BCT) for early-stage breast cancer has been proven to be as equally effective as mastectomy (MX) regarding local control, distant disease, disease-free, and overall survival (OAS).[1,2] This led the Consensus Development Conference of the National Cancer Institute of the United States on the treatment of early-stage breast cancer, to conclude in 1990

First Received: 15 April 2013

W. Gatzemeier, MD
e-mail: wolfgang.gatzemeier@humanitas.it

Published online: 02 October 2013

that BCT is an appropriate method of primary treatment for the majority of women with stage I and II breast cancer. It was deemed preferable, because it provides local control and survival rates equivalent to those of MX while preserving the breast with advantages of cosmetic appearance and quality of life (QOL).[3]

With these recommendations, WBI represents an integral component of BCT to control subclinical disease and hence to decrease local recurrence rate. However, from retrospective observations, it is well known that a high percentage of patients treated with BCT without WBI remain free of local recurrence even after long-term follow-up. For such patients, radiotherapy would represent "overtreatment".

Results of randomized trials comparing BCT with and without radiation therapy showed a significant increase of ipsilateral breast tumor recurrence in the nonirradiated group. The rate at 5 years was between 2 and 20 % with irradiation and between 27 and 42 % without irradiation.[4–8] Improvement in local control ranged from 10 to 36 % with the application of radiation therapy, but none of the studies has demonstrated a statistically significant difference in OAS between the treatment groups. Nevertheless, these results suggest that almost half of patients may have been overtreated with the application of radiotherapy. Unfortunately, so far none of the trials—older and more recent ones—dealing with the topic was able to define a uniform and reliable risk factor profile that would enable one to determine a group of patients at low risk for local recurrence in whom radiation therapy could be safely omitted.[4–12]

RATIONALE OF THE STUDY RT 55–75

For the reasons mentioned above, the role of radiation in BCT is still heavily debated. Important motivations to answer the question regarding which patients could forgo WBI within the context of BCT are as follows:

The most significant benefit would be a more widespread distribution of BCT, in particular, in areas where radiotherapy is not available, thereby avoiding unnecessary mastectomies. Additional important aspects in this context are the avoidance of inconvenience and risk of side-effects of radiation treatment, resulting in an improvement of QOL for the patient. A further point to mention is the treatment of IBR. Because MX is still considered the treatment of first choice in patients with ipsilateral breast tumor recurrence after BCS and WBI, it must be taken into consideration that reconstruction with prosthesis is connected with a higher rate of complications if WBI is applied. Finally, rationalization of workload in radiotherapy divisions and cost reduction for the NHC, the patients, and society would ensue.

In this context, the Milan Cancer Center randomized trials explored all the main approaches of locoregional control of breast cancer.[5,13–16] In line with the concept of tailored treatment in breast cancer management, the challenge of the Milan Cancer Center Conservation Program is to offer as individualized a treatment as possible to patients according to the different clinical and biological features of both patient and disease, hence the minimum treatment required for adequate control without compromising the therapeutic effect.[16] The Milan III was a randomized study comparing quadrantectomy axillary dissection and radiotherapy (QUART) and quadrantectomy and axillary dissection without radiotherapy (QUAD).[15]

After 10 years medium follow-up, the following results were observed. There was no difference between the two treatment arms in terms of OAS. Patients treated with surgery alone experienced a significantly higher incidence of local relapse compared with the group that received postoperative radiotherapy (23.5 vs. 5.8 %). An interesting result of the study refers to the association between IBR incidence and patients' age. In patients not treated with radiotherapy and younger than age 45 years a high IBR rate (7.4 × 100 women-years of observation) was observed, whereas the rate was more than halved in women from age 46–55 years (3.1) and was even lower in women aged between 56 and 65 years (1.7). In women older than age 65 years, the difference between the two treatment arms disappeared completely.[15] In addition, the EIC appeared to be an important risk factor for IBR in patients not treated with postoperative radiotherapy, whereas in patients who received WBI, no increased risk due to the presence of EIC component was evident.[15] These findings taken together formed the basis for the rationale of the study presented.

STUDY DESIGN AND ELIGIBILITY OF PATIENTS

The RT 55–75 trial represents a randomized, controlled, clinical trial to assess the role of WBI in postmenopausal women with early breast cancer undergoing conserving surgery. The main eligibility criteria included: age 55–75 years, unifocal invasive carcinoma of the breast <2.5 cm in largest diameter at the histological evaluation, and absence of EIC and LVI. Patients were eligible regardless of the status of hormonal receptors and tumor grading. Exclusion criteria were the presence of histologically positive margins, EIC, LVI, more than three involved axillary lymph nodes, history of previous invasive cancer of any site, and contraindications to irradiation.

PATIENTS AND METHODS

From January 2001 to December 2005, 749 postmenopausal patients from 11 centers in Italy were randomly assigned to BCS+WBI (arm 1:373 patients) or BCS alone

(arm 2:376 patients). The study was approved by the Ethical Committee of the Maugeri Foundation (IRCCS). All patients signed informed consent before randomization.

Patients' Accrual, Registration, Randomization, and Stratification

Participating centers were required to send a request for recruitment to the data center. Information of patients eligible for the study was scheduled and recorded on a personal computerized form containing: *Personal data:* (a) age, menopausal status; (b) tumor characteristics (site, dimension); (c) staging procedures lung X-ray, bone scan, liver ultrasound; (d) *Histological and biological evaluation results:* tumor size, grading, histologic type, intraductal component, vascular and/or lymphatic invasion, receptor status, Ki-67 status.

All eligible patients were entered into the study. No patient was excluded before randomization.

The randomization and stratification procedure was centralized and managed entirely online. For each center, an autonomous randomization list was in place and treatment allocation was stratified per site according to the above-mentioned variables. All data were collected in a single database, and the procedures for adding and updating of information were subject to numerous interactive controls to ensure a high quality standard and consistency.

The main patient and tumor characteristics were fairly well balanced between the treatment groups (Table 1). The Chi square test did not show any statistically significant difference in the two arms for each single variable.

Because the lost to follow-up rate during the study was higher than expected (approximately 8 %), the accrual target was increased to 750. At last data analysis, 67 patients were lost to follow-up: 38 (10.2 %) in arm 1 and 29 (7.7 %) in arm 2. The main reason was noncompliance of the patients (Structure 1).

Primary Treatment

Surgery All patients underwent complete wide resection of the breast tumor (in contrast to the traditional quadrantectomy, where 2–3 cm of normal tissue surrounding the tumor, the overlying skin and of the underlying fascia had to be excised,[16] a modified quadrantectomy with margins of 1 cm of healthy-appearing tissue in all directions around the lesion, a small rim of the overlying skin and of the underlying fascia was mandatory). The specimen was inked and a gross margin evaluation was conducted intraoperatively together with the pathologist. If the gross margin was less than 1 cm, re-resection was performed. Tumor size and margin status were evaluated microscopically at definitive histology according to standard procedures. All margins had to be proven histologically negative. Microscopic margin width was not recorded. In clinically negative axillary lymph nodes, a sentinel node biopsy was performed followed by an axillary dissection only in cases of metastatic involvement. In clinically positive nodes, an axillary lymph node dissection was performed immediately.

Radiotherapy Radiation treatment was administered by opposite tangential fields. Use of high-energy radiation sources was 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 (5 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 5 fractions). Radiotherapy was administered and recorded (target volume, dose delivered, set-up, simulation) according to the standard radiotherapy treatment of early breast cancer AIRO 1997 recommendations.[17] Hypofractionation technique was not permitted.

Adjuvant Treatment Systemic adjuvant therapy was administered in accordance with institutional policies or at the discretion of the treating physician.

Follow-up Patients were invited to return every 6 months during the following 5 years and subsequently every 8 months. Clinical examination, annual X-ray mammography, plus breast ultrasound control were performed where necessary.

The following study endpoints were recorded: invasive and in situ local recurrence, second primary tumor (in the same breast), contralateral breast tumor, 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 randomization, the Kaplan–Meier method was used for survival analysis with 95 % confidence interval, and the log rank test (alpha = 0.05) was employed to evaluate the difference between the two arms. The R 2.13.1 software was used for statistical analysis.

From previous studies on BCS+WBI with similar patient inclusion criteria, the local recurrence-free survival had been calculated to be approximately 97 % at 5 years after treatment. In patients treated with BCS alone, the relative risk of LR should not show a 2.5-fold increase in comparison with patients receiving RT after BCS.

With α-error (two-sided) of 5 % and a power of 90 %, hypothesizing an accrual period of 3.5 years and a lost to

TABLE 1 Tumor and patients baseline characteristics

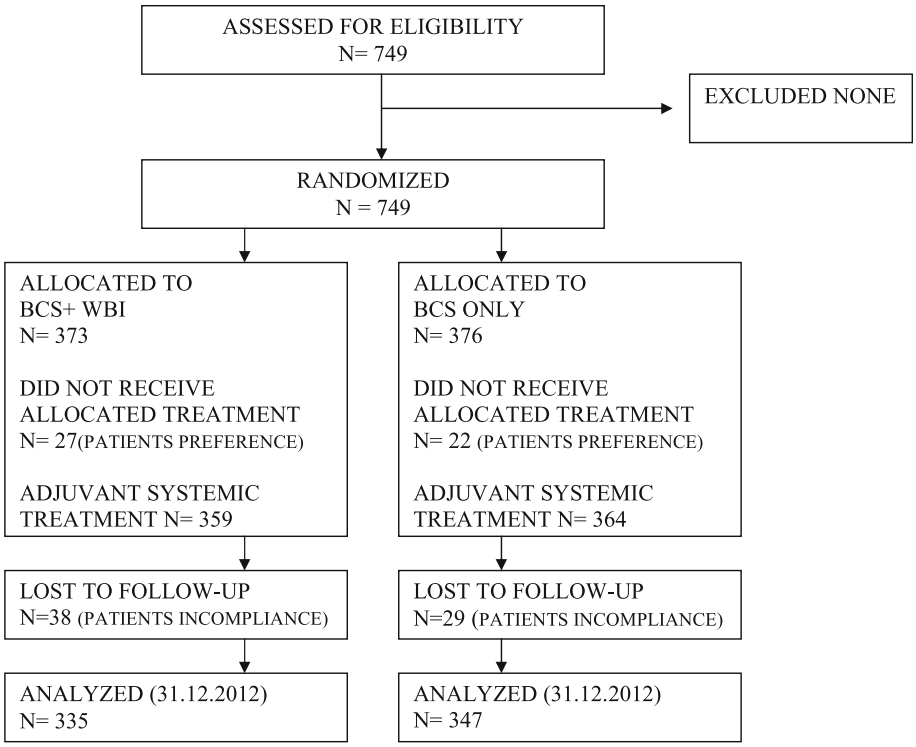
	BCT		BCT+WBI		*p* value (chi square test)
	N = 376		*N* = 373		
	N	%	*N*	%	
Age (year)					0.49
55–64	165	43.9	173	46.4	
65–75	211	56.1	200	53.6	
Tumor size (mm)					0.53
≤5	23	6.1	18	4.8	
6–10	117	31.1	109	29.2	
11–20	191	50.8	208	55.8	
21–25	45	12.0	38	10.2	
Lymph node status					0.54
Negative	305	81.1	314	84.2	
Positive (max 3 positive nodes)	61	16.2	51	13.7	
Not reported	10	2.7	8	2.1	
HR status					0.4
ER+ PgR+	290	77.1	297	79.6	
ER+ PgR−	59	15.7	46	12.3	
ER− PgR−	27	7.2	30	8	
Grading (Bloom–Richardson)					0.21
G1	103	27.4	102	27.3	
G2	233	62.0	220	59	
G3	32	8.5	47	12.6	
Unknown	8	2.1	4	1.1	
Ki67 (%)					0.98
0–10	231	61.4	233	62.5	
11–20	80	21.3	73	19.6	
21–30	31	8.2	33	8.8	
31–50	22	5.9	21	5.6	
51+	9	2.4	11	2.9	
Not reported	3	0.8	2	0.5	
Type of surgical procedure					0.81
Quadrantectomy only	2	0.5	1	0.3	
Quadrantectomy+SNB	248	66.0	249	66.8	
Quadrantectomy+SNB+AD	35	9.3	34	9.1	
Quadrantectomy+AD	91	24.2	89	23.9	
Adjuvant systemic treatment					0.83
No	12	3.2	14	3.8	
HT	309	82.2	300	80.4	
CHT	36	9.6	35	9.4	
CHT+HT	19	5.1	24	6.4	

HR hormone receptor, *ER* estrogen receptor, *PgR* progesterone receptor, *AD* axillary dissection, *HT* hormonal treatment, *CHT* chemotherapeutic treatment, *SNB* sentinel node biopsy

follow-up of ≤5 %, 700 were needed in this unilateral log-rank study. Due to a higher than expected lost to follow-up rate during the study (∼8 %), the accrual target was increased to 750. At the last data analysis, 67 patients were lost to follow-up, 38 (10.2 %) in arm 1 and 29 (7.7 %) in arm 2, mainly due to noncompliance.

Endpoints: The primary endpoint was the cumulative incidence of IBR (to include both local recurrence and

STRUCTURE 1 Consort diagram RT 55–75



second primary in the ipsilateral breast), defined as the time elapsed from the date of randomization to the documented occurrence of the event. Secondary endpoints were distant disease-free survival (DDFS) and OAS.

RESULTS

After a median follow-up of 108 months (last analysis 31.12.2012), the following events were documented (Table 2).

In-Breast Recurrence: (Total 28)

In the surgery+WBI arm (1), 12 IBRs were observed: 7 (1.98 %) in the index quadrant and 5 (1.41 %) in other quadrants. In the surgery-only arm (2), 16 IBR occurred: 7 (1.92 %) in the index quadrant and 9 (2.47 %) in other quadrants.

The cumulative incidence of IBR was 3.4 % in the surgery+WBI and 4.4 % in the surgery-only arm (Fig. 1). Six contralateral tumors (1.59 %) were documented in arm 1 and five (1.34 %) in arm 2, respectively.

Nodal Recurrence

No nodal recurrence was observed.

Contralateral New Primary: (Total 11)

In the surgery+WBI arm, six (1.61 %) contralateral breast cancers were observed and five (1.33 %) in the surgery-only arm, respectively.

Distant Disease Progression

Distant recurrences were observed in 26 patients (6.9 %) in arm 1 (liver 2, lung 4, bone 12, and multiple sites 8) and in 28 patients (7.53 %) in arm 2 (liver 3, lung 3 bone 11, and multiple sites 11).

TABLE 2 Type of disease progression

Treatment arm	Type of disease progression					Total
	No	Distant	Local (other quadrants)	Local (index quadrant)	Contralateral BC	
BCT+WBI (arm 1)	329 (88.20 %)	26 (6.97 %)	5 (1.34 %)	7 (1.88 %)	6 (1.61 %)	373
BCT alone (arm 2)	327 (86.97 %)	28 (7.45 %)	9 (2.39 %)	7 (1.86 %)	5 (1.33 %)	376
Total	656	54	14	14	11	749

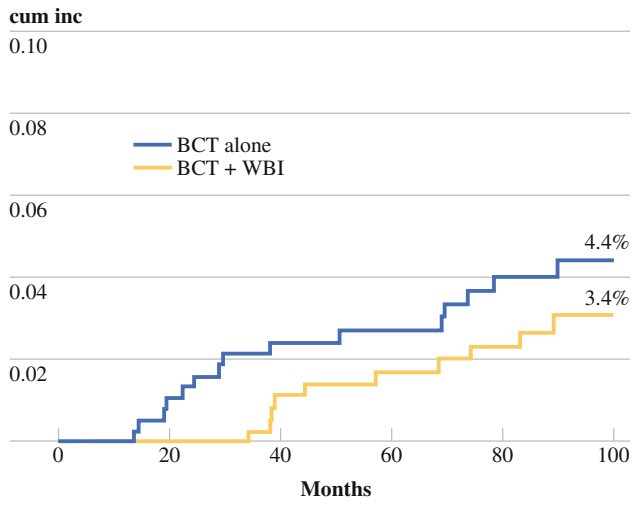


FIG. 1 Nine-year cumulative incidence of in-breast recurrence

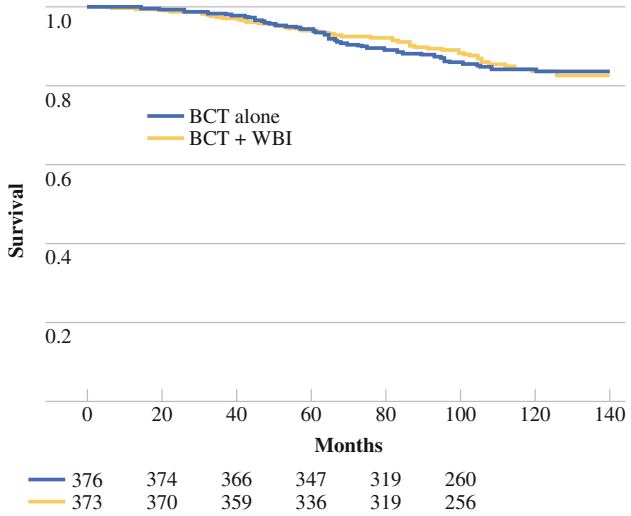


FIG. 2 Overall Survival (108 months)

Adjuvant treatment was administered to all patients in arm 1 (20 patients received hormonal therapy, 4 patients received chemotherapy, and 2 patients received a combined treatment). Of the 28 patients in arm 2, 24 patients received adjuvant therapy (16 patients received hormonal therapy, 6 patients received chemotherapy, and 2 patients received a combined treatment).

Median time to progression was 43.1 month in arm 1 and 41.9 month in arm 2. No significant statistical difference could be demonstrated in this regard between the two groups ($p = 0.8451$).

Overall Survival

Overall survival at 108 months was 81.4 % [95 % confidence interval (CI) 77.4–85.6] in arm 1 and 83.7 % (95 % CI 79.8–87.8) in arm 2, respectively (Fig. 2).

Distant Disease-Free Survival

DDFS was 86.9 % in arm 1 (95 % CI 83.3–90.6) and 85.5 % (95 % CI 81.9–89.3) in arm 2, respectively (Fig. 3).

Breast Cancer-Specific Deaths

Breast cancer-specific deaths occurred in 26 patients (6.9 %) in arm 1 and 29 patients (7.8 %) in arm 2.

Deaths from Other Malignant Diseases

Deaths from other malignant diseases occurred in eight patients (2.2 %) in arm 1 and four patients (1.1 %) in arm 2.

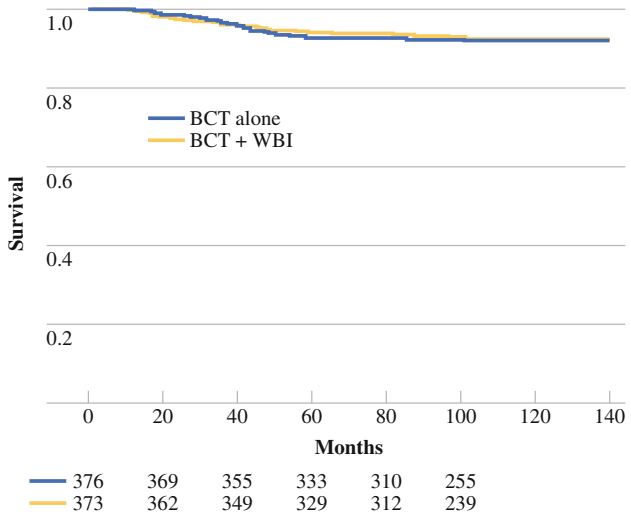


FIG. 3 Distant Disease Free Survival (108 months)

Deaths from Other Causes

Deaths from other causes were observed in 17 patients (4.51 %) arm 1 and 20 patients (5.4 %) in arm 2.

A total of 22 of the 376 patients (5.9 %) allocated to surgery only had breast irradiation administered, and 27 of 373 women (7.2 %) allocated to surgery followed by irradiation failed to receive postoperative RT. This crossover rate was mainly due to patient preference after randomization.

DISCUSSION

The question of whether WBI is necessary after BCS has been addressed in clinical trials since the 1980s. Those trials investigated the extent of the surgical procedure (quadrantectomy- wide excision- lumpectomy) with or without irradiation as well as clinical and biological factors to define a patient population where irradiation could be safely omitted.[4–15] Unfortunately, until now none of the trials was able to satisfactorily identify a group of patients with sufficiently low risk for IBR, appropriate to guide daily clinical practice to avoid irradiation.

The scientific and ideological background of the trial presented was based on results of the Milan Cancer Institute conservation program trials aiming to explore in greater depth the specific biological and clinical factors that might predict whether the application of WBI is of benefit in lowering the risk of IBR.[5, 13–16] The definition of inclusion criteria for the study presented was based in particular on observations and results of the Milan III trial,[15] e.g., age, known as an independent risk factor for IBR,[18] EIC, and LVI.

The study population presented is highly selected, homogeneous, and well-balanced between the treatment groups. More than 50 % of the patients were aged 65 years or older, 88 % had pT1 disease, and nodal status was pN0 in 85 %. Furthermore, ER-receptor status was positive in 92 % of the patients, grading was G1 or G2 in 87 %, Ki-67 was $\leq$20 % in 82 % of the patients, and the presence of EIC or LVI at histological evaluation represented an exclusion criteria.

All patients had complete wide resection of the primary tumor with at least 1 cm of healthy-appearing tissue in all directions around the lesion, a small rim of the overlying skin, and of the underlying fascia (modified quadrantectomy). Histopathologically proven negative margins were mandatory. Additional information on microscopic margin width was not recorded.

After 9 years of median follow-up, the rate of IBR was very low in both arms confirming the presumed low-risk profile of the study population for IBR. No significant statistical difference could be demonstrated in this regard and furthermore, no significant statistical difference was found regarding OAS and DDFS (Fig. 3) between the treatment groups.

Among the 28 IBRs, no predominant phenotype related to tumor size, histological type, node status, HR status, Ki67 levels, and grading could be identified. These results are in line with previous findings of the above-mentioned Milan Cancer Center III trial.[15]

An important factor to maintain local control seems to be the uniform surgical approach in all centers, hence a wide resection with gross margins of at least 1 cm around the tumor, a small rim of the overlying skin, and of the underlying fascia (modified quadrantectomy). Whether less surgery would result in the same local control cannot be extrapolated from the study results. Nonetheless, completion of WBI did not further improve local control significantly.

Endocrine treatment, which is related to the relative risk reduction as described in various publications,[19–23] seems to contribute to local as well as systemic control. In the study population, 92 % of patients were ER-receptor positive and the vast majority received hormonal treatment.

CONCLUSIONS

The study results may represent an aid for clinicians and patients in the complex decision-making process with regard to the appropriate indication for radiation therapy in postmenopausal patients with low risk for IBR after BCS, in order to minimize overtreatment. In addition, this information might offer a useful tool for patients who prefer to avoid WBI and otherwise would opt for MX—due to geographical reasons, physical fitness, psychological reasons, or costs.

Adequate treatment tailoring, in an era of rising health care costs will play an increasingly important role in the future as one takes into consideration an aging population and a rising incidence of breast cancer in elderly subjects. Last but not least, another important aspect of this trial is related to feasibility. Participating centers were located throughout Italy, encompassing community and university hospitals. The decision to propose a multicenter study was intended to obtain reproducible data in regard to Italian daily clinical practice of breast cancer treatment, as represented by these centers.

ACKNOWLEDGMENT The authors express gratitude to Pinuccia Valagussa, Statistical Centre National Cancer Institute, Milan, Italy, for her support in statistical analysis and data management and William Russell-Edu, Librarian, European Institute of Oncology, Milan, Italy for the final editing.

REFERENCES

1. Veronesi U, Saccozzi R, Del Vecchio M, Banfi A, Clemente C, De Lena M, Gallus G, Greco M, Luini A, Marubini E. Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast. *N Engl J Med.* 1981;305:6–11.
2. Fisher B, Bauer M, Margolese R, Poisson R, Pilch Y, Redmond C, Fisher E, Wolmark N, Deutsch M, Montague E. Five-year results of a randomized trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. *N Engl J Med.* 1985; 312:665–73.
3. NIH Consensus Conference. Treatment of early-stage breast cancer. *JAMA.* 1991;265:391–5.
4. Fisher B, Anderson S, Bryant J, Margolese R, Deutsch M, Fisher E, Jeong J, Wolmark N. Twenty-year follow-up of a randomized

trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med*. 2002;347:1233–41.
5. Veronesi U, Luini A, Galimberti V, Zurrida S. Conservation approaches for the management of stage I/II carcinoma of the breast: Milan Cancer Institute Trials. *World J Surg*. 1994;18: 70–5.
6. Clark RM, Whelan T, Levine M, et al. Randomized clinical trial of irradiation following lumpectomy and axillary dissection for node-negative breast cancer: an update. *J Natl Cancer Inst*. 1996;88:1659–64.
7. Forrest AP, Stewart HJ, Evering D, et al. Randomized controlled trial of conservation therapy for breast cancer: 6-year analysis of the Scottish trial. *Lancet.* 1996;348:708-13.
8. Liljegren G, Holmberg L, Bergh J, Lindgren A, Tabár L, Nordgren H, Adami HO and the Uppsala-Örebro Breast Cancer Study Group. 10-year results after sector resection with or without postoperative radiotherapy for stage I breast cancer: a randomized trial. *J Clin Oncol.* 1999;17:2326–33.
9. Winzer KJ, Sauerbrei W, Braun M, et al. Radiation therapy and tamoxifen after breast-conserving surgery: updated results of a 2×2 randomised clinical trial in patients with low risk of recurrence. *Eur J Cancer*. 2010;46:95–101.
10. Malmstrom P, Holmberg L, Anderson H, et al. Breast conservation surgery, with and without radiotherapy, in women with lymph node-negative breast cancer: a randomised clinical trial in a population with access to public mammography screening. *Eur J Cancer.* 2003;39:1690–7.
11. Schnitt SJ, Hayman J, Gelman R, et al. A prospective study of conservative surgery alone in the treatment of selected patients with stage I breast cancer. *Cancer.* 1996;77:1094–100.
12. Holli K, Saaristo R, Isola J, Joensuu H, Hakama M. Lumpectomy with or without postoperative radiotherapy for breast cancer with favourable prognostic features: results of a randomized study. *Br J Cancer*. 2001;84:164–9.
13. Veronesi U. Luini A. Del Vecchio M, et al. Radiotherapy after breast-preserving surgery in women with localized cancer of the breast. *N Engl J Med*. 1993;328:1587–91.
14. Veronesi U, Marubini E. Del Vecchio M, et al. Local recurrences and distant metastases after conservative breast cancer treatment: partly independent events. *J Natl Cancer Inst.* 1995;87:19–27.
15. Veronesi U, Marubini E, Mariani L, Galimberti V, Luini A, Veronesi P, et al. Radiotherapy after breast-conserving surgery in small breast carcinoma: long- term results of a randomized trial. *Ann Oncol*. 2001;12:997–1003.
16. Veronesi U, Stafyla V, Luini A, Veronesi P. Breast cancer: from "maximum tolerable" to "minimum effective" treatment. *Front Oncol.* 2012;2:125.
17. AIRO 1997 Standard di riferimento nell'irradiazione del cancro della mammella in stadio iniziale. A cura di Valdagni R (coordinatore), Amichetti M, Bignardi M, Cazzaniga LF, Ciocca M, Cosentino D, Gatti MG, Guenzi M, Lozza L, Maiorana A, Orecchia R, Pacini P, Zucali R. Rusconi Editore; 1997.
18. Locker AP, Ellis IO, Morgan DA, Elston CW, Mitchell A, Blamey RW. Factors influencing local recurrence after excision and radiotherapy for primary breast cancer. *Br J Surg.* 1989;76: 890–4.
19. Hughes KS, Schnaper LA, Berry D, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. *N Engl J Med.* 2004;351:971–7.
20. Hughes KS, Schnaper LA, Cirrincione C, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 or older with early breast cancer. *J Clin Oncol.* 2010;28:69s (suppl; abstr 507).
21. Fyles AW, McCready DR, Manchul LA, et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. *N Engl J Med.* 2004;351:963-70.
22. Fisher B, Bryant J, Dignam JJ, et al. Tamoxifen, radiation therapy, or both for prevention of ipsilateral breast tumor recurrence after lumpectomy in women with invasive breast cancers of one centimeter or less. *J Clin Oncol*. 2002;20:4141–9.
23. Darby S, McGale P, Correa C, et al. Effect of radiotherapy after breast conserving surgery on 10-year recurrence and 15-year breast cancer death: Meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet.* 2011;378:1707-16.