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Original article

Radiotherapy after breast-conserving surgery in small breast carcinoma: Long-term results of a randomized trial

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Summary

Background: Breast-conserving surgery followed by radiotherapy is a widely accepted form of treatment in patients with breast cancer of limited extent. Many attempts have been made to identify subgroups of patients who might avoid radiotherapy.

Patients and methods: Between 1987 and 1989, 579 women with carcinoma of the breast were randomly assigned to quadrantectomy, axillary dissection and radiotherapy (299) and to quadrantectomy with axillary dissection without radiotherapy (280). Eligible patients were women with a breast carcinoma less than 2.5 cm in maximum diameter up to 70 years of age. Primary endpoints were intra-breast tumour reappearance (IBTR) and all-cause mortality.

Results: The number of IBTRs was significantly higher in patients treated with surgery alone (59 cases out of 273; 10-year crude cumulative incidence of 23.5%) than in patients treated with surgery plus radiotherapy (16 cases out of 294; 10-year crude cumulative incidence of 5.8%). The difference in IBTR frequency between the two treatments appeared to be particularly high in women up to 45 years of age, tending to decrease with increasing age up to no apparent difference in women older than 65 years. Overall survival curves for the two groups, did not differ significantly (P = 0.326). However, a limited survival advantage was evident after radiotherapy for node-positive women.

Conclusions: After breast-conserving surgery radiotherapy appears indicated in all patients up to 55 years of age, in patients with positive axillary nodes, and in patients with extensive intraductal component at histology. The data suggest that radiotherapy may be avoided in patients older than 65, and may be optional in women aged 56–65 years with negative nodes.

Key words: breast-conserving surgery, radiotherapy, small breast carcinoma

Introduction

Breast-conserving surgery is a widely accepted form of treatment in patients with breast cancer of limited extent [1, 2]. In order to reduce the risk of local recurrences, conservative procedures imply a postsurgical treatment with radiotherapy, which in the majority of the cases is applied to the whole breast with a dosage varying from 50–60 Gy, with or without a boost on the scar [3–5]. Attempts were conducted in many centers to identify subgroups of patients who might avoid radiotherapy with controversial results. Most reports showed that postoperative radiotherapy considerably reduces the risk of local recurrences but does not substantially influence survival [6–10]. However, recent Bayesian meta-analysis of the published trials showed a small survival advantage in patients treated with radiotherapy [11].

In the present paper we report the results of a 12-year follow-up of a randomized trial on 579 patients with breast carcinoma, comparing an extensive breast resection (quadrantectomy) followed by postoperative radiotherapy with the same surgical procedure without radiotherapy.

Patients and methods

Eligible patients

Between 1987 and 1989, 579 women with carcinoma of the breast admitted to the Milan National Cancer Institute were randomly assigned to 1 of 2 treatments: 299 patients were assigned to quadrantectomy, axillary dissection and radiotherapy, and 280 patients to quadrantectomy with axillary dissection without immediate radiotherapy Eligible patients were women with an invasive carcinoma of the breast less than 2.5 cm in maximum diameter at pathological examination, up to 70 years of age, without previous malignant diseases. Women who developed the breast carcinoma during pregnancy or lactation were not eligible. Randomisation was performed immediately after surgery (quadrantectomy and axillary dissection). The randomisation of the patients was centrally managed by the Institute Trial Office. The investigators contacted the data manager immediately after surgery and, after inclusion and exclusion criteria had been checked, the eligible patients were registered and assigned to receive quadrantectomy alone or quadrantectomy plus radiotherapy according

Table 1. Main series characteristics.

	Quadrantectomy (n = 273)		Quadrantectomy with radiotherapy (n = 294)	
	n	%	n	%
Age (years)				
≤35	12	4.4	11	3.7
36–45	51	18.7	66	22.4
46–55	104	38.1	109	37.1
56–65	83	30.4	83	28.2
>65	23	8.4	25	8.5
Primary tumour site				
Outer quadrant	187	68.5	193	65.6
Inner/central quadrant	86	31.5	101	34 4
Primary tumour size (cm)				
≤1.0	74	27 1	75	25.5
1.1–2.0	156	57.1	167	56 8
>2.0	42	15.4	47	16.0
NA	1	0.4	5	1.7
Axillary-node involvement				
Negative nodes	182	66.7	211	71.8
1–3 positive nodes	70	25.6	58	19 7
4–9 positive nodes	13	4.8	19	6.5
≥10 positive nodes	8	2 9	6	2.0
Histology				
Infiltrating ductal carcinoma	159	58.2	182	61.9
Infiltrating lobular carcinoma	53	19.4	50	17.0
Infiltrating tumours with extensive intraductal component	42	15 4	41	13.9
Other infiltrating tumours	19	7.0	21	7.1
Adjuvant treatment in node-positive women				
Chemotherapy	48	52.7	49	59.5
Tamoxifen	40	44.0	27	32.1
None	3	3.3	7	8.3

to a computer-generated, permuted-blocks randomization list. The study was approved by the Institute Ethical Committee and informed consent was obtained from all the participating patients.

In 12 patients the margins of the resection were found to contain tumour tissue (5 patients assigned to quadrantectomy with radiotherapy and 7 assigned to quadrantectomy alone); consequently, these patients were excluded, since they were candidates for a second operation or radiotherapy.

The main series characteristics are reported in Table 1. Small discrepancies with the figures given in the previous paper are due to extensive data checking carried out when trial data were included in a clinical database on breast-conservation surgery.

There were negligible differences between the two treatment groups in age, site and size of the primary carcinoma, histologic characteristics, prevalence of axillary invasion and the adjuvant treatments administered The two groups of patients appear, therefore, comparable.

Surgery

Quadrantectomy consisted of extensive breast resection, including a portion of the skin overlying the tumour and the underlying fascia. Axillary dissection always included total removal of all lymph nodes of the three levels up to the apex of the axilla.

Radiotherapy

Patients randomised to quadrantectomy and radiotherapy received radiation therapy from a cobalt unit or a 6-MeV linear accelerator, starting four to six weeks after surgery. The breast was treated with two opposing tangential fields (a total of 50 Gy given over a five-week period, with a daily target dose of 2 Gy) and then with a boost dose to the tumour bed with an orthovoltage unit (10 Gy in five fractions).

Patients who had been randomized to surgery only but experienced local recurrence, were offered radiotherapy with the same dosages after the excisional biopsy of the recurrence.

Follow-up

Follow-up was strict and included routine clinical examination every four months and mammography, chest radiography, bone scanning, and ultrasonography of the liver every year. If a local recurrence was suspected, mammography and a fine-needle biopsy were performed. The follow-up duration ranged from 10 to 136 months (median 109 months, i.e., 9 years)

Adjuvant treatment

Patients with positive axillary nodes were treated with adjuvant medical therapy: premenopausal patients and postmenopausal patients negative for estrogen receptors received chemotherapy (a regimen of cyclophosphamide, methotrexate, and fluorouracil), and postmenopausal patients positive for estrogen receptors received tamoxifen. Ten patients with positive nodes declined adjuvant treatment.

End points

Primary endpoints were intra-breast tumour reappearance (IBTR) and all-cause mortality. Secondary endpoints were contralateral breast carcinoma, regional or distant metastases, and other primaries. We defined as IBTR all breast carcinomas appearing in the operated breast during the follow-up.

Statistical methods

Cumulative hazard curves for IBTR and overall survival curves for each treatment group were obtained with the Kaplan–Meier method and statistically compared with the logrank test. Ten-year crude cumulative incidence of IBTR was estimated as described by Marubini and Valsecchi [12]. Time to death and time to any neoplastic event (IBTR, contralateral breast carcinoma, regional or distant metastases, and other primaries, whichever occurred first) were computed from the date of surgery.

To investigate treatment effects in different patient strata, multivariate analyses were deemed inappropriate, due to the limited number of end point events For exploratory purposes, we computed the event rate (number of events over the cumulative observation time) according to main patient and disease characteristics.

Results

Intra-breast tumour reappearances (IBTR)

The number of IBTRs was significantly higher in patients treated with surgery alone (59 cases out of 273) than in patients treated with surgery plus radiotherapy (16 cases out of 294). Cumulative hazard curves are drawn in Figure 1; the difference between the two treatment groups

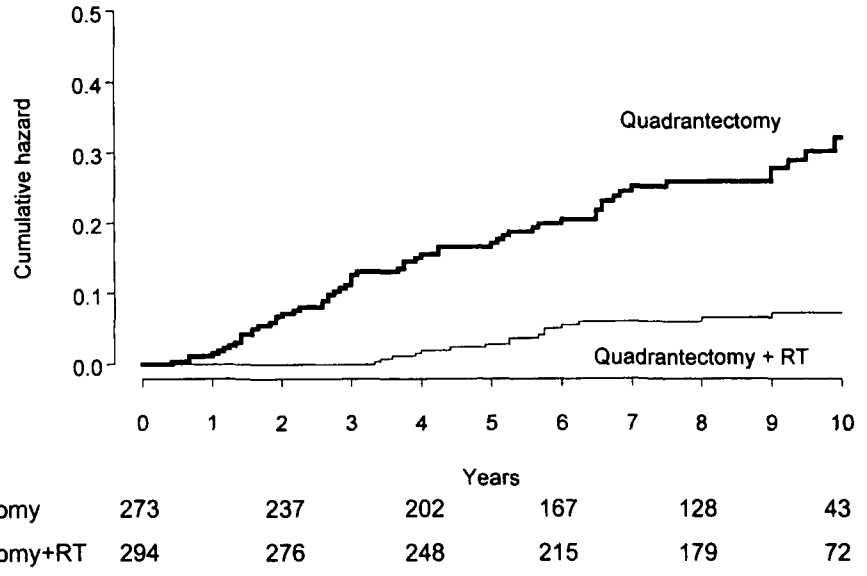


Figure 1. Cumulative hazard curves for ipsilateral breast tumour reappearance according to treatment assignment.

Table 2. Number of intra-breast tumour reappearances (N) and corresponding rates (× 100 women-years of observation) according to patient age and tumour characteristics.

	Quadrantectomy		Quadrantectomy with radiotherapy	
	N	Rate	N	Rate
Overall	59	3.3	16	0 7
Age (years)				
≤45	27	42 9	7	9.1
46–55	21	20.2	6	5 5
56–65	10	12.1	2	2.4
>65	1	4 4	1	4.0
Primary tumour size (cm)				
≤1.0	15	20 3	3	4.0
1.1–2.0	35	22.4	11	6.6
>2.0	9	21.4	1	2.1
Axillary-node involvement				
Negative	35	19.2	11	5.2
Positive	24	26.4	5	6.0
Histology				
Infiltrating ductal carcinoma	30	18.9	9	5.0
Infiltrating lobular carcinoma	10	18 9	3	6.0
Infiltrating tumours with extensive intraductal component	17	40.5	3	7.3
Other infiltrating tumours	2	10 5	1	4 8

was highly significant ($P < 0.001$). Ten-year crude cumulative incidence of IBTR (SE) was 23.5% (2.8%) in patients treated with surgery alone and 5.8% (1.4%) in patients treated with surgery plus radiotherapy.

Table 2 reports the event rates according to established prognostic factors such as patient age, tumour size, axillary-node involvement, and histology. To avoid sparse data, some of the categories in Table 1 were collapsed.

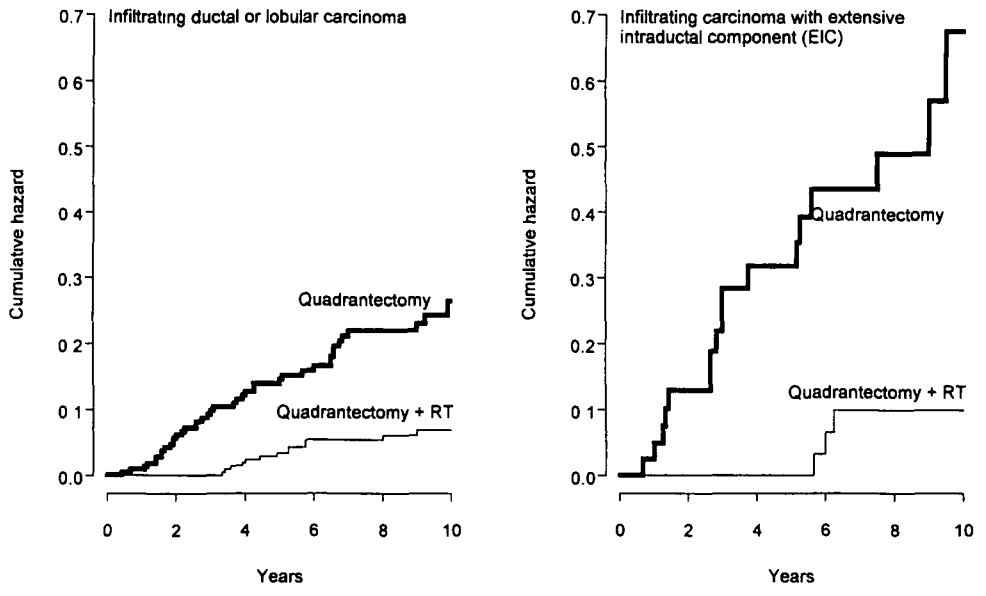
In the quadrantectomy with radiotherapy arm, the event rate was low on average (0.71 × 100 women-years of observation) and barely affected by age and tumour characteristics. In patients treated with surgery alone, the event rate was higher (3.25 × 100 women-years of observation) and more variable depending on the different characteristics considered. Particularly high rates were observed in women up to 45 years of age and in the presence of infiltrating carcinoma with EIC (Figure 2). In contrast, relatively low rates were observed in women between 56 and 65 or more than 65 years of age. The rate in the latter age category overlapped with the corresponding rate observed in the quadrantectomy with radiotherapy arm.

As regards the site of the local recurrences in the breast from Table 3 it appears that the distribution of IBTR is mainly concentrated in the resection area, both in the patients treated with surgery alone (48 out of 56, 86%) and in patients treated with RT (11 out of 13, 85%). The number of cases that occurred in other ipsilateral quadrants was similar to the number of cases occurring in the contralateral breast. The 59 patients in the quadrantectomy arm who experienced IBTR were offered a second breast-conserving treatment. However, only 39 women accepted this treatment while the remaining 20 requested a mastectomy. Mastectomy was also performed in seven women who relapsed after a second breast-conserving treatment. In the quadrantectomy with radiotherapy arm, 11 patients out of the 16 who experienced IBTR underwent mastectomy for either first (10 cases) or second (1 case) relapse.

Other events

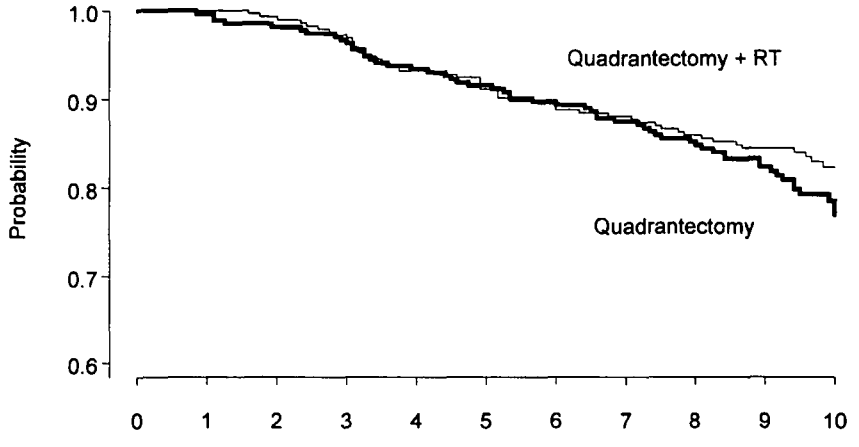
The contralateral breast carcinomas were 22 in total, without differences among the 2 groups: 12 occurred in women treated with quadrantectomy and 10 in women who had quadrantectomy and radiotherapy.

Distant metastases as first event occurred in 96 patients out of 579, 40 among women treated with quad-



At risk												
Quadrantectomy	231	202	173	145	111	40	42	35	29	22	17	3
Quadrantectomy+RT	253	238	214	184	156	61	41	38	34	31	23	11

Figure 2. Cumulative hazard curves for ispsilateral breast tumour reappearance according to the histology of primary carcinoma.



At risk						
Quadrantectomy	273	268	255	240	222	95
Quadrantectomy+RT	294	292	274	261	238	109

Figure 3. Survival curves according to treatment assignment.

rantectomy and 56 among women treated with quadrantectomy and radiotherapy.

Primary carcinomas in other organs appeared in 25 patients without differences between the two treatments: 10 events in the quadrantectomy group and 15 in the other group.

Mortality

In the overall series of treated patients there were 109 deaths. Of these, 83 were due to mammary carcinoma (47 deaths among women treated with quadrantectomy and 36 among women treated with quadrantectomy and radiotherapy); 26 deaths were unrelated to breast cancer (10 among women treated with quadrantectomy and 16 among treated with quadrantectomy and radiotherapy). Overall survival curves for the two groups, drawn in Figure 3, did not differ significantly (P = 0.326). Ten years after surgery, survival estimates were 76.9% in the quadrantectomy group and 82.4% in the quadrantectomy plus radiotherapy group.

Death rates according to established prognostic factors are shown in Table 4. In the quadrantectomy with radiotherapy arm, as expected, death rates tended to increase with age, tumour size and axillary-node involvement, whereas low mortality was observed for infiltrating carcinomas other than ductal, lobular, or with EIC. Similar patterns were observed in the quadrantectomy

Table 3. Site of IBTR in ipsilateral breast.

	Quadrantectomy (N 59)[a]	Quadrantectomy with radiotherapy (N. 16)[a]	Total
Scar area	48 (85%)	11 (84%)	59
Other quadrants	8 (15%)	2 (16%)	10

[a] Three cases missing.

Table 4. Number of deaths (N) and corresponding death rates (× 100 women-years of observation) according to patient age and tumour characteristics.

	Quadrantectomy		Quadrantectomy with radiotherapy	
	N	Rate	N	Rate
Overall	57	2.4	52	2.0
Age (years)				
≤45	10	15.9	10	13.0
46–55	22	21.2	22	20.2
56–65	23	27.7	13	15.7
>65	2	8.7	7	28.0
Primary tumour size (cm)				
≤1 0	9	12.2	7	9.3
1 1–2.0	38	24.4	29	17.4
>2.0	10	23.8	15	31.9
Axillary-node involvement				
Negative	26	14.3	36	17.1
Positive	31	34.1	16	19.3
Histology				
Infiltrating ductal carcinoma	38	23.9	33	18.1
Infiltrating lobular carcinoma	10	18.9	7	14.0
Infiltrating tumours with extensive intraductal component	7	16.7	11	26.8
Other infiltrating tumours	2	10 5	1	4.8

arm, but with a remarkable rate difference between the two arms for node-positive women. Survival curves according to treatment and nodal involvement are drawn in Figure 4. The two curves differed significantly (P = 0.038) in node-positive patients but not in node-negative patients. Notably, the high rates of intra-breast tumour reappearance after quadrantectomy alone in women up to 45 years of age or with infiltrating carcinomas with EIC (Table 2) did not apparently translate into an increased mortality. As regards patients aged >65 years, who showed no benefit of radiotherapy in terms of IBTR, a slight, non-significant increase in mortality was observed for women receiving radiotherapy, a difference likely due to random variations, given the limited number of cases.

Discussion

Breast quadrantectomy traditionally implies the post-operative treatment of the mammary gland with radiotherapy. Whether the importance of radiotherapy lies only in reducing the risk of local recurrences or also in reducing mortality is the question we posed ourselves many years ago. We initiated this trial 13 years ago in order to provide an answer to this problem. Additional motivations for the trial were that 1) avoiding *radiotherapy*, at least in some subgroups, would mean a

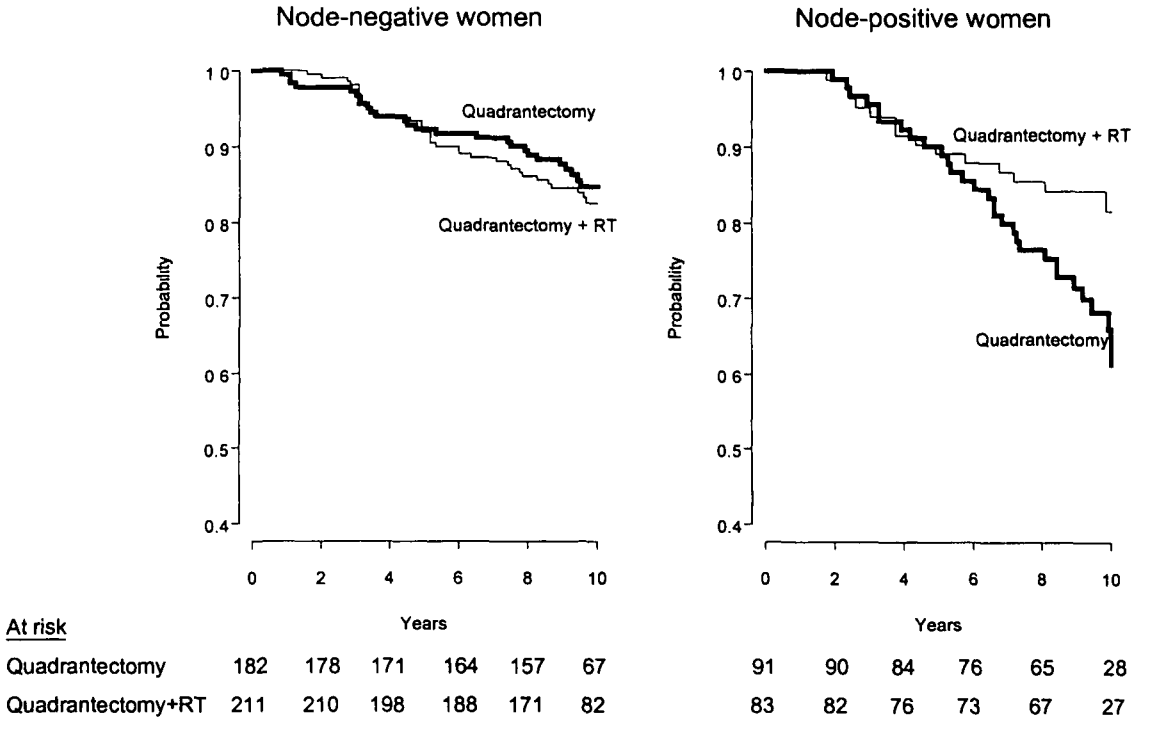


Figure 4 Survival curves according to treatment assignment in node-negative and node-positive women.

reduced burden on the patients and a reduced cost to the health system; 2) in many countries *radiotherapy* is not easily available, thereby unnecessarily inducing patients to undergo a mastectomy [13]; 3) although beneficial in reducing local recurrences, *radiotherapy* carries some long term side effects, such as lung fibrosis, some risks of cardiac failure and increased risk of soft tissue sarcoma [14]. Moreover, reduced vascular supply to the breast could render any reconstructive surgery in a second operation difficult [15].

The most relevant fact in our trial is that although the group of patients treated with surgery alone without radiotherapy showed a high rate of local recurrences, overall survival was not significantly lower than the survival of patients treated with postoperative radiotherapy. In other words our data show that local recurrences may considered to be linked mainly to causes independent of those which are responsible for cancer cell dissemination. This is in line with the interpretation of the natural history of breast cancer, which considers that the prognosis of breast cancer patients is mainly the result of the intrinsic ability of cancer cells to spread and implant in distant organs. This characteristic may be the result of a number of DNA mutations which confer upon the cancer cell the ability to disseminate. Local recurrences are, on the contrary, more connected with other variables such as the extent of the surgical resection, which may be incomplete, or the extensive multifocality of primary carcinoma, a condition frequent in young women, or the presence of extensive intraductal components [16].

A careful analysis of the site of IBTR in the follow-up of our patients, showed that the majority of IBTR occurred in the scar area in both arms of the trial. As regards the quadrantectomy group, IBTRs occurring in other ipsilateral quadrants (8 events, Table 3) were similar in number with contralateral carcinomas (12 events). While radiotherapy on the scar area aims to reduce the incidence of true local recurrences, irradiation of the other quadrants may be considered a preventive measure to reduce the risk of new ipsilateral carcinomas. According to our data it is conceivable to suggest that radiotherapy should be concentrated only in the area of the breast where the primary tumour originated.

No significant difference in survival was found in overall treatment comparison. However, the analysis by subgroups showed for patients with positive axillary nodes a small improved survival when treated with postoperative radiotherapy. We cannot offer a clear explanation of this finding, which was also observed in previous studies [11]. One may argue that in node-positive patients the internal mammary nodes are frequently involved so that radiotherapy may have been beneficial by destroying those metastatic deposits. However, the finding of a previous surgery trial [17], showing no beneficial effect of internal mammary chain removal, make the hypothesis unlikely. Alternatively, it may be so that a favourable joint effect in node-positive patients arises from postoperative radiotherapy and adjuvant medical treatment, which in our cases were administered simultaneously. Finally, being a post-hoc analysis, the result may be simply due to chance.

As previously reported [9], local disease control worsened in the absence of radiotherapy. In fact, 59 IBTRs occurred in the quadrantectomy group, compared to 16 in patients who also received radiotherapy. This implied 27 and 11 mastectomies, respectively, in the two arms.

An interesting result of our study refers to the association between IBTR incidence and patients' age. In patients not treated with radiotherapy and less than 45 years of age we observed a high IBTR rate (7.4 × 100 women-years of observation), whereas the rate was more than halved in women from 46 to 55 years of age (3.1) and was even lower in women between 56 and 65 (1.7). In women over 65 the difference between radiotherapy-treated and radiotherapy-untreated women disappeared completely: the low rate observed in such an age category (0.5) translates into a 10-year IBTR risk not higher than about 5% with both treatments. A sensible conclusion is therefore that women over 65 who undergo a local extensive resection (wide excision, sector resection, quadrantectomy) may be spared postoperative radiotherapy. The same policy may be applied to women over 55 although an increase of risk of local recurrence is still present. Our results are different from those reported in other studies: in the Forrest et al. study [7] the risk of local recurrence in women over 60 not receiving RT was 29.7% and in the Clark et al. trial [8] women over 50 experienced a recurrence risk of 22.4%. On the contrary, in the Liliegren trial [6] a subgroup of women at low-risk of local recurrences was identified, i.e., women over 55 with a non-comedo or a non-lobular carcinoma (recurrence rate 6.1%) who, according to the authors, could avoid postoperative radiotherapy [6]. No data by age groups were reported in the NSABP study [2].

The differences observed in the Milan and Swedish trials compared to other series may be due to the different surgical approaches in breast conserving treatments. Our traditional technique has been the '*quadrantectomy*', which consists of a wide excision, including a small portion of the overlying skin and of the underlying fascia. This operation is very similar to the 'sector resection' adopted by the surgeons of the Swedish trial [6]. Other Centres may adopt less extensive operations such as the '*lumpectomy*' which may be of variable extent according to different surgeons.

The low rate of local recurrences in women over 55 may be explained by the anatomical difference of the mammary gland in young and old women. In young women the breast is a well-structured, well-functioning gland with well-developed ductal trees, while in old women the breast is simply composed of fatty tissue with scattered islands of residual mammary gland. In the latter condition the wide excision is linked with a low risk of local recurrences, while in premenopausal women the multifocality and the peritumoral spread is more extensive.

The extensive intraductal component appeared to be important risk factor for IBTR [18] in patients not treated with postoperative radiotherapy, whereas in patients submitted to radiotherapy no increased risk due to the presence of extensive intraductal component was evident (Figure 2).

Conclusions

The conclusions of our trial, as regards the implications for clinical practice, can be referred only to treatment programs which considered small breast carcinomas (<2.5 cm ∅) and an extensive breast resection (quadrantectomy).

As there is a limited survival advantage with postoperative radiotherapy in node-positive patients we believe that in these patients radiotherapy is indicated; 1) patients with histology showing E.I.C. should receive postoperative RT, as the incidence of local recurrences is extremely high in those patients; 2) due to the rather high rate of local recurrences in patients up to 55 not treated with postoperative radiotherapy regardless of the nodal status, we suggest that RT should be administered to these women; 3) although the numbers are small, women older than 65 do not show an advantage in either terms of local recurrences or in terms of survival with adjunctive radiotherapy. We think that radiotherapy in this subgroup might be avoided regardless of the nodal status, provided that the surgical resection is extensive and adequate; 4) for women aged 56–65 with negative axillary nodes, considering the limited risk of local recurrences and the absence of survival advantage with radiotherapy, the indication of postoperative radiotherapy may be decided per case after an explanatory dialogue with the patients; 5) as the site of local recurrences is mainly that of the scar of the previous resection, it may be reasonable in the future to concentrate the RT on the area of the breast where the primary carcinoma was located.

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