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Special Paper

Breast Conservation is a Safe Method in Patients with Small Cancer of the Breast. Long-term Results of Three Randomised Trials on 1,973 Patients

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Breast conservation has become well-established in the treatment of early mammary carcinoma. However, a standardised treatment modality has not emerged. We have analysed the data from 1,973 patients treated in three consecutive randomised trials by four different radiosurgical procedures: Halsted mastectomy, quadrantectomy plus radiotherapy, lumpectomy plus radiotherapy, and quadrantectomy without radiotherapy, to compare the outcomes of these procedures in terms of local recurrence rate and overall survival. Eligibility criteria were similar in the three trials, and comparability between the four subgroups was excellent. Median follow-up for all patients was 82 months. The annual rates of local recurrence varied markedly according to the treatment. Patients treated with Halsted mastectomy and quadrantectomy plus radiotherapy had low annual rates of local recurrence (0.20 and 0.46, respectively) while both lumpectomy plus radiotherapy and quadrantectomy without radiotherapy had significantly higher rates (2.45 and 3.28, respectively). Patients under 45 years of age had a much higher incidence of local recurrences, while in women over 55 years local recurrences were much less frequent. Overall survival curves were identical in the four groups of patients, so that the three breast conserving radiosurgical procedures had the same survival rates as Halsted mastectomy. However, local recurrence rates were markedly influenced by the treatment method, patient age and specific histological features.

Key words: breast cancer, conservative surgery, recurrence rate, randomised trials
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INTRODUCTION

CONSERVING THE breast is one of the main objectives in treating patients with mammary carcinoma today. However, this objective must be made compatible with good local control of the disease so as to keep the risk of local recurrences as low as possible. Various types of locoregional treatment have been proposed and implemented, with different surgical techniques, radiotherapeutic methods and chemotherapeutic schedules [1–16]. Several procedures have been tested in a number of randomised trials [6–16], but so far a standardised treatment protocol has not emerged. One of the open questions concerns the amount of mammary tissue around the primary tumour to be removed, and a second concerns the need for, and the type of, radiotherapy to be applied. Whether the same type of treatment should be applied to all patients or different policies to various groups according to age and histological type of the primary carcinoma are additional issues.

To try to answer these questions, we have analysed the data obtained from three consecutive clinical randomised studies conducted at the Milan Cancer Institute from 1973 to 1989, involving 1,973 patients. The trials compared four different types of locoregional procedures (Halsted mastectomy, quadrantectomy plus radiotherapy, lumpectomy plus radiotherapy and quadrantectomy alone), conducted on very similar populations of patients with similar eligibility criteria, treated at one institute by the same team of surgeons, radiotherapists, medical oncologists and pathologists.

PATIENTS AND METHODS

The 1,973 patients analysed here were treated as part of three randomised trials addressing the issue of the best conservative treatment for breast cancer. The first trial (Milan I) compared Halsted mastectomy with quadrantectomy, axillary dissection and radiotherapy (QU.A.RT), the second (Milan II) compared QU.A.RT with tumourectomy (lumpectomy), axillary dissection and radiotherapy (T.A.RT), while the third (Milan III)

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compared QU.A.RT with quadrantectomy and axillary dissection without radiotherapy (QU.A.D).

Milan I

From 1973 to 1980, 701 patients with small breast carcinoma were randomised to either Halsted mastectomy (349 patients) or QU.A.RT (352 patients). Patients less than 70 years of age with invasive breast carcinoma 2 cm or less at pathological examination were eligible [7].

Milan II

This trial accrued 705 patients from 1985 to 1987. Eligible patients were under 70 years, with the largest breast carcinomas less than 2.5 cm in diameter at pathological examination. They were randomised to QU.A.RT (360 patients) or T.A.RT (345 patients) [13].

Milan III

567 women were accrued in 2 years (1988–1989). Eligibility criteria were identical to those in Milan II and patients were randomised to QU.A.RT (294 patients) or QU.A.D (273 patients) [14].

Follow-up

The patients of all three trials were checked at regular quarterly intervals for the first 5 years and subsequently on a semiannual basis. Chest X-ray, bone and liver scan and mammography were performed annually, together with a thorough clinical investigation. The median duration of follow-up for the entire series was 82 months, and the corresponding figures for the three trials were 192, 79 and 52 months, respectively.

Pathology

The criteria adopted for the pathological examination were identical in all trials; most of the specimens and slides were examined and reviewed by the same group of pathologists. Classification criteria, including the evaluation of extensive intraductal component (EIC), were reviewed by a panel of pathologists in 1985 and in 1988. Resection margins were evaluated in trials II and III. In trial II only a minority of patients treated with quadrantectomy had positive margins (7 of 176 evaluated cases), while 46 of 289 evaluated patients treated by lumpectomy had positive resection margins. Our protocol stipulated that patients with positive margins in both groups of trial II should not be treated by re-excision but were to be followed in the same way as other patients [13]. In trial III, the few cases in both groups (12 altogether) with positive resection margins were excluded, in order to eliminate a bias: it would have been unacceptable not to give radiotherapy to patients with involved resection margins [14].

Surgery

Halsted mastectomy was performed in trial I according to the classic criteria, with removal of both pectoral muscles. Only in the last 2 years of the trial was the major pectoral muscle partially spared. Quadrantectomy is an operation that removes a 2–3 cm portion of normal mammary tissue around the primary carcinoma, together with portions of overlying skin and underlying pectoral fascia by means of a radial incision defining a cone-shaped excision piece. Whenever the tumour was located in the upper outer quadrant, the skin incision was prolonged to perform the axillary dissection in continuity. Tumourectomy (lumpectomy) is a breast resection that removes the primary carcinoma with a narrow margin of 1 cm of normal tissue. In all 1,973 patients, axillary dissection was total, with removal of the lymph nodes up to the third level.

Radiotherapy

All patients treated with QU.A.RT received irradiation with a cobalt unit or a 5 MeV linear accelerator, starting 4–6 weeks after surgery. The breast was treated with two opposing tangential fields (total 50 Gy given in 5 weeks with a daily target dose of 2 Gy) followed by a boost of 10 Gy in five fractions to the tumour bed with an orthovoltage unit of electrons.

Patients treated with T.A.RT in trial II received both external and interstitial radiotherapy. External irradiation was started 4 weeks after surgery and the technique was the same as that given after quadrantectomy. The difference was the total dose (45 Gy) given over 5 weeks with a daily dose of 1.8 Gy. After 2–3 weeks, wires of ^{192}Ir were implanted interstitially to give a boost of 15 Gy directly to the tumour bed.

Adjuvant treatments

Most patients with positive axillary nodes were treated with adjuvant medical therapy: pre- and postmenopausal patients negative for oestrogen receptors received chemotherapy with CMF (cyclophosphamide, methotrexate, fluorouracil), and postmenopausal patients positive for oestrogen receptors received tamoxifen for 2 years. The policy for adjuvant treatments remained substantially the same during the time covered by the three trials.

Comparability

Randomisation criteria were very strict in all trials and within each, the patients belonging to the two arms were very similar as regards the main variables. Since in the present study we compared patients from three trials, accrued over different time periods, comparability was particularly verified. In Table 1 the patients treated by the four different procedures are subdivided according to age, site, size and nodal status. No statistically significant differences between the three trial populations with regard to these variables were found. The eligibility criteria were, in fact, similar in the three trials, the only slight difference

Table 1. Distribution of 1,973 patients according to age, site and size of primary carcinoma, axillary node involvement, by type of treatment

	Halsted $n = 349$	QU.A.RT $n = 1006$	T.A.RT $n = 345$	QU.A.D $n = 273$
Age (years)				
≤ 45	116 (33%)	313 (31%)	108 (31%)	63 (23%)
46–55	120 (34%)	366 (36%)	136 (39%)	104 (38%)
> 55	113 (32%)	327 (33%)	101 (29%)	106 (39%)
Site				
Upper outer quadrant	145 (42%)	513 (51%)	190 (55%)	138 (51%)
Other sites	204 (58%)	493 (49%)	155 (45%)	135 (49%)
Size (cm)				
< 1	159 (48%)	325 (33%)	97 (28%)	74 (27%)
1–2	173 (52%)	547 (56%)	203 (60%)	156 (57%)
> 2	1 (0.3%)	103 (11%)	41 (12%)	42 (15%)
Not evaluable	16	31	4	1
Axillary nodes				
Positive	86 (25%)	298 (30%)	120 (35%)	91 (33%)
Negative	263 (75%)	708 (70%)	225 (65%)	182 (67%)

being the size of primary carcinoma; in trial I only patients with a primary carcinoma of 2 cm or less were included, whereas in trials II and III the maximum size was extended to 2.5 cm. However, there were only 188 cases between 2 and 2.5 cm, of a total of 1973 cases (9.5%). Considering that there is little, if any, influence of size of primary carcinoma on the risk of local recurrence [17], which is the main end-point of the present study, we believe that this slight difference in eligibility criteria does not constitute a major bias.

End-points

The primary end-point of this study was local recurrence. We defined a local recurrence as any new cancer nodule appearing on the skin or subcutaneous tissue or in the breast within 3 cm of the scar line. A lesion appearing in other quadrants of the breast, more than 3 cm from the scar, was defined as a second ipsilateral carcinoma. The second important end-point was overall survival in patients treated by the different procedures.

Statistical methods

Time to local recurrence (as first neoplastic event) and time to death (whatever the cause) were measured from the date of randomisation. Survival and cumulative incidence curves were constructed using the Kaplan–Meier method [18]. Comparisons between curves were made by means of the log-rank test [19]. Annual rates of local recurrence were computed and compared statistically by fitting exponential survival models to the data, since plots of the cumulative hazard functions in the different subgroups of patients were approximately linear [17].

It was estimated that the case series would have at least an 80% power to reveal a 10% or greater between-group difference in 5 year survival with a two-sided test, at the 5% significance level.

RESULTS

The incidence rates of local recurrence as first event are shown in Table 2. The cumulative incidence according to treatment type is reported in Figures 1 and 2. The Halsted and QU.A.RT treatments showed much lower incidences of local recurrence than T.A.RT and QU.A.D, with the latter protocol associated with the highest frequency of recurrence. The difference between the four treatment groups was statistically significant ($P \leq 0.0001$).

Analysis according to age revealed different incidence curves for recurrence in different age groups (Figure 3, Table 3): in women aged less than 45 years there was a progressive increase in local recurrences from Halsted through QU.A.RT and T.A.RT to QU.A.D (T.A.RT versus QU.A.D, $P = 0.002$); while in women of age 46–55 years there was a clear separation between the treatments: low risk of recurrence in Halsted and QU.A.RT and high risk in T.A.RT and QU.A.D. The curves for the latter two were superimposable. In patients over 55 years,

Table 2. Number and annual rates of local recurrences according to type of treatment

Treatment	Number	Local recurrences	Annual rates (× 100)
Halsted	349	8 (2.3%)	0.20
QU.A.RT	1006	33 (3.3%)	0.46
T.A.RT	345	44 (12.8%)	2.45
QU.A.D	273	32 (11.7%)	3.28

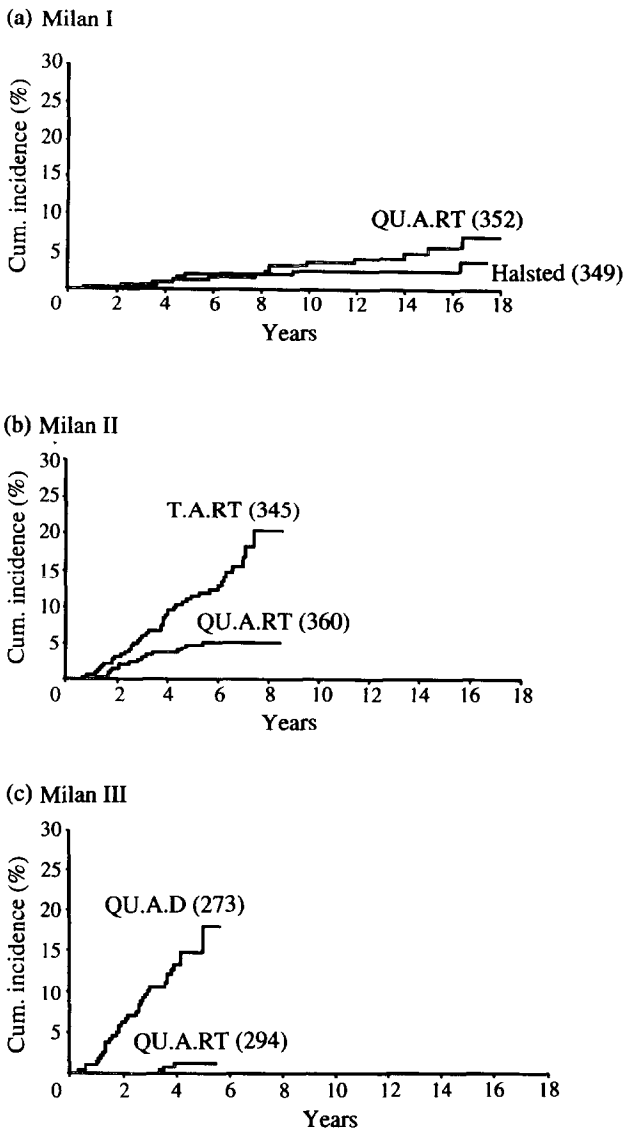

Figure 1. Cumulative (Cum.) incidence of local recurrences in the three trials.

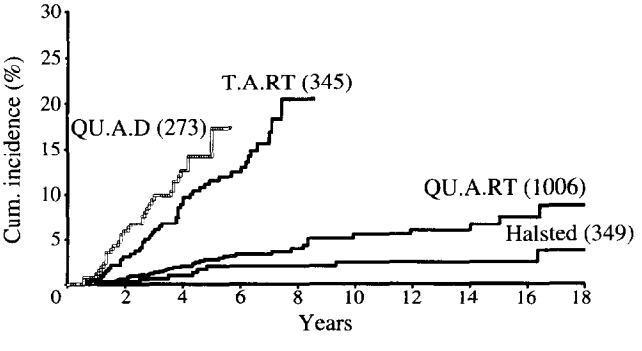

Figure 2. Cumulative (Cum.) incidence of local recurrences according to treatment (all patients).

although Halsted and QU.A.RT were still characterised by low incidence of recurrence compared to somewhat higher incidences in QU.A.D and T.A.RT, the statistical significance of the differences was smaller or non-existent.

Analysis according to axillary node involvement showed that

Table 3. Number and annual rates of local recurrences according to age and type of treatment

Age (years)	Treatment	Number	Local recurrences	Annual rates (× 100)
≤ 45	Halsted	116	3 (2.6%)	0.22
	QU.A.RT	313	21 (6.7%)	0.91
	T.A.RT	108	14 (12.9%)	2.58
	QU.A.D	63	15 (23.8%)	6.93
46–55	Halsted	120	1 (0.8%)	0.07
	QU.A.RT	366	8 (6.7%)	0.29
	T.A.RT	136	21 (15.4%)	2.92
	QU.A.D	104	11 (10.6%)	2.99
> 55	Halsted	113	4 (3.5%)	0.35
	QU.A.RT	327	4 (1.2%)	0.19
	T.A.RT	101	9 (8.9%)	1.68
	QU.A.D	106	6 (5.7%)	1.53

for node-negative patients, the QU.A.D and T.A.RT treatments were very similar, while in node-positive patients T.A.RT was significantly better than QU.A.D ($P = 0.002$; Figure 4). In patients with involved nodes, QU.A.RT was somewhat better than Halsted, although the difference was not statistically significant. Thus, among node-positive patients who also received systemic treatments, those undergoing radiotherapy (QU.A.RT and T.A.RT) had a lower incidence of local recurrence than node-negative patients. However, for both Halsted and QU.A.D patients, the rates of recurrence in the respective node-positive and node-negative cases were equal.

In cases treated with T.A.RT in trial II, the finding of positive resection margins was linked to a higher rate of local recurrence (8/46, 17.4%) than that observed in cases with negative margins (21/243, 8.6%).

The recurrence curves differed according to whether the tumours were with or without EIC at pathological examination. The advantage of Halsted and QU.A.RT over QU.A.D and T.A.RT was much greater in EIC-positive patients than in EIC-negative patients (Figure 5). Analysis according to the size of primary carcinoma revealed that the differences in local recurrence rate between tumours smaller and larger than 1 cm in diameter were constant across the four treatment groups.

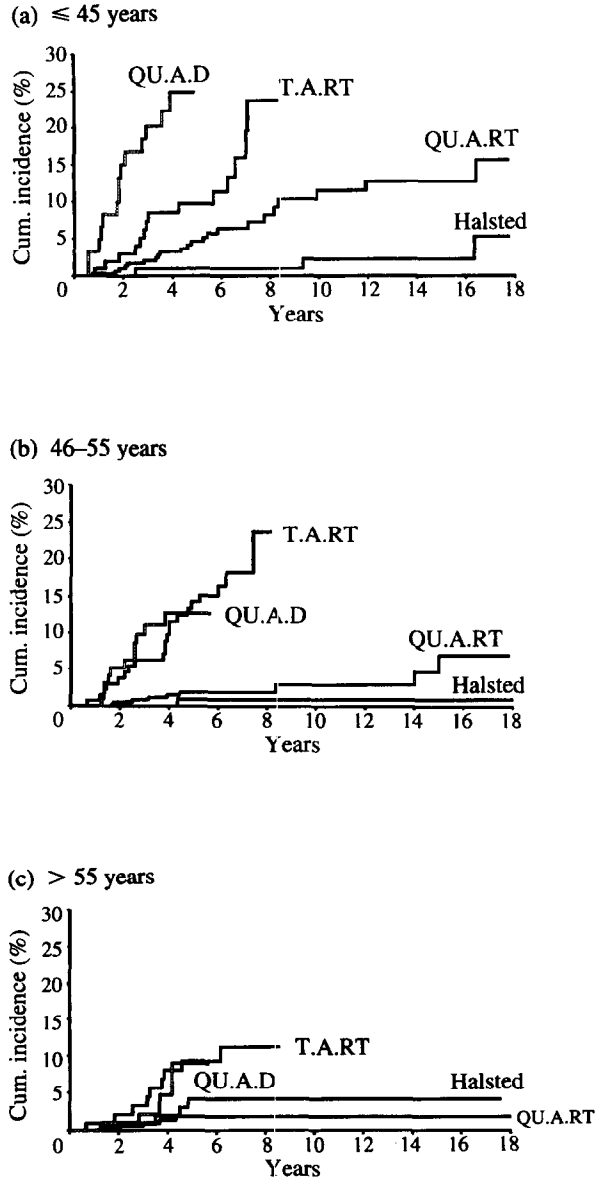

Figure 3. Cumulative (Cum.) incidence of local recurrences according to age of patients.

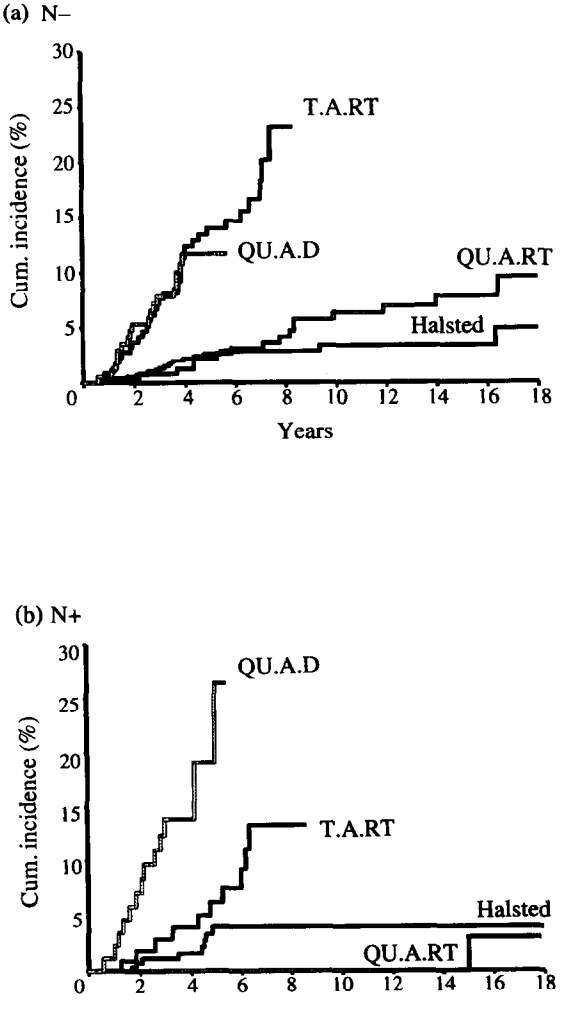

Figure 4. Cumulative (Cum.) incidence of local recurrences according to axillary nodal involvement.

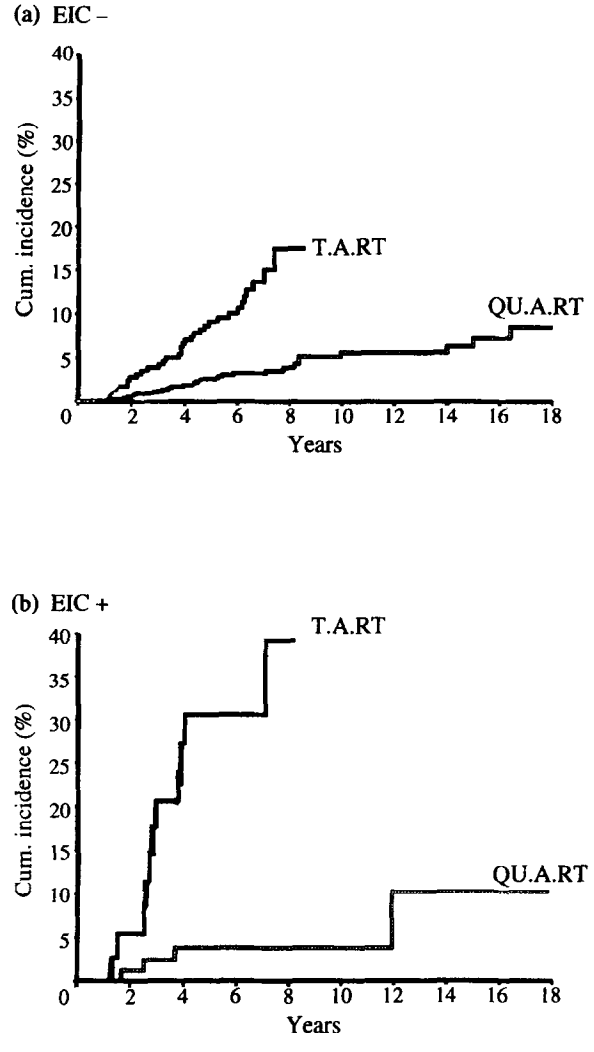

Figure 5. Cumulative (Cum.) incidence of local recurrences according to the presence or absence of extensive intraductal component (EIC) in T.A.RT and QU.A.RT patients.

Overall survival curves according to treatment are shown in Figure 6. No differences were revealed.

DISCUSSION

It is not the aim of this paper to analyse in detail the characteristics of local ipsilateral recurrences, the time of their appearance or their susceptibility to surgical rescue. Nor did this study intend to correlate the risk of local relapse with biological characteristics of the primary, such as hormone receptors, proliferative index, ploidy, etc. These issues were the subject of two of our recent studies [17, 20]. Our aim was to compare different treatment modalities in terms of local failure rate and overall survival, according to patient age and the pathological features of the primary tumour.

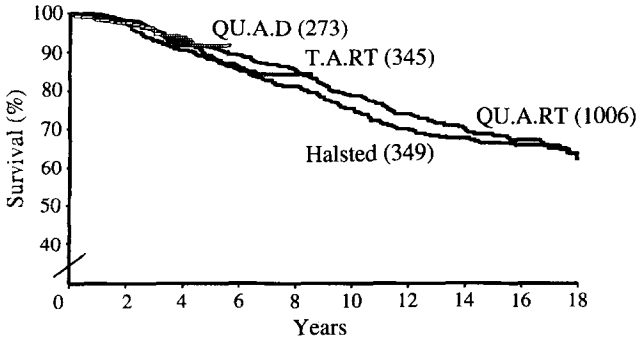

Figure 6. Overall survival of patients treated with different surgical radiological procedures.

We are aware of the statistical difficulties that arise in the meta-analysis of our three different trials, which involves an analysis of subgroups not present in the original study designs. However, we believe that this type of evaluation is important as it can identify unexpected trends that may suggest new hypotheses to be tested in further studies.

What emerges from our data is that the combination of quadrantectomy plus radiotherapy provides a level of local control very close to that obtained with Halsted mastectomy. A wide resection technique like quadrantectomy allows breast conservation yet provides good protection against local recurrence, while postoperative radiotherapy also contributes significantly to lowering the rate of recurrence. A direct correlation between quantity of tissue resected and risk of local failure has been reported in other, mainly retrospective, studies [5, 21, 22]. An interesting finding of the present study is the considerable difference between age groups in terms of local failure. In women aged less than 45 years, mastectomy is superior to other treatments, while among the conservative procedures QU.A.RT is somewhat better than T.A.RT and both are better than quadrantectomy without radiotherapy, showing that radiotherapy plays a fundamental role in this age group. This is not surprising, considering that in younger women breast carcinoma originates in a well-developed and hormonally stimulated gland where extensive multifocality, multicentricity and intraductal extensions of the primary carcinoma are not uncommon [23]. The pattern of recurrence in women around the age of menopause (46–55 years) is very different and here quadrantectomy plus radiotherapy definitely give the best results compared to the other two conservative procedures. Finally, in postmenopausal women (> 55 years) the differences between the various types of treatment are greatly reduced and both quadrantectomy without radiotherapy and lumpectomy with radiotherapy appear acceptable treatments, all showing low rates of local recurrence.

The cumulative incidence rates of local recurrence in node-negative and node-positive patients differ considerably. The two treatments involving radiotherapy (QU.A.RT and T.A.RT) gave better results in node-positive patients who also received systemic adjuvant therapies, than in node-negative patients, while the two treatments without radiotherapy (Halsted and QU.A.D) gave similar results in both groups. This difference may indicate that chemotherapy alone does not reduce the incidence of local recurrence, while radiotherapy and chemotherapy might have a synergistic effect in reducing such a risk.

Our study also shows that EIC is an important risk factor for local recurrence only where surgical resection was narrow. Thus, in patients receiving limited surgical resection and radiotherapy (T.A.RT) the local recurrence rate varied markedly with EIC positivity, while in patients treated by extensive surgical resection followed by radiotherapy (QU.A.RT) the difference between EIC-negative and EIC-positive patients, in terms of local recurrence rate, was minimal (Figure 5). These results are in line with findings repeatedly reported by the Boston groups [21, 24, 25].

As regards resection margins evaluated in trial II patients

treated by T.A.RT, our study confirms a higher rate of local recurrence in margin-positive (17.4%) than in margin-negative patients (8.6%). This suggests that whenever resection margins are found to be positive, re-excision is appropriate. Alternatively, the relatively high rate of local recurrence in patients with negative margins, in spite of radiotherapy, shows that the pathological finding of clear margins does not assure a low risk of recurrence.

Finally, it is important to emphasise that the overall survival curves of patients treated by the four locoregional approaches are identical. This result is in line with our previous reports [7, 11] and with the results of the NSABP (The National Surgical Adjuvant Breast and Bowel Project) randomised trial B06 [26] and shows that the long-term survival of breast cancer patients is not influenced by the type of local treatment and that the prognosis for breast cancer patients is mainly determined by the presence or absence of occult metastatic foci in distant organs. Thus, Halsted mastectomy and the three conservative procedures compare very well in spite of the more favourable distribution by size of the primary tumour in the Halsted patients. We must add, however, that although techniques differed, all patients were treated by a selected group of experienced surgical oncologists and radiotherapists. The care with which these operations were performed is demonstrated indirectly by the fact that in none of the 1,973 patients, all receiving complete axillary dissection, was an axillary recurrence observed.

What then should be the impact of our findings on treatment strategies for breast cancer? Firstly, it clearly emerges that radiotherapy is of fundamental importance in young women. Secondly, the advantage of quadrantectomy plus radiotherapy in women of menopausal age compared to other conservative treatments is enormous, so that QU.A.RT or a similar procedure should become the treatment of choice in patients aged 46–55 years. Thirdly, in patients aged over 55 years with quadrantectomy, additional radiotherapy may be less important than in younger age groups. The fourth point is that patients whose primary carcinoma shows the presence of an EIC must be treated with an operation involving extensive resection of the mammary gland followed by appropriate radiotherapy. Our fifth point is that cases with positive resection margins should be re-excised. Finally, the synergism between radiotherapy and chemotherapy suggests further studies, particularly to clarify whether the combination of chemo- and radiotherapy as pre-operative treatment, to reduce the extent of surgery, also reduces the risk of local recurrence.

As a final remark, we would like to stress that our incidence rates for local recurrence are in line with the expected rates derived from the pathological analysis conducted by Holland and colleagues [25, 27] illustrating once more the fundamental role of the pathologist in the planning and evaluation of treatment for primary breast carcinoma.

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