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Conservation Approaches for the Management of Stage I/II Carcinoma of the Breast: Milan Cancer Institute Trials

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The most recent analysis of the results of three major trials on breast conservation carried out at the Milan Cancer Institute between 1973 and 1988 showed that breast conservation consisting of a wide breast resection (quadrantectomy) plus radiotherapy is a safe procedure, and that there are no differences in long-term survival (up to 19 years) compared with women who have undergone Halsted's mastectomy. The studies also showed that reducing the extent of surgery from quadrantectomy to lumpectomy increases the risk of local recurrence by nearly three times, as does withdrawing radiotherapy. However, in women older than 55 years, quadrantectomy alone (without radiotherapy) may yield good results. Among the risk factors for local recurrence, a young age and the presence of an extensive intraductal component are the most significant.

There were three main reasons at the end of the 1960s for the development of conservative therapy for breast cancer: (1) evidence of the failure of aggressive surgical and radiologic therapies (dissection of internal mammary lymph nodes, radical radiotherapy to regional lymph nodes); (2) the large-scale use of mammography, which can reveal tumors in a preclinical phase and considerably anticipate the diagnosis of breast cancer; and (3) a more biologic and less mechanical concept about the evolution of breast cancer. In fact, it appeared clear that the prognosis of a patient with breast cancer is linked above all to the presence of occult foci of metastatic cells in distant organs, whereas extension of local-regional treatment assumes a limited role.

The many attempts to substitute ablative surgery of the breast with conservative methods consisted up to the 1960s of small surgical series and series of cases almost exclusively treated with radiotherapy. Although overall the results of these studies were encouraging, the fact that they did not derive from randomized clinical studies hindered their incorporation into clinical practice, so Halsted's mastectomy almost exclusively maintained its position for treatment of breast cancer up to the 1980s.

In the first controlled clinical study conducted in London by the Guy's Hospital group during the 1960s, the cure rate was negatively affected in women treated by breast resection and radiotherapy, and their long-term survival curves were significantly lower than those treated by radical mastectomy. An accurate analysis conducted many years after termination of the study showed that the difference in cure rate, in favor of Halsted's mastectomy, was limited to T1 cases. Hayward and Caleffi [1] commented on these data in 1987. They observed that the percentage of occult metastases at the time of surgery was probably high in cases with tumors more than 2 cm in diameter, so that extension of local surgery was not determinant in the outcome. In contrast, radical surgery had an important curative role for small carcinomas limited to the breast. However, another comment about the Guy's Hospital study is that the conservative treatment applied then cannot be considered adequate today because axillary dissection was not performed—not even in cases with clinically positive lymph nodes—and because the radiotherapy dose (30 Gy) was largely insufficient.

The results of that study did not encourage the initiation of other randomized clinical studies. When, together with Banfi and Saracci, I proposed an international multicentric randomized study to the Committee of Experts of the World Health Organization in 1968 and 1969, the reactions initially were unfavorable. The proposal was accepted only after much discussion at the meeting of December 1969 [2].

The novelty of the proposal was a conservative technique, which was aggressive at the mammary level [wide surgery, defined as quadrantectomy, followed by high energy (50 Gy) radiotherapy plus a boost dose of 10 Gy to the tumor bed], complete axillary dissection, and the elimination of radiotherapy to regional lymph nodes. This method, called QUART, proved to be so satisfactory that today, 25 years later, it is widely used, though with some variations.

Milan I Study

The randomized study Milan I, carried out at the Milan National Cancer Institute, compared Halsted's mastectomy with QUART in 701 cases. Other randomized studies with small series were carried out separately during the same period and with analogous methodologies at Villejuif, Moscow, and Bucharest. The design of the study was simple. The patients were randomized to two groups: one that utilized Halsted's mastectomy (at the beginning of the 1970s it was the treatment of choice) and another that utilized quadrantectomy and axillary

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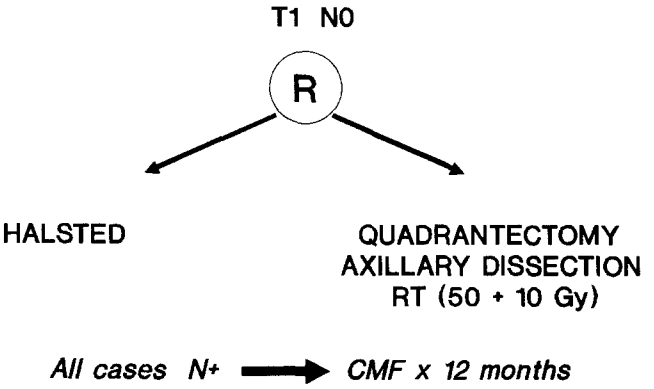

Fig. 1. Design of the randomized therapeutic Milan I study.

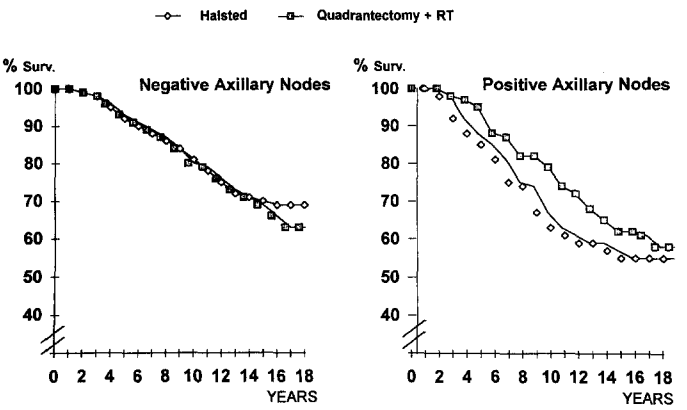

Fig. 2. Milan I study: overall survival in relation to lymph node status.

dissection followed by radiotherapy to the breast (Fig. 1). Patients with an infiltrating breast carcinoma clinically less than 2 cm in diameter and without suspicion of axillary lymph node involvement were admitted to the study. Recruitment, which began in 1973, was satisfactory; and patients entered the study at an average of 100 a year. It was therefore possible to close the enrollment in 1980 with 701 patients treated by the two methods (349 by radical mastectomy and 352 by QUART) [3]. Analysis of the series showed an excellent comparability of the two groups owing to the strict rules of randomization applied. In fact, the patients were randomized in the operating room after confirmation on an excisional biopsy of the histologic nature and the limited size of the tumor.

A delicate problem was that of informed consent. The patients were informed of the two surgical possibilities, ablative and conservative; and only those who accepted both interventions were included in the study. During the first 2 years there were many patients who, after consulting with their personal physician, refused the conservative option and therefore underwent mastectomy outside the study. In contrast, the situation was reversed toward the end of the study, and many patients refused to undergo mastectomy. Even among the physicians at the Institute the psychological situation changed, and skepticism (widespread at the beginning of the study) progressively attenuated until it was transformed to enthusiastic support when the first results became available.

The most recent analysis of the results of the study [4] showed superimposable survival curves for the two groups. Moreover, an analysis by subgroups showed a certain advantage (not statistically significant) in patients with positive axillary lymph nodes treated by QUART with respect to those who underwent mastectomy (Fig. 2). During the first 3 years of the study, patients with positive axillary lymph nodes were randomized again after the surgery, and half of the cases received adjuvant radiotherapy to the ipsilateral supraclavicular lymph nodes. Analysis of this small series (56 cases) showed that no advantage was gained by supraclavicular radiotherapy, and the practice was abandoned in 1975. Instead, all patients with positive axillary lymph nodes received two cycles of chemotherapy (cyclophosphamide/methotrexate/5-fluorouracil) per month.

An interesting and comparable finding comes from the observation of local recurrences. First, it was difficult to separate the true local recurrences (i.e., relapses of residual tumor cells after the radiotherapy-surgical treatment) from new ipsilateral carcinomas due to malignant transformation of normal mammary cells. Despite this difficulty, in conceptual terms it seemed essential because we were dealing with two biologically different events. We also wanted to know whether radiotherapy to the breast had a long-term oncogenic effect. We therefore defined as local recurrences those carcinomas that appeared on the skin, subcutaneously, or in the breast within 3 cm of the surgical scar. Nodules that appeared in other quadrants and in any case more than 3 cm from the surgical scar were instead defined as new tumors.

Table 1. Results of the Milan I trial comparing Halsted's mastectomy and quadrantectomy + radiotherapy (QUART).

Result	Halsted (n = 349)	QUART (n = 352)
Local recurrence	8	17
Second ipsilateral primary tumor	—	6
Contralateral tumor	28	22

The data on local recurrences are reported in Table 1. It can be seen that there were only a few recurrences with Halsted's mastectomy as expected, and a rather small number of local recurrences with QUART. Seventeen of the patients treated conservatively developed a local recurrence (4.8%), whereas 6 patients of the same group developed a new ipsilateral tumor. However, it is noteworthy that, other than the small number of local recurrences, these events did not have a noticeable impact on the prognosis. In fact, of the 17 QUART patients who had a recurrence (most of whom were then treated by total mastectomy), 10 are alive without evidence of disease at 6 to 14 years after detection of the recurrence, and 7 have died from metastatic disease. Of the eight patients with local recurrences after radical mastectomy, only two are alive; six developed metastases and died. In the final analysis, the number of patients who died after local recurrence was therefore substantially the same in the two groups.

The small number of local recurrences can certainly be ascribed, at least in part, to the quality of the surgical intervention. In fact, when we decided about 20 years ago to use quadrantectomy as the conservative operation, we intended to

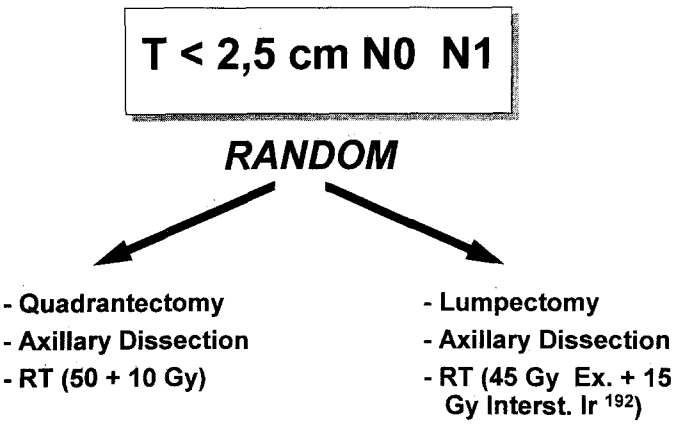

Fig. 3. Design of the randomized therapeutic Milan II study.

eliminate as much as possible the portion of the ductal tree anatomically linked to the primary breast cancer.

An important observation of the study concerns the absence of an oncogenic effect from the radiotherapy. One of the elements opposing the conservative therapy was in fact the idea that such a substantial dose of ionizing radiation on the one hand could control residual tumor cells following surgery but on the other hand could trigger a neoplastic transformation of normal cells of the remaining mammary tissue. In reality, the long-term results after many years have removed this doubt and absolved radiotherapy of the suspicion of oncogenicity, at least for epithelial mammary cells of adult women. Only six second primary breast cancers appeared in breasts treated by radiotherapy and surgery, and even the number of contralateral breast cancers was smaller in the QUART group (20 cases) than in the mastectomy, nonirradiated group (25 cases). If one considers that in the QUART group the contralateral breast received a dose of 0.5 Gy in the most lateral part and up to 10 to 15 Gy in the medial part, one could expect a considerable increase in the number of contralateral carcinomas in irradiated cases with respect to mastectomy cases. Instead, the opposite was true, and the fact that the number was smaller leads us to conclude that radiotherapy had no oncogenic action but perhaps even a protective action [5].

Milan II Study

The results of the Milan I trial were published in 1981, and the data were consolidated after some time, we then began to critically reevaluate the experience. The doubts and uncertainties mainly concerned the weight, in terms of therapeutic efficacy, of surgery and radiotherapy. Both treatments were performed with the objective of radicality, so it was therefore difficult to discern to what degree the good results were due to the surgery and to what degree to the radiotherapy.

To dispel this uncertainty, in 1985 we began a new randomized study (Milan II) to compare the quadrantectomy-radiotherapy treatment with one that placed the therapeutic weight almost totally on radiotherapy. The new treatment consisted in simple excision of the primary tumor, without the scope of radicality but exclusively reductive, followed by intense radiotherapy to the breast (45 Gy on the total breast and about 15 Gy with ^{192}Ir applied interstitially in the site of the surgical wound). All patients were treated by complete axillary dissection. Eligibility criteria were similar to those of the Milan I study, except that patients with tumors up to 2.5 cm in diameter were included, as were those with clinically positive axillary nodes (Fig. 3).

Table 2. Milan II trial: first unfavorable event.

Event	QUART (n = 360) No.	%	TART (n = 345) No.	%
Local recurrence	15	4.2	39	11.3
Second ipsilateral carcinoma	4	1.1	7	2.0
Total local failures	19	5.3	46	13.3
Contralateral tumor	15	4.2	18	5.2
Distant metastases	61	16.9	47	13.6

QUART: quadrantectomy + radiotherapy; TART: tumorectomy + radiotherapy.

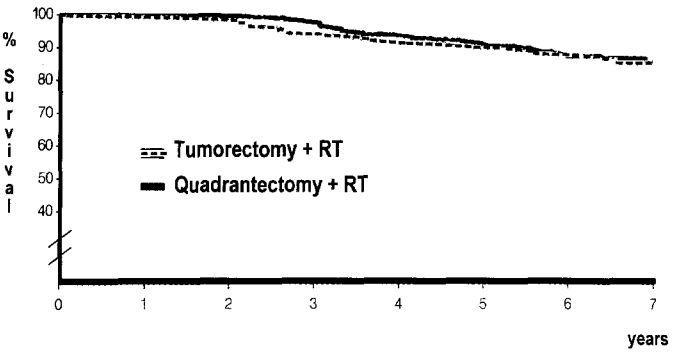

Fig. 4. Milan II study: overall survival for the two arms.

The randomized study was carried out from 1985 to 1987 and recruited 705 patients: 360 were treated with QUART and 345 were treated by tumorectomy, axillary dissection, and radiotherapy (TART). The comparability in this study was also excellent, and there were no significant differences between the two groups as regards the main prognostic variables [6].

The results concerning local recurrences are reported in Table 2. Local relapses were again limited in the cases treated by QUART (15 recurrences and 4 new carcinomas; in all 5.3%), whereas in the group treated by TART there were 46 local relapses (39 recurrences and 7 new carcinomas, or 13.3%). The difference was important, and thus one should reflect on the opportunity of reducing the degree of the surgery. The incidence of contralateral carcinomas was similar in the two groups (15 in the QUART group and 18 in the TART group). Actuarial survival curves were identical at 7 years, which confirms that differences in local recurrence do not appreciably affect the prognosis (Fig. 4).

Analysis of local recurrences by subgroups showed some interesting data. The rate of local recurrences in relation to tumor size in the cases treated by QUART was different from that in the cases treated by TART. In the first group there was a progressive increase in the number of local recurrences with increasing tumor size, but this was not true for the second

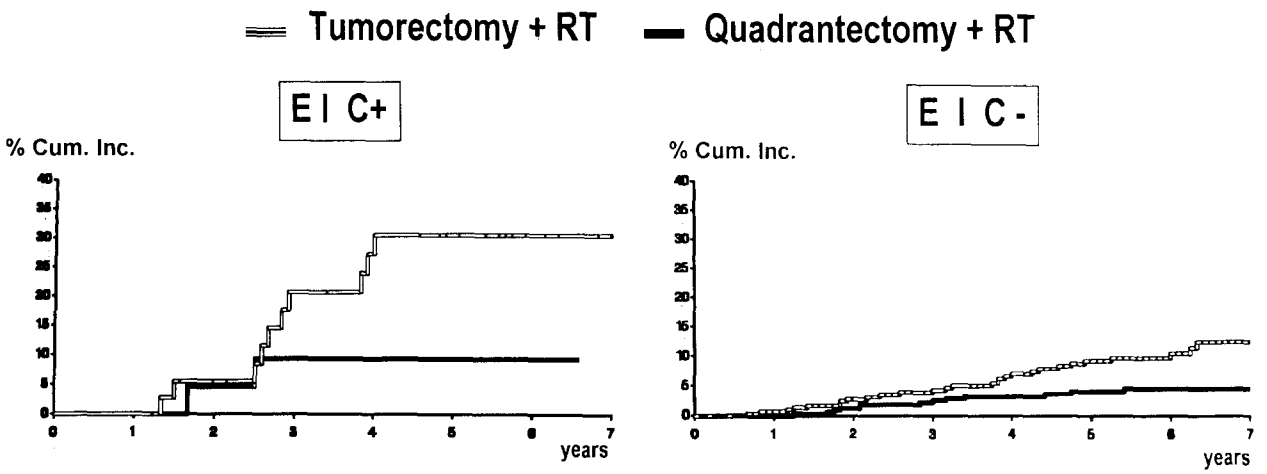

Fig. 5. Milan II study: incidence of local recurrence in relation to the presence of an extensive intraductal component (EIC).

group. Although the numbers are too small to draw conclusions, it can be hypothesized that in the cases treated by QUART (which envisions 2–3 cm of grossly healthy margin), the surgery was less radical with large tumors because with increasing tumor size the extent of peritumor interstitial spread is probably increased. Instead, in the case of tumorectomy (an intervention declared to be nonradical, only reductive), complete sterilization of the tumor foci is linked to biologic conditions of radioresistance of malignant cells, independent therefore of the size of the mass.

Another important finding emerged from analysis of local recurrences in relation to the presence or absence of the histopathologic characteristic defined as "extensive intraductal component" (EIC) (Fig. 5). The presence of EIC increased the risk of local recurrences in patients treated by QUART as well as in those treated by TART. However, the difference was much more accentuated in cases who underwent tumorectomy (11 recurrences in 38 cases, 28%) than in those who underwent quadrantectomy (2 recurrences in 22 cases, 9%). This result occurs because the limited removal of healthy peritumor tissue inevitably leads, in cases with intraductal diffusion, to persistence of the disease in an increased number of cases and because the breast cancer, with its intraductal spread, seems less radiosensitive than the common infiltrating form.

A final interesting observation from the Milan II study concerns the importance of the presence of positivity for malignant cells at the margins of the surgical resection. The resection margins were accurately examined in all cases of tumorectomy, whenever possible. When such margins were positive, rather than performing another wider resection the patient was given the same radiotherapy programmed for the other cases. Such a procedure was in line with the principles of tumorectomy—an intervention by definition not radical, only reductive. The resection margins were also examined for positivity in the quadrantectomy cases; but given the small percentage of positive cases among the first 120 cases, we decided to suspend the examination. Among the TART group, positive resection margins were found in 46 of 289 patients (15.9%) in whom the examination was possible. There were 8 patients (17.4%) with local recurrences in this subgroup, an incidence

Table 3. Rate of local recurrences according to positive and negative margins in the Milan II trial.

	Quadrantectomy + RT			Lumpectomy + RT		
Margins	No.	LR	%	No.	LR	%
Assessed	178	7	3.9	289	29	10.0
Positive	8	1	12.5	46	8	17.4
Negative	170	6	3.5	243	21	8.6
Not assessed	182	8	4.4	56	5	8.9
Total	360	15	4.2	345	34	9.9

LR: local recurrence.

superior to that of cases with negative margins (21 of 243, or 8.6%) (Table 3). The difference was not great.

What do these data tell us? First, the negativity of the margins must not be an element that assures the surgeon of a hypothetic radicality. Even among cases with negative margins the number of local recurrences was high, thereby demonstrating that the examination is not reliable. In contrast, positivity of the margins certainly indicates incomplete surgery and therefore a high risk of local relapse of the disease. The third observation is that 17% of patients with positive margins (and so with a highly probable persistence of tumor cells) had a recurrence, which implicitly shows that radiotherapy was able to completely eradicate residual tumor cells in the other 83% of the cases. The latter finding thus offers experimental evidence that about one of five mammary carcinomas is radioresistant.

Milan III Study

With the end of the Milan II study, we began a randomized study to evaluate the efficacy of the quadrantectomy itself, without the support of radiotherapy. The design of this Milan III study envisioned a randomized comparison between QUART and the simple intervention of quadrantectomy plus axillary dissection without radiotherapy (QUAD) (Fig. 6). The latter was instead administered in the case of recurrence. In a certain sense, the comparison was therefore between quadrantectomy plus prophylactic radiotherapy and quadrantectomy

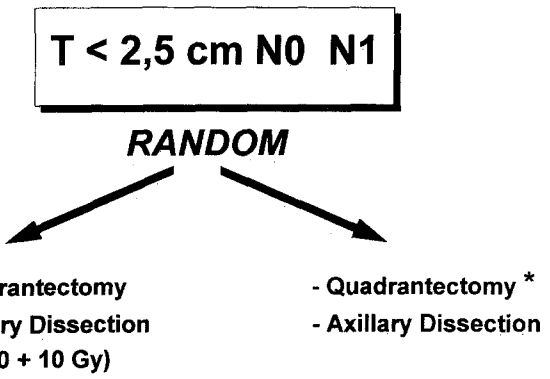

Fig. 6. Design of the randomized therapeutic Milan III study. * RT only in case of a local recurrence.

Table 4. Milan III trial: first event in the two groups.

Type of event	Quadrantectomy (no.)	
	+ RT (n = 294)	No RT (n = 273)
Local recurrence	1	24
New ipsilateral carcinoma	0	4
Contralateral tumor	2	5
Distant metastases	21	16
Other tumor	4	3

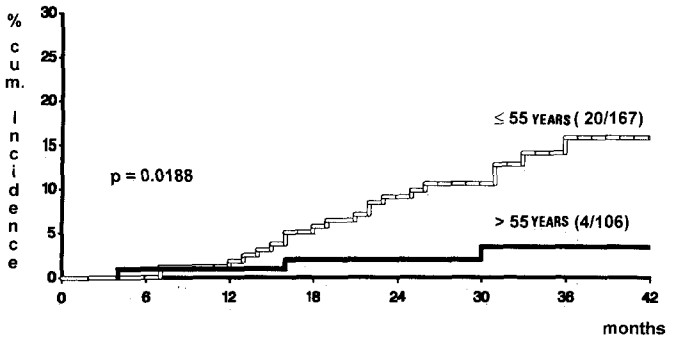

Fig. 7. Milan III study: incidence of local recurrence in relation to patient age.

plus therapeutic radiotherapy (i.e., limited to those cases in which it was really necessary because the quadrantectomy had not been radical). Eligibility criteria were the same as for the Milan II study. Milan III was carried out from 1988 to 1989: 567 women were randomized, 294 to the QUART arm and 273 to the arm of quadrantectomy without radiotherapy.

The results [7] demonstrated a considerable difference in the incidence of local recurrences between the two treatment groups. In fact, there were 24 (8.8%) local recurrences in the 273 patients treated only by quadrantectomy, whereas only 1 (0.3%) local recurrence was observed among the patients treated with QUART (Table 4). It should be noted, however, that in patients over 55 years of age the incidence of local recurrence was rather low even in women treated only by quadrantectomy, which led us to conclude that there is a considerable difference in the reaction to treatment of patients

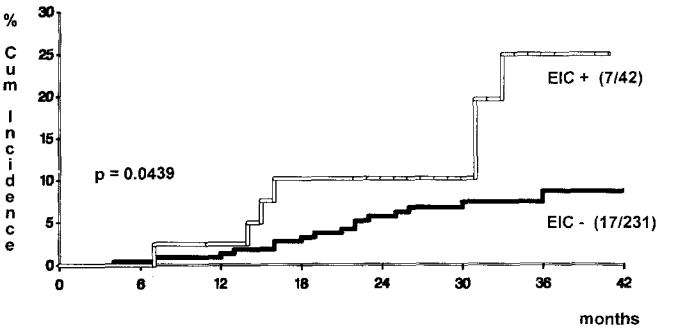

Fig. 8. Milan III study: incidence of local recurrence with quadrantectomy in relation to the presence of an extensive intraductal component (EIC).

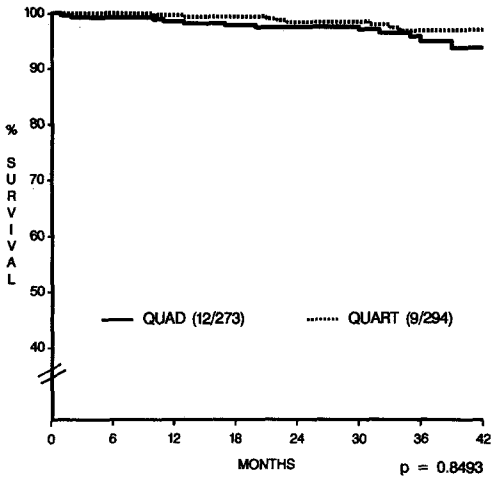

Fig. 9. Milan III study: overall survival of the two treatment arms. QUART: quadrantectomy, axillary dissection, radiotherapy; QUAD: quadrantectomy, axillary dissection.

before and after the menopause (Fig. 7). In fact, the mammary gland atrophies during the menopause, and the breast becomes a mass of adipose tissue with scattered islands of fibroepithelial tissue. It is thus conceivable that a simple partial surgery, performed with the usual criteria of oncologic radicality, can be resolving without complementary radiotherapy.

Moreover, the Milan III study confirmed the predictive value of EIC for local recurrences (Fig. 8). Patients with positive axillary lymph nodes had a slightly higher (not significant) incidence of local recurrences than patients with negative axillary lymph nodes. Survival was similar in the two groups (Fig. 9).

Résumé

L'analyse des principaux essais récents d'interventions conservatrices pour cancer du sein, pratiqués à l'Institut du Cancer de Milan entre 1973 et 1988, a montré que la résection large [quadranectomie] associée à la radiothérapie est sûre et que la survie à distance (recul jusqu'à 19 ans) est comparable à celle obtenue après mastectomie selon Halstead. Ces mêmes études ont montré que l'absence de radiothérapie associée augmentait

le risque de récidive et que la tumorectomie ("lumpectomie") était associée à un risque de récidive locale trois fois plus élevé. Chez la femme de 55 ans ou plus, cependant, la quadranectomie isolée reste valable. Parmi les facteurs de risque de récidive locale, on note l'âge jeune et la présence de composant intracanalaire étendu.

Resumen

Los más recientes análisis de los resultados de tres ensayos clínicos mayores sobre conservación de la glándula mamaria, realizados en el Instituto de Cáncer de Milán entre 1973 y 1988, demuestran que la conservación de la glándula mamaria mediante una amplia resección parcial (cuadrantectomía) combinada con radioterapia es un procedimiento seguro y que no se observan diferencias en la sobrevida a largo plazo, en seguimiento hasta de 19 años, en comparación con la mastectomía de Halsted. Tales estudios demostraron que, al reducir la resección de una cuadrantectomía a una tomorectomía, se aumenta el riesgo de recurrecia en casi tres veces y no prescribir radioterapia también incrementa en forma importante las tasas de recurrecia local. Sin embargo, en mujeres mayores de 55 años, la cuadrantectomía sola, sin radioterapia, puede dar buenos resultados. Entre los factores de riesgo de recurrencia local, la edad joven y la presencia de un extenso componente de carcinoma intraductal son los principales.

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