

Comparison of Halsted Mastectomy with Quadrantectomy, Axillary Dissection, and Radiotherapy in Early Breast Cancer: Long-Term Results

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Abstract—From 1973 to 1980 we randomly assigned 701 patients with breast cancer measuring less than 2 cm in diameter and with no palpable axillary lymph nodes to Halsted radical mastectomy (n 349) or to 'quadrantectomy' with axillary dissection and radiotherapy to the ipsilateral breast tissue (n 352). The two groups were comparable in age distribution, size and site of primary tumor, menopausal status, and frequency of axillary metastases. The average follow-up time was 103 months. Actuarial curves show no difference between the two groups in the disease-free interval after surgery or in the overall survival rate. At 8 yr the disease-free survival was 77% for the patients in the Halsted group and 80% for those in the 'quadrantectomy' group, and the overall survival was 83 and 85% respectively. We conclude that small breast cancers may be safely treated with the conservative treatment described. In our opinion total ablative operations are not justified.

INTRODUCTION

EARLY detection of breast cancer by mammography and cancer-detection programs and the increasing demand for less mutilating procedures have led to an increasing use of conservative procedures in the treatment of breast cancer. Although many papers in the past 20 yr have presented the results of several types of conservative techniques—surgical, radiologic, or combined—only a limited number of controlled clinical trials have compared the efficacy of various treatments. One early trial [1] showed a reduced survival rate in patients treated with a conservative procedure compared with that in patients treated with mastectomy, but other controlled studies have shown similar early results after both conservative and extensive ablative procedures [2, 3].

At the National Cancer Institute in Milan, a clinical trial comparing the Halsted mastectomy with the quadrantectomy plus axillary dissection and radiotherapy (QUART) was begun in 1973. Early results were published in 1981 [4]. We now present an analysis of 12 years' experience.

PATIENTS AND METHODS

Patients with clinical or mammographic evidence of a breast cancer less than 2 cm in diameter without palpable lymph nodes ($T_1 N_0$) were randomly assigned to one of two treatment groups.

Patients assigned to one group were treated with the Halsted mastectomy. In the last 2 yr of the trial, the extent of mastectomy was slightly reduced by allowing preservation of a large portion of the major pectoralis muscle. Fifty-four patients underwent this modified procedure. Those in the other group underwent a 'quadrantectomy'. Before random assignment, the patients were informed about both surgical procedures, and only patients who accepted both treatments were included in the trial.

Patients were stratified according to menopausal status and randomized (by means of random permuted blocks of eight patients) after the excisional biopsy was performed.

'Quadrantectomy' describes the removal of the entire quadrant of the breast containing the primary carcinoma, together with the overlying skin and the fascia of the major pectoral muscle. The axillary lymph nodes were excised during the

quadrantectomy either en bloc, or in discontinuity, through a separate incision. All the axillary lymph nodes up to the apex of the axilla were removed, and the minor pectoral muscle was totally removed.

Patients with either *in situ* lobular carcinoma or noninfiltrating ductal carcinoma were excluded, as were patients who were more than 70 yr old or who had had previous malignant disease of any type. In seven cases, noninvasive carcinoma (lobular and ductal) was found in the removed quadrant in addition to the primary invasive carcinoma. These cases were not excluded from the study.

Irradiation of the breast was an integral part of the treatment. A dose of 5000 rad (50 Gy) calculated at the midplane of the breast was delivered through two opposing tangential fields with high-energy photons (a cobalt unit or a 6 MeV linear accelerator) and with a conedown of 1000 rad (10 Gy) to the tumor bed with a short-distance, high-voltage röntgen therapy (300 keV, local skin distance 15 cm, and Cu half-value layer, 5.5 mm). Radiotherapy was started 20–30 days after surgery and was completed within 6 weeks. Until the end of 1975, patients of both groups who had positive nodes were randomly assigned to receive adjuvant radiotherapy to supraclavicular and homolateral internal mammary nodes (4000–4500 rad—40–45 Gy—for 4–5 weeks). From 1976 to 1980, the lymph node regions were not irradiated.

Beginning in 1976, all patients with positive nodes were treated with 12 cycles of the chemotherapy with the cyclophosphamide-methotrexate-fluorouracil (CMF) regimen. Chemotherapy was started 15–30 days after surgery. In the quadrantectomy group it was simultaneous with radiotherapy in most cases. The average quantity of drugs administered was similar in the two treatment groups.

All the patients were followed at quarterly intervals. A chest X-ray examination was requested every 6 months for the first 5 yr and then once a year. A complete bone scan or X-ray study was performed yearly.

The average follow-up time was 103 months. Five patients (0.7%) were lost to follow-up.

Data were entered monthly according to the information derived from the follow-up examinations. The calculation of the life tables was performed by the Kaplan–Meier method [5], and the curves were compared by the log-rank test, after adjustment for nodal involvement and for adjuvant therapy.

RESULTS

A total of 701 evaluable patients were entered into the trial: 349 were treated with the Halsted mastectomy and 352 with the conservative pro-

cedure. The two groups were completely comparable. There were no significant differences between them in any of the variables considered, such as age, menopausal status, quadrant of tumor site, histologic features, dimension of the primary cancer, incidence of axillary metastases, or previous biopsy examination. The primary cancer measured less than 1 cm in diameter in 44.4% of the patients in the Halsted group and in 46.0% in the quadrantectomy group. Microscopical evidence of axillary metastases was found in 24.6% of the patients treated with the Halsted mastectomy and in 27.0% of those treated with quadrantectomy. Breakdown according to the number of lymph nodes involved showed no significant difference between the two treatment groups.

The results were evaluated according to three major criteria: the relapse-free interval and overall survival rate of the patients, the incidence of local recurrences, and the incidence of second primary tumors in the ipsilateral and the contralateral breasts.

Survival

At 10 yr from the beginning of the trial the actuarial calculation of the survival shows no difference between the two groups. When both the relapse-free interval and the overall survival rate were evaluated, the curves were superimposable (Fig. 1). When the series was stratified according to axillary involvement, the advantage of the conservative treatment (quadrantectomy) in the patients with positive axillary-node was significant in the curves for relapse-free survival ($P = 0.03$), but not in those for the overall survival rate ($P = 0.08$) (Fig. 2). When the relapse-free survival was evaluated according to the number of involved axillary nodes, the difference was more evident in cases with one node involved and less evident in cases with two to three nodes involved. There was no difference among cases with four or more nodes involved.

The number of patients who died from breast cancer was 38 in the quadrantectomy group and 51 in the Halsted group (Table 1). Table 2 shows the actuarial 8-yr and 10-yr survival according to treatment.

Table 1. Causes of death

	Halsted	QU A RT
Breast cancer	51	38
Other cancers	8	9
Other causes	8	9
Total	67	56

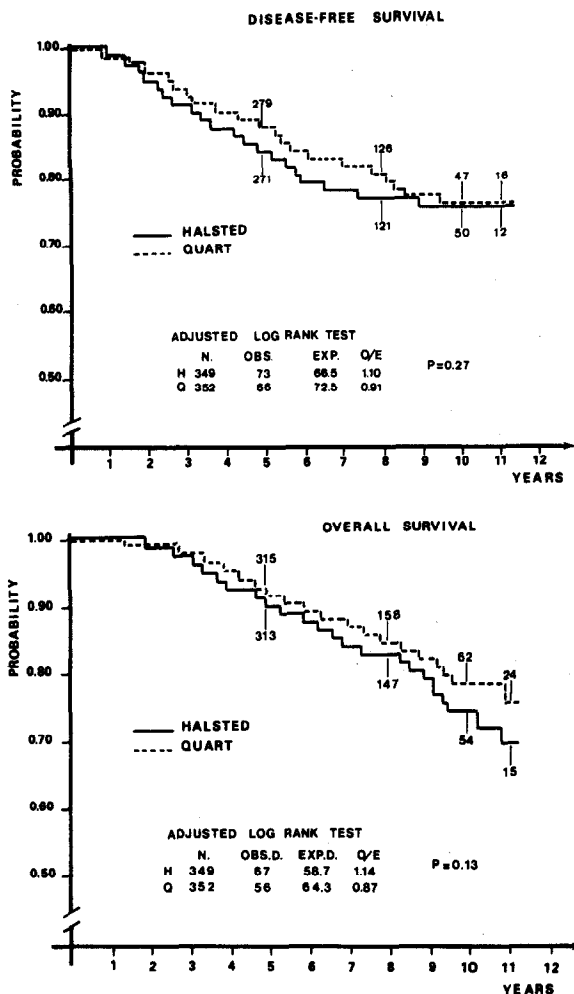


Fig. 1. Disease-free and overall survival rates according to type of treatment.

Table 2. Actuarial 8 and 10-yr survival in patients treated with Halsted or QUART (per cent of patients; \pm S.E.)

	Halsted		QUART	
	8 yr			
	%	S.E.	%	S.E.
Overall survival	83 ± 2.2		85 ± 2.1	
Disease-free survival	77 ± 2.4		80 ± 2.4	
	10 yr			
	%	S.E.	%	S.E.
Overall survival	78 ± 3.3		79 ± 2.9	
Disease-free survival	76 ± 2.6		77 ± 2.9	

In the first 2 yr of the trial, patients in both groups who had positive axillary nodes were further randomly assigned to receive either no further treatment or adjuvant radiotherapy to regional node stations. As of this writing, 16 of 23 patients without further radiotherapy and 16 of 33 patients treated with regional radiotherapy remain free of disease.

Local recurrences

Seven recurrences were observed among both the cases treated with quadrantectomy plus axillary dissection and radiotherapy and the patients treated with the Halsted mastectomy. In addition, seven new ipsilateral primary carcinomas were observed in the patients in the quadrantectomy group (Table 3). The criteria for distinguishing a local recurrence from a second primary tumor were the following: (1) site in the breast (nodules in

Table 3. Local recurrences, second primary breast cancers according to treatment group

Variable	Treatment	
	Halsted	QUART
Local recurrences	7	7
Second primary tumors		
Ipsilateral breast	—	7
Contralateral breast	16	18

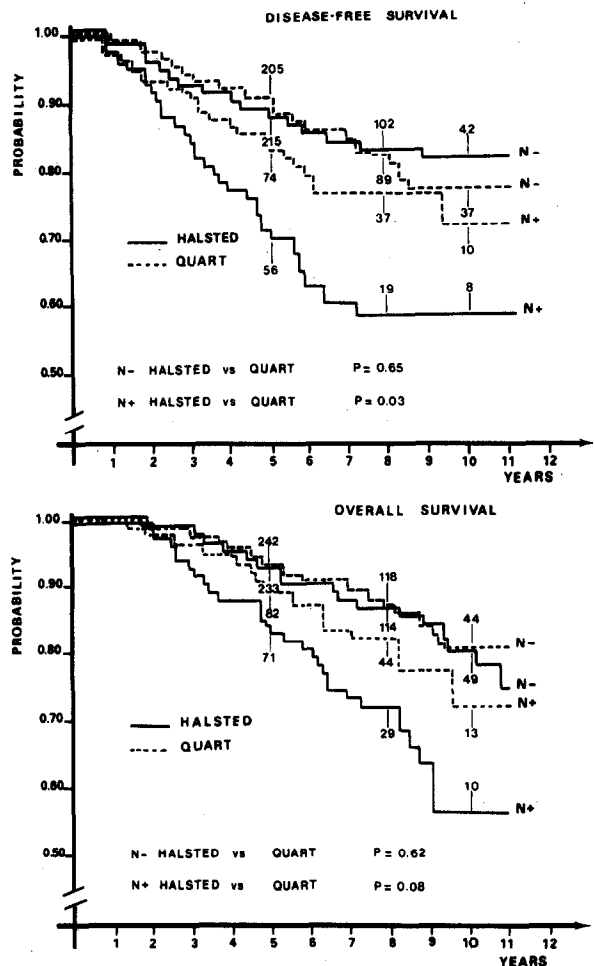


Fig. 2. Disease-free and overall survival rates of patients treated with Halsted mastectomy and with quadrantectomy, axillary dissection and radiotherapy (QUART), according to presence (N+) or absence (N-) of axillary node metastases.

the same quadrant were considered likely to be recurrences, whereas those in distant quadrants likely to be second primary tumors); (2) superficiality (nodules in the subcutaneous tissue or in the skin were all considered recurrences); (3) histologic type (in three cases the nodules were clearly of different histologic types, and this qualified them as second primary tumors). Most recurrences in both groups occurred in the early years after treatment (Fig. 3).

Ipsilateral and contralateral second carcinomas

This trial provides an opportunity to evaluate the incidence of a new carcinoma that is possibly related to radiation. In fact, this study, including subsets of patients given different levels and distribution of doses to the operated and contralateral breast, represents an 'experimental model'. One group (the Halsted group) received no radiotherapy, whereas in the other group the affected breast received radiotherapy at full doses (50 + 10 Gy) and the contralateral breast received a low but measurable level of irradiation. Accurate dosimetric evaluation through lithium fluoride dosimeters showed that the median scattered dose to the contralateral breast was approx. 1–2 Gy—except for the very internal portions of the median quadrants, which received 10–20 Gy because of the direct contribution from the external tangential field. So far, we have observed seven cases of second primary carcinomas in the ipsilateral breast as compared with 18 cases in the contralateral breast.

A problem of comparability is presented by the direct and scattered irradiation of the contralateral breast that occurs during the radiotherapy of the operated breast. Despite the lack of homogeneity of the dose distribution in the contralateral breast, the 18 contralateral new carcinomas were distributed by quadrants according to normal rates. Moreover, the incidence of contralateral carcinomas after conservative treatment was not statistically higher than that in the nonirradiated Halsted group, in which 16 contralateral carcinomas have been detected to date (Fig. 3).

DISCUSSION

These data show that the conservative treatment (quadrantectomy plus axillary dissection and radiotherapy) applied in our trial was not inferior, as regards long-term survival, to the Halsted mastectomy. All the cases accrued to the trial have now had more than 5 yr of follow-up from the time of the operation, and the first cases treated have had 12 yr of follow-up. Since the long-term survival curves are superimposable in the two groups of patients, it is reasonable to consider the results as conclusive. As regards the relapse-free survival, in

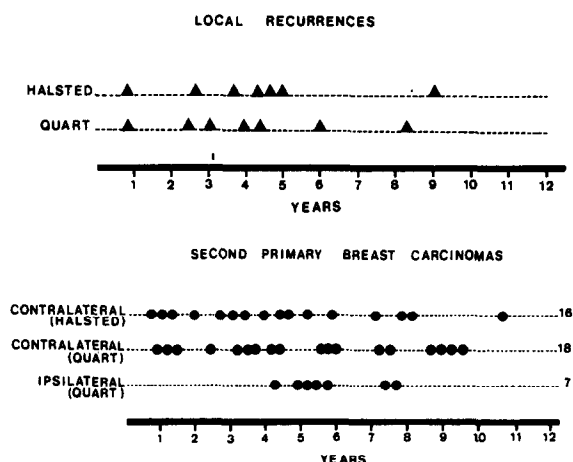


Fig. 3. Length of time after surgery before local recurrences and timing of appearance of second primary carcinomas in the ipsilateral and contralateral breasts in the patients who underwent quadrantectomy (QUART), and of contralateral carcinomas in the patients who underwent Halsted mastectomy.

some subsets of patients (those with one to three positive axillary nodes) the quadrantectomy procedure was better than the Halsted mastectomy. The incidence of local recurrences was low, similar to that for the Halsted mastectomy. The low incidence of local recurrences after quadrantectomy has fulfilled our expectations. In fact, when the trial was designed 15 yr ago, the decision to combine the quadrantectomy with aggressive radiotherapy was made for two reasons. The first was that a too limited resection would increase the chances of a local recurrence, because in a certain percentage of cases satellite foci of the primary carcinoma may be present around the tumor, and an extensive resection (like the removal of the full quadrant) would reduce this risk to a small percentage. Secondly, it was thought that this limited percentage would be further decreased by radiotherapy, which could sterilize the residual cancer cells, with the exclusion of the radioresistant cases. With 15% estimated to be the risk of leaving residual cancer cells and 15% to be the percentage of radioresistant cases, the theoretically expected rate of local recurrences was estimated to be 2%, which was in fact roughly the observed rate.

One could ask oneself what the results of the trial would have been if the control treatment, instead of the Halsted mastectomy, had been a modified radical mastectomy. As was shown in a randomized study, patients treated with the modified operation alone have an increased rate of local recurrences as compared with patients operated on with the Halsted technique [6]. One would therefore logically conclude that the quadrantectomy procedure plus axillary dissection and radiotherapy is probably safer than the modified radical mastectomy alone as regards local control of the disease.

An important issue remains the risk of carcinogenesis from breast irradiation. This hypothetical risk is one of the deterrents to the use of radiation in the treatment of primary breast carcinoma [7, 8]. Although a longer follow-up will be necessary to evaluate this factor, until now there has been no evidence of such a risk. If breast cancer is a multifocal disease in a certain percentage of cases, it may be that radiotherapy has a sterilizing effect on the multiple occult foci of *in situ* or invasive carcinoma in the treated breast, whereas in the opposite breast a number of occult microcarcinomas may develop into overt cancers.

Whether both the extensive resection of the breast performed with a quadrantectomy and the aggressive radiotherapy are necessary or whether one of the procedures may be sufficient to control the disease cannot be established from the present study. The two procedures were combined to minimize the risk of local recurrences, and this objective was in fact achieved. Additional studies are required to evaluate less aggressive conservative treatments. However, the preliminary

results from the National Surgical Adjuvant Breast Project Trial [3] show that conservative surgery alone, without radiotherapy, may result in a considerable increase in local recurrences, although the survival rates seem to be unaffected.

A final comment is required as regards the choice of the patients to be submitted to the quadrantectomy procedure. We can limit the eligibility to patients with carcinomas of 2 cm or less at macroscopic evaluation, without palpable axillary nodes. The low rate of local recurrences may indicate that the conservative procedure may be safely applied to tumors of larger size (perhaps of 2.5 or 3.0 cm). As regards the axillary involvement, the results show that the patients with axillary metastases at pathological examination who were treated with quadrantectomy plus axillary dissection and radiotherapy had long-term survival that was not inferior (and was perhaps superior) to that of the patients who had Halsted mastectomy. Therefore, it appears logical to extend the indication for the quadrantectomy procedure to patients with palpable axillary nodes.

REFERENCES

1. Hayward JL. The Guy's Hospital trial on breast conservation. In: Harris JR, Hellman S, Silen W, eds. *Conservative Management of Breast Cancer. New Surgical and Radiotherapeutic Techniques*. Philadelphia, Lippincott, 1983, 77-90.
2. Sarrazin D, Lê MG, Fontaine MF, Arriagada R. Conservative treatment versus mastectomy in T₁ or small T₂ breast cancer. A randomized clinical trial. In: Harris JR, Hellman S, Silen W, eds. *Conservative Management of Breast Cancer. New Surgical and Radiotherapeutic Techniques*. Philadelphia, Lippincott, 1983, 101-114.
3. Fisher B, Bauer M, Margolese R, Poisson R, Pilch Y, Redmond C, Fisher E, Wolmark N, Deutsch M, Montague E, Saffer E, Wickerham L, Lerner H, Glass A, Shibata H, Deckers P, Ketcham A, Oishi R, Russell I. Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. *N Engl J Med* 1985, **312**, 665-673.
4. Veronesi U, Saccozzi R, Del Vecchio M, Banfi A, Clemente C, De Lena M, Gallus G, Greco M, Luini A, Marubini E, Muscolino G, Rilke F, Salvadori B, Zecchini AM, Zucali R. 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.
5. Kaplan EL, Meier P. Nonparametric estimations from incomplete observations. *J Am Stat Assoc* 1958, **53**, 457.
6. Maddox WA, Carpenter JT, Laws HL, Soong SJ, Cloud G, Urist MM, Balch CM. A randomized prospective trial of radical (Halsted) mastectomy versus modified radical mastectomy in 311 breast cancer patients. *Ann Surg* 1983, **198**, 207-212.
7. McGregor DH, Land CE, Choi K, Tokuoka S, Lin PI, Wakabayashi T, Beebe GW. Breast cancer incidence among atomic bomb survivors, Hiroshima and Nagasaki, 1950-1969. *J Natl Cancer Inst* 1977, **59**, 799-811.
8. Shore RE, Hempelmann LH, Kowaluk E, Mansar PS, Pasternak BS, Albert RE, Haughie GE. Breast neoplasms in women treated with X-rays for acute post-partum mastitis. *J Natl Cancer Inst* 1977, **59**, 813-822.