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FIVE-YEAR RESULTS OF A RANDOMIZED CLINICAL TRIAL COMPARING TOTAL MASTECTOMY AND SEGMENTAL MASTECTOMY WITH OR WITHOUT RADIATION IN THE TREATMENT OF BREAST CANCER

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Abstract In 1976 we began a randomized trial to evaluate breast conservation by a segmental mastectomy in the treatment of Stage I and II breast tumors ≤ 4 cm in size. The operation removes only sufficient tissue to ensure that margins of resected specimens are free of tumor. Women were randomly assigned to total mastectomy, segmental mastectomy alone, or segmental mastectomy followed by breast irradiation. All patients had axillary dissections, and patients with positive nodes received chemotherapy.

Life-table estimates based on data from 1843 women indicated that treatment by segmental mastectomy, with or without breast irradiation, resulted in disease-free, distant-disease-free, and overall survival at five years that was no worse than that after total breast removal. In fact, disease-free survival after segmental mastectomy plus radiation was better than disease-free survival after total mastecto-

my ($P = 0.04$), and overall survival after segmental mastectomy, with or without radiation, was better than overall survival after total mastectomy ($P = 0.07$, and 0.06 , respectively). A total of 92.3 per cent of women treated with radiation remained free of breast tumor at five years, as compared with 72.1 per cent of those receiving no radiation ($P < 0.001$). Among patients with positive nodes 97.9 per cent of women treated with radiation and 63.8 per cent of those receiving no radiation remained tumor-free ($P < 0.001$), although both groups received chemotherapy.

We conclude that segmental mastectomy, followed by breast irradiation in all patients and adjuvant chemotherapy in women with positive nodes, is appropriate therapy for Stage I and II breast tumors ≤ 4 cm, provided that margins of resected specimens are free of tumor. (N Engl J Med 1985; 312:665-73.)

ANECDOTAL information has been presented by the pioneers¹⁻⁶ and more recent proponents⁷⁻¹¹ of breast preservation for the management of primary breast cancer. Although they have not clearly determined the relative merits of such a therapeutic approach by comparing it directly with more conventional methods of management, those observers have demonstrated that patients could survive free of disease after limited surgery and radiation therapy. The rationale that was employed to justify the use of the regimen is obscure. There was no biologic principle that directed the endeavor. In many instances the procedure was performed because patients refused a recommended radical mastectomy.² Thus, despite early and more recent efforts, important issues remain that preclude the universal acceptance and use of a more conservative approach to breast-cancer management.

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Even the few clinical trials that have evaluated breast conservation¹²⁻¹⁵ have failed to establish definitively the worth of such therapy.

Our findings in a previous clinical trial (Protocol B-04) indicated that patients treated by total mastectomy without axillary-node dissection and pectoral-muscle removal were at no higher risk of distant disease or death than were those undergoing a Halsted radical mastectomy.¹⁶ In view of these findings and because of the increasing practice of breast conservation despite the paucity of information available from clinical trials to determine its efficacy, we began a new study (Protocol B-06) in 1976 to evaluate the worth of local tumor excision with or without radiation therapy. The operation employed, a segmental mastectomy, completely abandoned conventional concepts of cancer surgery, removing only enough breast tissue to ensure that the margins of the resected surgical specimen were free of tumor. The study was designed to determine (1) the effectiveness of segmental mastectomy for breast preservation, (2) whether radiation therapy reduces the incidence of tumor in the ipsilateral breast after segmental mastectomy, (3) whether breast

conservation results in a higher risk of distant disease and death than does mastectomy, and (4) the clinical importance of tumor multicentricity. This report presents the five-year life-table estimates obtained from the trial.

METHODS

Selection of Patients

Women undergoing treatment for primary operable breast cancer and fulfilling specific eligibility criteria were participants in the trial. The tumor had to be confined to the breast or to the breast and ipsilateral axillary nodes on clinical examination, and the primary tumor had to be 4 cm or less in its largest dimension and movable in relation to the skin, underlying muscle, and chest wall, with no clinical evidence of skin involvement. Patients were eligible if the axilla was free of palpable nodes or if palpable nodes were movable in relation to the chest wall and neurovascular bundle (Stage I or II; T_{1,2}N_{0,1}M₀). In addition, the breast had to be of sufficient size and the tumor located so that the cosmetic result after removal of the tumor would be acceptable. Other criteria of eligibility and ineligibility were similar to those used in our prior trials.¹⁶⁻¹⁸

Protocol Design

Patients were randomly assigned to one of three treatment groups: total mastectomy, segmental mastectomy, or segmental mastectomy followed by breast irradiation. Women in all treatment groups had an axillary dissection. All resected segmental-mastectomy specimens were examined pathologically to ensure that the margins were free of tumor. A total mastectomy was carried out at the time of the segmental mastectomy if it was impossible to obtain tumor-free margins or if the pathologist, upon completing the microscopic examination, noted tumor at the specimen margin. In these cases patients continued to participate in the study, remaining in the original group to which they had been assigned. Patients in the two segmental-mastectomy groups whose specimen margins were free of tumor and who subsequently had a tumor in the ipsilateral breast also underwent a total mastectomy and remained in the original group to which they had been assigned. As defined in the protocol before the start of the study, these patients who underwent breast removal were considered to have had a cosmetic failure but were not classified as having had a treatment failure unless the tumor was so extensive that it could not be completely removed by mastectomy. The occurrence of tumor in the breast after segmental mastectomy was not considered an event in the disease-free survival of a patient, since patients who underwent total mastectomy as their initial operation were not at risk for the occurrence of a breast tumor. All patients assigned to the three groups were followed with respect to disease-free survival, distant-disease-free survival, and overall survival. Failure times were computed from the time of the initial operation. Recurrences of tumor in the chest wall and operative scar, but not in the ipsilateral breast, were classified as local treatment failures. Tumors in the internal mammary, supraclavicular, or ipsilateral axillary nodes were classified as regional treatment failures. Tumors in all other locations were considered distant treatment failures. Patients classified as having any distant disease included those with a distant metastasis as a first treatment failure, a distant metastasis after a local or regional recurrence, or a second cancer (including tumor in the other breast). Overall survival refers to survival with or without recurrent disease.

All patients in the study who had one or more positive axillary nodes received systemic adjuvant therapy with melphalan and fluorouracil. The regimen employed was identical to that used in previous studies.¹⁸

Surgical Considerations

When total mastectomy was performed, the entire breast, including the pectoral fascia, was removed together with the axillary contents en bloc. Patients assigned to the segmental-mastectomy groups underwent resection of the tumor, with enough normal tissue removed to ensure that the specimen margins were tumor-free. Re-

moval of pectoral fascia or skin overlying the tumor was not required. The fascia was removed when it was necessary to obtain tumor-free margins, and a small ellipse of skin was sometimes removed to provide pathological orientation of the specimen. The axillary dissection and tumor removal did not have to be performed en bloc. Even when the tumor was in the upper outer quadrant, the axillary dissection and tumor removal were usually carried out through separate incisions to achieve a better cosmetic result. In axillary dissections, at least Level I and II nodes were removed. Axillary "sampling" was not employed in this study. The mean number of nodes removed was 15, which has been consistent in all our protocols regardless of whether a segmental, radical, or total mastectomy was carried out. Early experiences determined the type of incision and other details of surgical management necessary for the best cosmetic result. Minimal skin removal; curvilinear incisions; no reapproximation of breast, fatty, or subcutaneous tissue; and no drainage of the tumor site were all found to aid in improving the appearance of the breast postoperatively.

Breast Irradiation

The purpose of breast irradiation after segmental mastectomy was to treat the skin, breast tissue, muscle, lymphatics, and entire scar of the breast. Radiation therapy was begun no later than six weeks after segmental mastectomy in patients with negative nodes and no later than eight weeks after surgery in those with positive nodes. In patients with positive nodes radiation therapy was delayed to permit completion of the first course of adjuvant chemotherapy. A minimum of 5000 rad was administered, calculated at a depth equal to two thirds of the distance between the skin overlying the breast and the base of the tangential fields at midseparation. The maximal dose to the point of calculation did not exceed 5300 rad. The dose was given at a rate of 1000 rad per week (200 rad per day, five days a week). Both tangential fields were treated daily. Supplemental boosts of radiation to the operative area (use of external beam or interstitial implantation) and radiation of regional nodes were not employed.

Statistical Analysis

Between April 1976 and May 1978, patients were randomly assigned to treatment within each participating institution, after informed consent had been obtained, and were stratified by institution, using a block size of nine. During that time envelopes were employed for random assignment because of the frequency of a one-stage biopsy and definitive operation. In June of 1978 the use of envelopes was discontinued, and all enrollments were carried out by telephone communication with the Biostatistical Center. Patients were stratified by institution with a block size of six, and blocks were balanced across institutions. Because of patient and physician diffi-

Table 1. Distribution of Patients by Treatment Group and Protocol Status.*

| PATIENTS | TREATMENT GROUP | | | TOTAL |
|---|-----------------|-----|--------|---------------------|
| | TM | SM | SM+RTX | |
| | no. of patients | | | no. of patients (%) |
| Enrolled | 713 | 719 | 731 | 2163 (100.0) |
| Excluded | | | | |
| Refused protocol | 16 | 11 | 14 | 41 (1.9) |
| Noninvasive tumor | 9 | 9 | 14 | 32 (1.5) |
| Ineligible | 14 | 14 | 12 | 40 (1.9) |
| Refused assigned treatment | 78 | 41 | 55 | 174 (8.0) |
| Follow-up data not available † | 9 | 9 | 6 | 24 (1.1) |
| Nodal status unknown † | 1 | 3 | 5 | 9 (0.4) |
| Comparison of TM with SM or SM+RTX | 586 | 632 | 625 | 1843 (85.2) |
| Comparison of SM with SM+RTX (negative margins) | | 565 | 566 | |

*TM denotes total mastectomy plus axillary dissection, SM segmental mastectomy plus axillary dissection, and RTX radiation therapy.

†At the time of the analysis.

culty with the conventional randomization process in a situation in which the alternatives were loss or preservation of the breast.¹⁹ a "prerandomization" procedure was carried out, in which patients were randomly assigned to treatment after assessment of their eligibility but before the protocol was explained or consent was obtained. After treatment had been assigned, the protocol, including all three treatment regimens, was discussed with the patient, as in the conventional process of random assignment. Signed consent was obtained from patients who accepted the assigned treatment. Analyses were carried out both for all patients randomly assigned to a treatment group, regardless of whether or not they accepted the assignment, and for all eligible patients who accepted the assigned therapy and who had follow-up information at the time of this analysis (1843 patients). Since the conclusions of the two analyses did not differ, the findings presented here are from the patients who accepted the assigned therapy (Table 1). Patients refusing all participation have been excluded from the analyses.

Life tables were computed by the actuarial method,²⁰ and comparisons of the distribution of failure times were based on the summary chi-square test, with adjustment for the number of positive nodes.^{21,22} All P values were based on two-sided alternatives.

Patient Distribution

Between April 8, 1976, and January 27, 1984, when patient enrollment ended, 2163 women entered the trial (Table 1). All patients except for 41 (1.9 per cent) who refused to participate in the trial were followed for end results. Of the remaining 2122 patients, 1.5 per cent had noninvasive tumors and 1.9 per cent were found on medical review to be ineligible because of the presence or a history of conditions specifically documented in the protocol that precluded their entry into the study — e.g., tumors >4 cm, skin involvement, previous or concomitant cancer, or medical problems precluding any of the treatment options. Overall, 8.0 per cent of women did not accept the randomly assigned treatment but did agree to be followed (11 per cent of the total-mastectomy group, 6 per cent of the segmental-mastectomy group, and 8 per cent of the group assigned to segmental mastectomy plus radiation). At the time of this analysis (June 1984), follow-up data were not yet available for 1.1 per cent of patients in each of the treatment groups, and the nodal status was unknown in a few patients who had been enrolled in the study too recently for us to obtain such information.

Thus, 1843 (85.2 per cent) of the patients originally enrolled in the study were included in comparisons between total and segmental mastectomy and between total mastectomy and segmental mastectomy plus radiation therapy. Those comparisons represent all eligible patients in each group, regardless of whether or not there was tumor involvement of the specimen margins. Since specimen

margins with tumor were associated with factors related to an unfavorable prognosis — e.g., increased tumor size and positive nodes — exclusion of patients with positive margins would have biased the outcome in favor of the groups treated by local tumor excision. On the other hand, comparison of the two segmental-mastectomy groups included only patients with specimen margins that were free of tumor, since those with positive margins had undergone a total mastectomy.

Certain patient and tumor characteristics were examined with respect to the similarity of their distribution in three groups: (1) the 2090 women who accepted the protocol and had invasive tumors, (2) the 1843 patients included in the analyses, and (3) the 247 patients who were excluded. No major differences overall or between treatment assignments were observed, which might indicate that there was a bias in the groups used for analyses. Analyses of end results were performed separately for patients in the first and second groups. The results were similar and consequently are presented only for the second group (1843 women). The mean duration of follow-up was 39 months (5 to 99).

RESULTS

Tumor Involvement of Specimen Margins after Segmental Mastectomy

Of the 1257 patients who were initially treated by segmental mastectomy and are evaluated in this report, 10.0 per cent were found to have tumor at the margins of resected specimens and therefore subsequently had a total mastectomy. The incidence of positive specimen margins was approximately the same in the two segmental-mastectomy groups: 10.6 per cent in the segmental-mastectomy group (632 patients) and 9.4 per cent in the group undergoing segmental mastectomy and radiation therapy (625 patients). The incidence of positive specimen margins was related to certain patient and tumor characteristics. Evaluation according to patient age showed that about 10 per cent of patients ≤49 years and those ≥50 years had positive margins. A higher percentage of patients with positive nodes (15 per cent) than with negative nodes (7 per cent) had positive margins after segmental mastectomy, and the larger the number of positive axillary nodes, the higher the incidence of

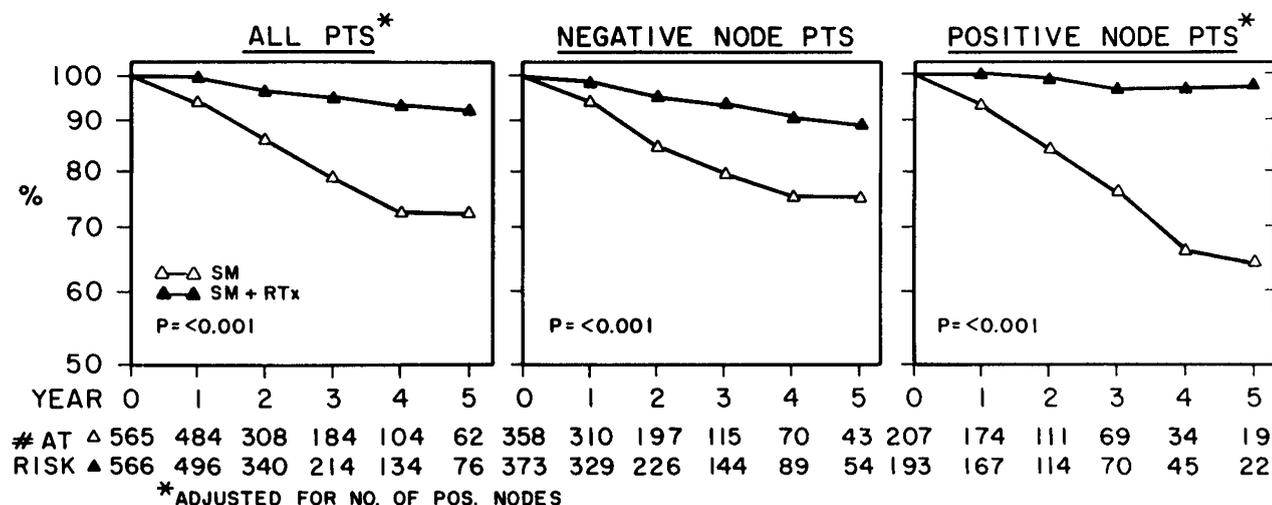


Figure 1. Life-Table Analysis Showing the Percentage of Patients Remaining Free of Breast Tumor after Segmental Mastectomy (SM) or Segmental Mastectomy with Breast Irradiation (SM+RTx).

positive specimen margins; 33 per cent of patients with ≥ 10 positive nodes had margins containing tumor. Women with larger tumors (2.1 to 4 cm) had a higher percentage of positive margins (13 per cent) than those with tumors between 0 and 2 cm (7 per cent). Women with centrally located tumors were most apt to have margin involvement.

Tumor Occurrence in the Ipsilateral Breast after Segmental Mastectomy with and without Breast Irradiation in Patients with Tumor-Free Specimen Margins

The value of breast irradiation is demonstrated by the cumulative incidence of a tumor in the ipsilateral breast after segmental mastectomy with and without radiation therapy. From the beginning of the study to the time of this analysis, 25 patients had a breast tumor after treatment by segmental mastectomy and postoperative irradiation, as compared with 93 patients in the group treated by segmental mastectomy alone. The incidence among patients with negative nodes was 22 in the group receiving radiation therapy and 54 in the group undergoing segmental mastectomy alone. Among patients with positive nodes, 3 treated with segmental mastectomy and radiation and 39 undergoing segmental mastectomy alone had subsequent tumor. Life-table analyses indicated the probability that patients would remain free of tumor in the ipsilateral breast during a five-year period after segmental mastectomy (Fig. 1). The addition of radiation therapy significantly decreased the probability that a tumor would occur ($P < 0.001$). At five years only 7.7 per cent of patients receiving radiation therapy had a recurrence of tumor in the ipsilateral breast, as compared with 27.9 per cent of those treated by segmental mastectomy without radiation. The advantage associated with the use of radiation therapy was observed in both patients with negative nodes ($P < 0.001$) and those with positive nodes ($P < 0.001$). Only 2.1 per cent of patients with positive nodes who were irradiated had a tumor, as compared with 36.2 per cent of those who did not undergo irradiation. When the probability of remaining free of a breast tumor after segmental mastectomy with or without radiation therapy was determined according to nodal status and tumor size, radiation therapy was observed to be beneficial for patients with negative or positive nodes and smaller (0 to 2 cm) or larger (2.1 to 4 cm) tumors. The probability of remaining free of a breast tumor after segmental mas-

tectomy with or without radiation therapy was examined according to the age of the patients, their nodal status, clinical tumor size, and tumor location (Table 2). Breast-tumor recurrence was lower in all circumstances for patients receiving radiation therapy.

Disease-Free Survival, Distant-Disease-Free Survival, and Overall Survival

When the women included in the analyses of disease-free, distant-disease-free, and overall survival were examined according to the distribution of certain patient and tumor characteristics within each treatment group, there was excellent agreement among the three groups (Table 3). Almost 60 per cent of the women were 50 years old or older. Slightly more than 60 per cent had negative nodes, and the majority of the others had only 1 to 3 positive nodes. In each treatment group only about 3 per cent of all patients had ≥ 10 positive nodes, and there was a fairly uniform distribution of patients with small (0 to 2 cm) and large (2.1 to 4 cm) tumors. Approximately 60 per cent of the tumors were lateral, about 20 per cent were medial, and the rest were central. A similar concordance existed among the three groups when the distribution of patients according to nodal status and clinical tumor size was evaluated. Examination of events (Table 4) that had occurred from the start of the study to the time of analysis (cumulative to 97 months after mastectomy) revealed that in all three groups, more than half the first reported treatment failures

Table 2. Patients Remaining Free of Tumor in the Ipsilateral Breast after Segmental Mastectomy with and without Radiation, According to Patient and Tumor Characteristics.*

| CHARACTERISTIC * | NO. OF PATIENTS | PATIENTS FREE OF BREAST TUMOR (LIFE TABLE) | | | | | |
|--------------------------|-----------------|--|----------------|-------------|----------------|-------------|----------------|
| | | AT 3 YEARS | | AT 4 YEARS | | AT 5 YEARS | |
| | | no. at risk | % | no. at risk | % | no. at risk | % |
| Age (yr) | | | | | | | |
| <49 | | | | | | | |
| SM | 233 | 84 | 75.6 \pm 3.4 | 59 | 70.6 \pm 4.0 | 40 | 70.6 \pm 4.0 |
| SM+RTX | 242 | 108 | 94.3 \pm 1.9 | 69 | 92.8 \pm 2.4 | 40 | 90.9 \pm 3.1 |
| >50 | | | | | | | |
| SM | 332 | 128 | 80.0 \pm 2.9 | 58 | 74.6 \pm 3.8 | 30 | 72.4 \pm 4.3 |
| SM+RTX | 324 | 131 | 95.5 \pm 1.5 | 80 | 93.5 \pm 2.1 | 50 | 93.5 \pm 2.1 |
| Nodal status | | | | | | | |
| Negative | | | | | | | |
| SM | 358 | 131 | 79.4 \pm 2.7 | 79 | 76.5 \pm 3.1 | 49 | 76.5 \pm 3.1 |
| SM+RTX | 373 | 158 | 93.6 \pm 1.6 | 101 | 90.9 \pm 2.2 | 62 | 89.6 \pm 2.5 |
| Positive | | | | | | | |
| SM | 207 | 81 | 76.2 \pm 3.8 | 38 | 66.5 \pm 5.3 | 21 | 63.8 \pm 5.7 |
| SM+RTX | 193 | 81 | 97.9 \pm 1.6 | 48 | 97.9 \pm 1.6 | 28 | 97.9 \pm 1.6 |
| Clinical tumor size (cm) | | | | | | | |
| 0-2 | | | | | | | |
| SM | 289 | 120 | 79.3 \pm 3.1 | 67 | 73.8 \pm 3.8 | 40 | 73.8 \pm 3.8 |
| SM+RTX | 298 | 142 | 97.4 \pm 1.2 | 85 | 95.2 \pm 2.0 | 52 | 93.5 \pm 2.5 |
| 2.1-4 | | | | | | | |
| SM | 263 | 91 | 77.1 \pm 3.2 | 50 | 72.3 \pm 4.0 | 30 | 70.1 \pm 4.4 |
| SM+RTX | 256 | 95 | 91.7 \pm 2.4 | 63 | 90.4 \pm 2.7 | 38 | 90.4 \pm 2.7 |

*Abbreviations are explained in Table 1. Plus-minus values are means \pm S.E.

were distant recurrences. There were few local failures in any group, with the lowest number occurring in the group receiving segmental mastectomy and radiation therapy. Second cancers and deaths from other causes were distributed equally across treatment groups.

Comparison of Total and Segmental Mastectomy

Life-table analyses were used to compare disease-free, distant-disease-free, and overall survival in all patients undergoing total mastectomy and in all those undergoing segmental mastectomy. The latter group included all women regardless of whether the specimen margins were positive or negative for tumor. Disease-free survival and distant-disease-free survival were remarkably similar in the two treatment groups (Fig. 2), with an advantage that approached significance ($P = 0.06$) in the segmental-mastectomy group. In terms of nodal status (negative or positive), no significant differences in disease-free or distant-disease-free survival existed between the total-mastectomy and segmental-mastectomy groups, as exemplified by the five-year life-table findings (Table 5). Among both patients with negative nodes and those with positive nodes, survival was higher for patients treated by segmental mastectomy; the advantage for patients with negative nodes was significant ($P = 0.05$).

Comparison of Total Mastectomy and Segmental Mastectomy plus Radiation Therapy

In this analysis the group of patients undergoing segmental mastectomy plus radiation therapy included all women whether or not their specimen margins

Table 3. Characteristics of 1843 Patients Included in Comparisons of Total Mastectomy with Segmental Mastectomy or with Segmental Mastectomy and Radiation Therapy.*

| CHARACTERISTICS | TM | SM | SM + RTX |
|-----------------|---------------|-----------|-----------|
| | (N = 586) | (N = 632) | (N = 625) |
| | % of patients | | |
| Age (yr) | | | |
| ≤49 | 42.3 | 41.2 | 43.8 |
| ≥50 | 57.7 | 58.8 | 56.2 |
| Nodal status | | | |
| Negative | 61.8 | 61.7 | 63.4 |
| Positive | 38.2 | 38.3 | 36.6 |
| 1–3 | 25.9 | 24.8 | 25.6 |
| 4–9 | 9.4 | 9.2 | 8.5 |
| ≥10 | 2.9 | 4.3 | 2.5 |
| Tumor size (cm) | | | |
| 0–2 | 52.9 | 49.4 | 51.5 |
| 2.1–4 | 44.5 | 48.4 | 46.1 |
| NA | 2.6 | 2.2 | 2.4 |
| Tumor location | | | |
| Lateral | 59.5 | 61.9 | 59.3 |
| Central | 15.9 | 13.7 | 15.7 |
| Medial | 21.7 | 22.5 | 21.3 |
| NA | 2.9 | 1.9 | 3.7 |

*NA denotes not available at the time of the analysis. Other abbreviations are explained in Table 1.

Table 4. Disease-Free Survival and Cumulative Incidence of Events within Each Treatment Group.*

| FIRST EVENT | TM | SM | SM + RTX |
|-------------------------------|-----------------|-----------|-----------|
| | (N = 586) | (N = 632) | (N = 625) |
| | no. of patients | | |
| First treatment failure | 99 | 106 | 80 |
| Local † | 27 | 25 | 4 |
| Regional | 18 | 20 | 14 |
| Distant | 52 | 59 | 62 |
| Location unknown | 2 | 2 | 0 |
| Second cancer | 14 | 21 | 16 |
| Death from another cause | 9 | 6 | 7 |
| Alive, no evidence of disease | 464 | 499 | 522 |
| Time in study (mo) | | | |
| Mean | 39.5 | 38.2 | 38.9 |
| Range | 5.5–97.2 | 5.0–97.1 | 4.7–98.7 |

*Abbreviations are explained in Table 1.

†Tumor occurring in the ipsilateral breast after SM was not considered a treatment failure (of any type) and therefore was included in the no-evidence-of-disease category.

were free of tumor. Life-table analyses failed to indicate an advantage in disease-free, distant-disease-free, or overall survival for patients treated by total mastectomy (Fig. 3). In fact, disease-free survival was higher ($P = 0.04$) and distant-disease-free survival was slightly higher (P not significant) in patients undergoing segmental mastectomy plus radiation. The observed survival benefit in this group approached significance ($P = 0.07$). A similar analysis of patients according to their nodal status (Table 5) indicated that at five years there were no significant differences between the two treatment groups. However, among patients with negative nodes, the group treated with segmental surgery and radiation had 10 per cent higher overall survival and disease-free survival rates — differences that approached significance ($P = 0.09$ and 0.1 , respectively).

Comparison of Segmental Mastectomy and Segmental Mastectomy plus Radiation Therapy

Only patients with specimen margins that were free of tumor were included in this comparison, since those with positive margins had undergone total mastectomy, as required by the protocol. Life-table analyses indicated that disease-free survival was higher in patients receiving radiation therapy in addition to segmental mastectomy ($P = 0.02$, Fig. 4). However, there were no significant differences between the two groups with respect to distant-disease-free or overall survival. Whereas among patients with positive nodes the three measures of survival were similar in the two treatment groups five years after surgery, among patients with negative nodes, disease-free and distant-disease-free survival were better for those undergoing segmental mastectomy and radiation therapy ($P = 0.005$ and 0.02 , respectively), but there was

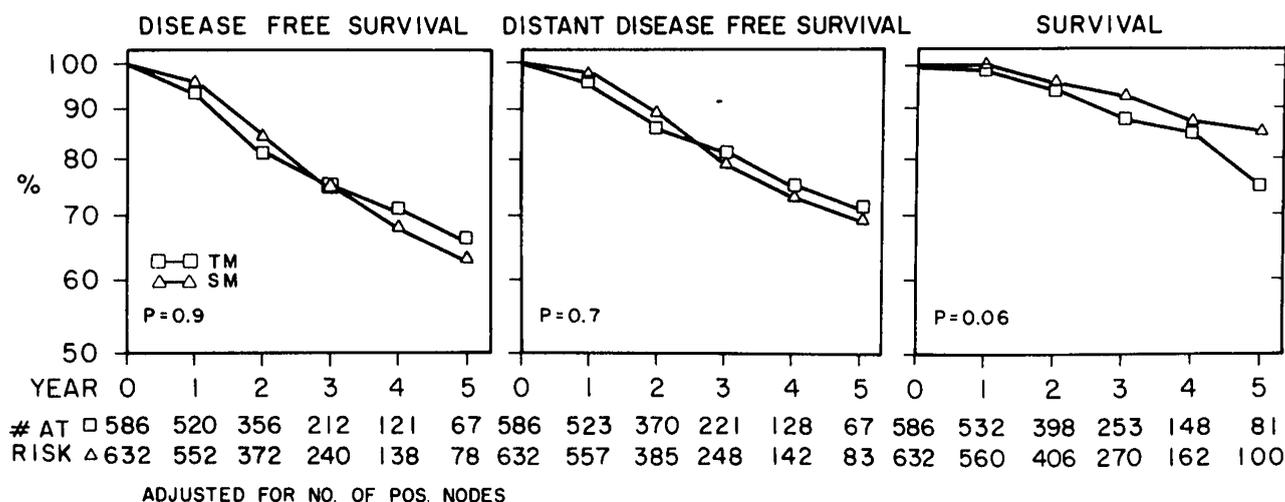


Figure 2. Life-Table Analysis Showing Disease-Free Survival, Distant-Disease-Free Survival, and Overall Survival of Patients Treated by Total Mastectomy (TM) or Segmental Mastectomy (SM).

no significant difference in overall survival between the two groups (Table 6).

DISCUSSION

The findings presented above clearly indicate the value of breast irradiation for reducing the incidence of tumor in the ipsilateral breast after segmental mastectomy. The five-year life-table results (Fig. 1) indicating that only 7.7 per cent of all patients treated with segmental mastectomy and radiation therapy had a recurrent tumor, as compared with 27.9 per cent of those undergoing segmental mastectomy without radiation, support this conclusion. Further evidence is found in the fact that only 2.1 per cent of patients with positive nodes receiving radiation therapy had a tumor at five years, as compared with 36.2 per cent of those who did not undergo irradiation, although both groups received the same chemotherapy. Those results, achieved with radiation therapy that did not include the use of either an external beam or interstitial implantation for supplemental therapy to the tumor excision site, approximate the incidence of recurrence (about 5 per cent) observed by proponents of such additive radiation.²³ Thus, the findings fail to indicate the need for a radiation boost to the excision site. Whether a boost of a particular type would contribute an additional advantage cannot readily be determined. Since some tumors recur in areas of the breast that are distant from the excision site, they are not likely to be prevented by a boost. Thus, the difference between results obtained with and without a particular type of boost is apt to be small. The size of the sample that would be required to conduct a

clinical trial to settle this issue hinders its undertaking. Further evaluation of our data with respect to the characteristics associated with tumor recurrence after radiation may indicate which patients would benefit from a boost.

Since all patients with positive nodes who received radiation therapy also received systemic adjuvant chemotherapy, the contribution of each to the inhibition of tumor recurrence in that cohort of women cannot be determined by our study. The observation that fewer tumors occurred in the breast after segmental mastectomy in patients with positive nodes (all of whom received a course of chemotherapy before starting radiation therapy) than in those with negative nodes (who received no chemotherapy) suggests that the two therapies may be additive, if not synergistic, in their effect.

Although radiation inhibits the recurrence of breast tumor, more than two thirds of our patients (72.1 per cent) who were treated by segmental mastectomy without radiation have remained free of tumor in the ipsilateral breast. Characteristics of patients who may

Table 5. Comparison of Total Mastectomy with Segmental Mastectomy and with Segmental Mastectomy plus Radiation Therapy According to Nodal Status.*

| END RESULTS | PATIENTS WITH NEGATIVE NODES | | | PATIENTS WITH POSITIVE NODES † | | |
|-------------------------------|-------------------------------|-----------------|--------------------|--------------------------------|----------------|--------------------|
| | TM (N = 362) | SM (N = 390) | SM + RTX (N = 396) | TM (N = 224) | SM (N = 242) | SM + RTX (N = 229) |
| | <i>percentage of patients</i> | | | | | |
| Disease-free survival | 71.9±3.5 | 68.1±3.5 (0.7) | 81.4±2.9 (0.1) | 57.9±5.3 | 54.8±5.7 (0.4) | 57.5±5.4 (0.6) |
| Distant-disease-free survival | 81.3±3.0 | 72.8±3.4 (0.2) | 85.3±2.6 (0.2) | 58.6±5.6 | 63.8±5.7 (0.2) | 61.3±5.4 (1.0) |
| Survival | 81.7±3.9 | 90.7±2.4 (0.05) | 91.6±2.1 (0.09) | 66.4±5.3 | 73.8±5.3 (0.3) | 75.2±4.5 (0.4) |

*Values represent life-table estimates of results five years after surgery, and are expressed as means ±S.E. Figures in parentheses are P values of comparisons between TM and either SM or SM + RTX. Abbreviations are explained in Table 1.

†Values are adjusted for the number of positive nodes (1 to 3, 4 to 9, or ≥10).

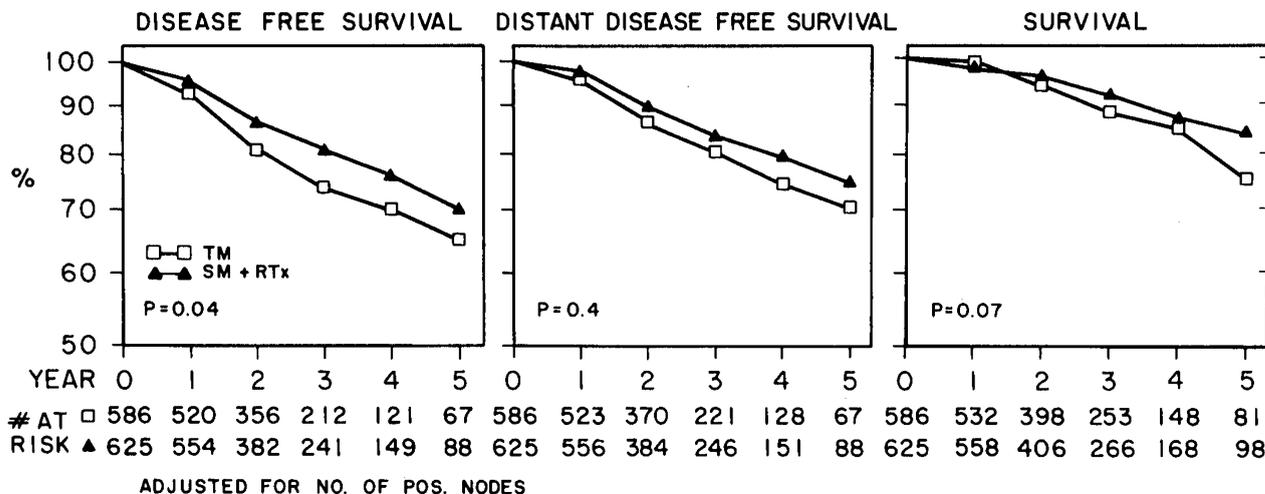


Figure 3. Life-Table Analysis Showing Disease-Free Survival, Distant-Disease-Free Survival, and Overall Survival of Patients Treated by Total Mastectomy (TM) or by Segmental Mastectomy plus Radiation (SM+RTx).

be at higher risk for tumor recurrence after segmental mastectomy — i.e., those who would benefit by radiation — have not been identified. Pathological discriminants and the receptor content of tumors are being examined to determine whether they may indicate which patients need radiation.

Our findings indicate that preservation of the breast (under the specific conditions of our protocol) has not resulted in an adverse effect on disease-free, distant-disease-free, or overall survival. It is important to note that when comparing each of the segmental-mastectomy groups with the total-mastectomy group, we included all patients in the segmental-mastectomy groups regardless of the status of their specimen margins. Thus, the failure to observe a poorer distant-disease-free or overall survival in the segmental-mastectomy groups cannot be attributed to exclusion of patients who were at higher risk.

Our trial differs from that of the National Cancer

Institute of Milan,¹⁴ which was restricted to patients with clinically negative nodes and tumors <2 cm. Only 25 per cent of the participants in our study met the criteria for that trial. The “quadrantectomy” used by the Milan group removed a large amount of skin and breast tissue, pectoral fascia, and pectoralis minor muscle. An en bloc dissection was performed in about 75 per cent of the patients. The operation we used was less extensive and did not include en bloc dissection. No difference in disease-free or overall survival has been observed at seven years between patients treated by Halsted radical mastectomy and those undergoing quadrantectomy.

The Guy’s Hospital trial,¹² which compared wide local excision with radical mastectomy, differs in several respects from both the trial reported here and the Milan study. Only postmenopausal patients were studied. All nodal staging was clinical, no axillary dissection was performed, and radiation used to

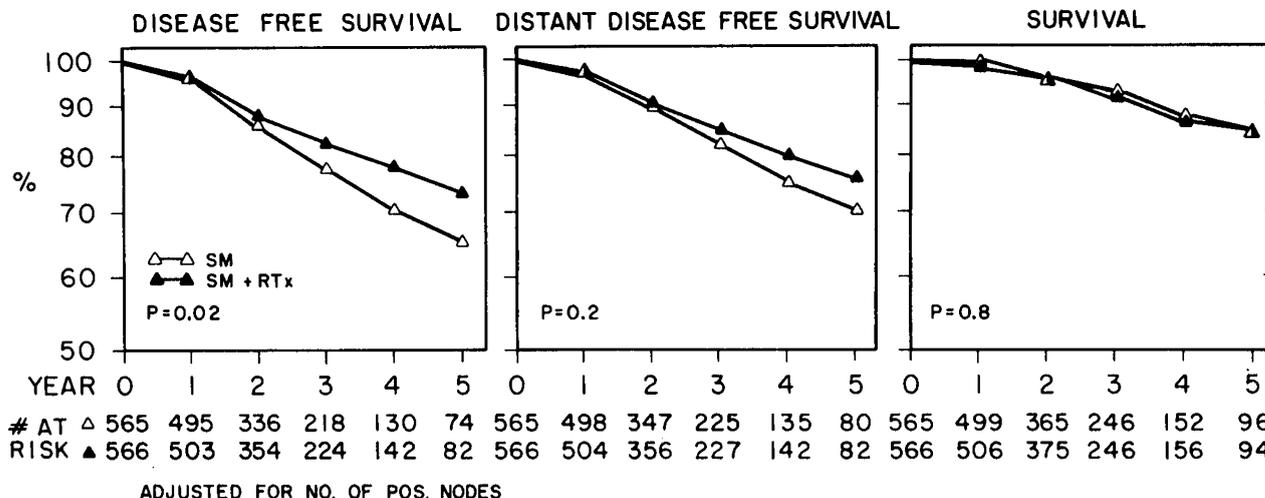


Figure 4. Life-Table Analysis Showing Disease-Free Survival, Distant-Disease-Free Survival, and Overall Survival of Patients Treated by Segmental Mastectomy (SM) or by Segmental Mastectomy with Radiation (SM+RTx) Who Had Specimen Margins Free of Tumor.

treat the axilla and breast was inadequate for local or regional disease control. Ten years after surgery there was a higher incidence of local and distant recurrence and a significantly lower survival among patients with involved axillary nodes who were treated by wide local excision; no differences were observed in those with uninvolved nodes. In a second Guy's Hospital study,¹³ in which patients with clinically uninvolved nodes were treated similarly to those in the first trial, there was a higher rate of local and distant recurrence and a decreased survival after wide excision. The major differences among the Milan trial, the Guy's Hospital trials, and ours make it impossible to relate the findings.

The results of our study lead us to conclude that segmental mastectomy and breast irradiation are suitable for the initial treatment of breast tumors that are no larger than 4 cm, provided that local excision can be achieved with tumor-free specimen margins and a satisfactory cosmetic result, and provided that patients with positive nodes also receive adjuvant chemotherapy.

We are indebted to Ms. Lynne Sidorovich, data manager of this study, and Mary Ketner, R.N., executive clinical coordinator of the National Surgical Adjuvant Breast Project, for their dedicated efforts.

APPENDIX I

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Table 6. Comparison of Segmental Mastectomy with Segmental Mastectomy plus Breast Irradiation, According to Nodal Status of Patients with Tumor-Free Specimen Margins.*

| END RESULTS | PATIENTS WITH NEGATIVE NODES | | PATIENTS WITH POSITIVE NODES † | |
|-------------------------------|-------------------------------|--------------------|--------------------------------|--------------------|
| | SM (N = 358) | SM + RTX (N = 373) | SM (N = 207) | SM + RTX (N = 193) |
| | <i>percentage of patients</i> | | | |
| Disease-free survival | 67.8 ± 3.7 | 80.9 ± 3.0 (0.005) | 56.5 ± 6.0 | 61.3 ± 5.8 (0.9) |
| Distant-disease-free survival | 72.8 ± 3.6 | 82.5 ± 3.4 (0.02) | 65.9 ± 5.9 | 64.5 ± 5.8 (0.4) |
| Survival | 90.3 ± 2.5 | 91.1 ± 2.2 (0.8) | 74.3 ± 5.5 | 78.8 ± 4.5 (0.8) |

*Values are life-table estimates of results five years after surgery, and are expressed as means ± S.E. Figures in parentheses are P values. Abbreviations are explained in Table 1.

†Values are adjusted for the number of positive nodes (1 to 3, 4 to 9, or ≥10).

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