# Survival Following Locoregional Recurrence After Breast Conservation Therapy for Cancer

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**We postulated that locoregional recurrence after limited surgery and radiotherapy for breast cancer might be associated with an additional survival hazard, similar to that of a second primary tumor with the same extent of local and regional disease. Using this hypothesis we examined the likely resultant effect on survival. Our calculations indicated that no statistically significant survival deficit due to such recurrence would be detectable until a randomized controlled trial comparing breast conservation with mastectomy had monitored more than 10,000 patients for more than 10 years. A simple mathematical model predicted 5-year survival rates in a cohort of patients treated with breast conservation of 75%, compared to 83% in those without locoregional recurrence. From the date of locoregional recurrence, a 61% 5-year survival rate was predicted, compared to 83% if no hazard was associated with locoregional recurrence. These predictions were compared with the actuarial survival rates of 499 patients with unilateral breast cancer, 49 of whom had developed locoregional recurrence. From the date of initial treatment, the 5-year survival rate of those whose disease recurred was 79%, compared to 88% for those without locoregional recurrence ($p = 0.19$). The actuarial 5-year survival rate from the date of locoregional recurrence was 63%. The similarity between the patient data and the predictions of the mathematical model indicates that locoregional failure after breast conservation therapy may result in reduced survival. The lack of a significant survival deficit in our cohort or in controlled trials comparing breast conservation therapy with mastectomy is compatible to the small size of the overall effect.**

A CHEST WALL recurrence after total mastectomy for breast cancer usually heralds the development of detectable metastases.[1] In contrast recurrence in the breast after breast conservation therapy does not necessarily denote the onset of life-threatening systemic disease. Patients can expect a disease-free survival in excess of 50% at 5 years after a breast tumor recurrence is effectively treated by wide local excision or mastectomy.[2-8] Such a local recurrence may be difficult to distinguish from a second primary on the basis of clinical features, histology, and, most importantly, subsequent outcome.

Studies comparing different primary treatment modalities for breast cancer have shown no consistent survival advantage for more extensive surgery or adjuvant radiotherapy,[9-13] although local control is improved. No reproducible effect on survival has been demonstrated in a randomized controlled surgical trial comparing breast conservation therapy with mastectomy.[14-17] Some investigators have concluded, therefore, that survival is independent of local treatment and that a local recurrence is a cosmetic failure with no impact on survival. Others believe that, although it may be too small to measure easily, there may yet be a survival deficit due to locoregional relapse.[18]

The probability of metastasis from a primary breast cancer is related to tumor size, nodal involvement, and such clinical features as skin invasion and chest wall involvement. We reasoned that these same prognostic factors might be predictive of additional metastatic risk in patients with a local or regional failure after breast conservation therapy. We used calculations based on this hypothesis to determine whether any of the published randomized controlled trials could have detected a relative decrease in survival (survival deficit) of this magnitude. We then calculated the probable effect of locoregional failure on the clinical course of breast conservation therapy patients treated at this institution.[19] The hypothesis was validated by directly comparing the theoretical predictions of survival outcome with the actual survival curves of these patients.

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## Patients and Methods

### *Patients*

The data set consisted of women treated for early breast cancer (stage 0–II; $T_{0-2}$, $N_{0-1}$) at the M. D. Anderson Cancer Center from 1955 to 1985, staged according to the 1988 American Joint Committee on Cancer classification.[20] Four hundred ninety-nine of these patients were treated for unilateral tumors with breast conservation, which included local excision of the primary tumor or, in later years, segmental mastectomy and axillary dissection, followed by irradiation. The treatment details have been reported elsewhere.[21] Median follow-up is now 5.3 years, and detailed information is available on the incidence, timing, site, and size of locoregional failures, and the subsequent clinical course.[21] Forty-nine patients have developed locoregional recurrence; their subsequent follow-up is for a median of 27 months.

### *Calculations*

*Sample size in randomized trials.* Formula 25 from Lachin[22] can be used to estimate the sample size required for a randomized controlled trial comparing mastectomy with breast conservation therapy to determine if the excess locoregional failure associated with the latter has the effect on survival rate predicted by our model. For simplicity chest wall recurrence after mastectomy is equated with metastasis. Consider a hypothetical 10-year prospective randomized controlled trial to compare one treatment (mastectomy) with another that allows a 10% excess locoregional recurrence rate (breast conservation). If it is assumed that all the recurrences occur at 3 years,[4,7,21,23] the first 3 years of patient accrual do not contribute any survival difference related to local failure; therefore the 10 years of study must start after 3 preliminary years, during which time patients are already being enrolled. If the proportional hazard for patients with locoregional control is taken to be 0.004/month (equivalent to a 5-year survival rate of 78.7%, which is plausible for patients with early breast cancer) and the additional hazard associated with locoregional failure is the same, increasing the hazard to the patient to 0.008 after recurrence, the average hazard for the 100% control group remains 0.004 while that for the 90% control group becomes $[(0.9 \times 0.004) + (0.1 \times 0.008)] = 0.0044$. We can assume that patients are accrued at random during the period of the study, and 100% follow-up is achieved until the end of the accrual period. A one-sided test is appropriate because it is unlikely that survival will be improved by locoregional failure, a power of 0.8 is reasonable,[24] and $p \leq 0.05$ can be understood to mean that the survival rates of the two groups are different.

The calculation predicts that 12,700 patients would be needed over the total of 13 years of this hypothetical trial to demonstrate a statistically significant difference in survival rate. A study with patient numbers equal to or greater than this; with a comparable or longer follow-up period; or a treatment that allowed a greater than 10% locoregional recurrence rate, earlier recurrences or recurrences with a higher equivalent stage might show a statistically significant survival rate deficit.

*Predicted survival curves.* A mathematical model was used to predict survival rates on the assumption that a locoregional recurrence is associated with an independent metastatic risk of the same magnitude and time course as that due to a similar primary tumor. A locoregional recurrence is clearly not really independent of the preceding primary tumor, but because it may behave in a way indistinguishable from that of an ipsilateral second primary, this assumption was deemed acceptable. First actuarial survival curves from historical patients treated here and elsewhere were used to estimate the hazard rate associated with each primary disease stage. (The hazard rate is defined as the probability of dying in a period of time after having already survived until the beginning of that period and is related to the actuarial survival). The absolute values used in the calculations were not critical, providing that higher-stage disease was assigned a higher numerical risk and the values chosen were approximately appropriate; those used are listed in Table 1. Increasing the hazard rates assigned to stage 0 to III tumors by 20% decreases the predicted proportion of patients surviving at 5 years from the date of locoregional failure by only 6%. Similarly decreasing the assigned rates by 20% increased the predicted 5-year survival rate by 7%. Each primary tumor stage was assigned an appropriate hazard rate.

The size, nodal involvement, and other clinical features of a locoregional recurrence were then used to assign a stage to each recurrence. For example a recurrence in the breast that measures less than 2 cm in diameter and without positive axillary nodes was equivalent to a stage I primary; a larger breast tumor or involved axillary nodes was equivalent to a stage II primary, and recurrent disease involving the skin or chest wall, or fixed or matted axillary nodes was considered equivalent to stage III. Most of the patients suffered only one locoregional relapse; therefore, for simplicity, only the first locoregional failure was con-

TABLE 1. *Hazard Rates and Corresponding 5-year Survival Rates Assigned to Patients with Stage 0 to III Breast Cancer*

| Stage | Hazard Rate ($\lambda$) Per Month | 5-year Survival Rate (%) |
|---|---|---|
| 0 | 0.00085 | 95 |
| I | 0.00271 | 85 |
| II | 0.00414 | 78 |
| III | 0.00996 | 55 |

sidered, and each was assigned a hazard rate according to its stage.

Survival was assumed to be an exponential function because extensive historical evidence shows that this provides a reasonable summary of survival experience:

$$p = e^{-\lambda t} \quad (1)$$

where p is the probability of surviving, λ is the hazard rate and t is time. The value of λ is thus defined for a particular group of patients by their actuarial survival rate: if the group has an average hazard rate of 0.0037 per month, the corresponding 5-year survival rate will be 80%

5-year survival rate = $e^{-}(0.0037 \times 60) = 0.8$.

A single patient who has two simultaneous tumors with hazard rates λ1 and λ2 can be expected to have a chance of being alive at time t of:

$$p = e^{-\lambda_1 t} \times e^{-\lambda_2 t} \quad (2)$$

because the overall probability of survival is given by the product of the probabilities related to independent contributing events. If, however, the second tumor occurs after an interval of time $t_R$:

$$p = e^{-\lambda_1 t} \times e^{-\lambda_2 (t - t_R)} \quad (3)$$

For a group of n patients, each with two tumors, the proportion, P, alive at time t is the average of the individual probabilities:

$$P = \left(\sum_{i=1}^{n} e^{-\lambda_{i1} t} \times e^{-\lambda_{i2}(t - t_R)}\right)/n \quad (4)$$

This fourth formula summarizes the overall effect of the hazards related to the primary tumors of all members of the group, each combined at the appropriate interval in time with the hazards associated with the second tumors, the locoregional recurrences. (The same mathematical formula would apply for a contralateral second primary.) The values of p at intervals in t can readily be calculated using a small computer.

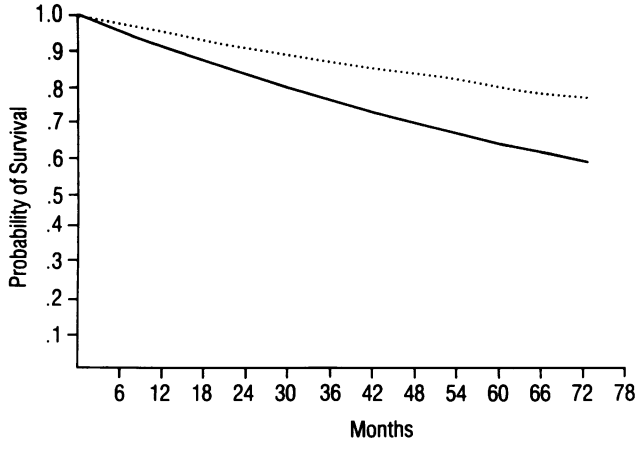


FIG. 1. Predicted chance of survival after diagnosis of a single tumor (upper curve) and two similar simultaneous tumors (lower curve).

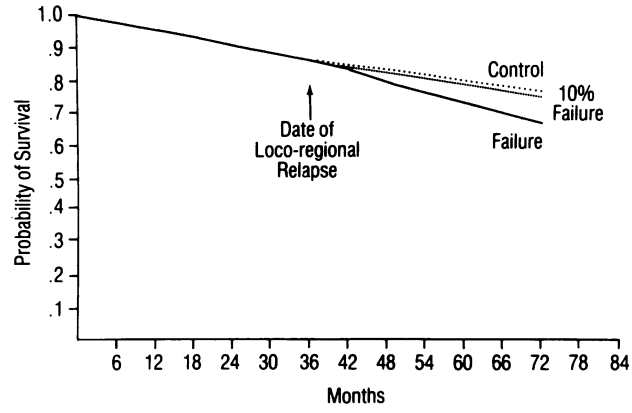


FIG. 2. Predicted chance of survival after initial tumor diagnosis. Upper curve: predicted survival probability after a single tumor. Lower curve: predictions when each patient has two tumors, the second occurring after 3 years. Middle curve: average chance of survival for a group of patients with tumors, of whom 10% develop a second tumor after 3 years.

A simple example of the effect is provided for a case in which the primary tumor is stage I and a second stage I tumor occurs simultaneously. Figure 1 compares a survival curve of this form with that belonging to the same hypothetical patient as if she had only one tumor. In Figure 2 the effect of a delay between one tumor and the other is illustrated, mimicking locoregional failure at 3 years. As expected the curves do not begin to diverge until the time of recurrence. In actuality, of course, most patients do not suffer a local or regional recurrence. The dotted line on Figure 2 shows the effect if only 10% have such a recurrence.

Using equation 4 and the details of the local and regional disease in our patients treated with breast conservation therapy (the known primary tumor stages, the equivalent stages of the locoregional recurrences that developed, and the intervals from the time of initial treatment at which failure was detected), we were able to model for that group of patients the predicted effect of locoregional failure on survival.

With the same logic, survival following locoregional failure can be described by the average of the products of the exponentials relating to the primary and recurrent tumors:

$$P = \left(\sum_{i=1}^{n} e^{-\lambda_{i1} t} \times e^{-\lambda_{i2} t}\right)/n \quad (5)$$

where t now represents time from recurrence.

## Results

### *Clinical Data*

In 499 treated breasts, 49 locoregional failures have occurred to date; the median time to failure was 42 months

(range, 12 to 120 months). The cumulative risk approximates 2% per year, so that for the patients who have been monitored for 10 years or more the actuarial failure rate was 19%. Overall, at 64 months median follow-up, the crude locoregional failure rate was 10%.

The majority of locoregional recurrences (84%) were confined to the breast, axillary nodes, or both. The remaining eight patients had extensive breast recurrence with chest wall involvement. Staging of locoregional failures, therefore, could be performed as for primary disease. Those that were confined to the breast, axilla, or both could be classified as $T_{0-2}$, $N_{0-1}$, stages 0 to II. The minority, involving skin or chest wall or fixed axillary nodes, were classified as $T_4$, $N_2$, stage III. A total of 16 patients had stage III recurrences, five because of involvement of the breast skin, three with fixed axillary nodes, and eight with extension of the breast tumor onto the chest wall. Table 2 lists the primary and recurrence stages for patients with unilateral disease. Although a few patients had recurrences of a lower stage than the original primary, most had more advanced disease. For example all four failures after treatment of *in situ* breast cancer were invasive. Advanced, stage III recurrence usually developed only in patients with a stage II primary; only two had a previous stage 0 or I tumor.

All recurrences were treated with much the same strategy as is a primary breast cancer of the same stage, except that additional irradiation was generally inappropriate.[25] The sites of failure and treatment approaches used are summarized in Table 3. Surgery was generally used for resectable tumor and systemic therapy, mostly chemotherapy, as first-line treatment for more advanced disease, followed by resection if the tumor responded. Median follow-up from the date of locoregional recurrence was 27 months.

The 5-year actuarial survival rate of patients who developed locoregional recurrences was 79%, compared to 88% for those without locoregional failure. The corresponding figures at 10 years were 64% and 72% (Fig. 3). These differences do not reach statistical significance ($p = 0.19$). Although roughly comparable for stage at initial treatment, age, tumor site, and so on, the average initial stage in those who failed is slightly higher than that of those who did not. This may account, at least in part, for the trend toward reduced survival in those patients with locoregional recurrence. However, in a separate study, we have identified two matched controls for each patient with locoregional failure and comparison of the survivals of these groups shows the same pattern: the 5-year survival rate of those failing was 79% (± 6% SE) compared to the control value of 88% ± 3.5% (SE). From the date of locoregional failure (rather than the date of initial treatment), the 5-year survival rate of the 49 patients with locoregional recurrence was 63% (Fig. 4).

TABLE 2. *Stages* of Unilateral Primary Tumors and Subsequent Recurrences (49 patients)*

| Primary Stage | Number Treated | Recurrence Stage I | II | III | Total |
|---|---|---|---|---|---|
| 0 | 39 | 2 | 1 | 1 | 4 |
| I | 231 | 12 | 8 | 1 | 21 |
| II | 229 | 5 | 5 | 14 | 24 |
| Total | 499 | 19 | 14 | 16 | 49 |

* American Joint Committee on Cancer staging of primary disease[20] and equivalent stage of subsequent relapse.

TABLE 3. *Sites of Disease and Treatment of Locoregional Recurrence*

| No. of Sites | Recurrence | Treatment of Locoregional Relapse: Surg | Surg + Syst | Syst | None |
|---|---|---|---|---|---|
| 33 | Breast only | 23 | 10 | | |
| 5 | Breast + axilla | 1 | 4 | | |
| 3 | Axilla without breast | | 2 | 1 | |
| 8 | Chest wall + breast | | 3 | 4 | 1* |
| 49 | Total | 24 | 19 | 5 | 1 |

* One patient refused treatment.

Surg, surgery (wide local excision 6, simple mastectomy 18, modified radical mastectomy 14, radical mastectomy 1, wide excision of breast ± chest wall 3, axillary dissection 1, debulking 1).

Syst, systemic therapy (chemotherapy 18, tamoxifen 3, both 5, chemotherapy + estrogens 1, chemotherapy + oophorectomy 1).

## *Calculated Survival Curves*

Of the 49 patients with unilateral breast cancer who had a locoregional failure, four had initially received breast

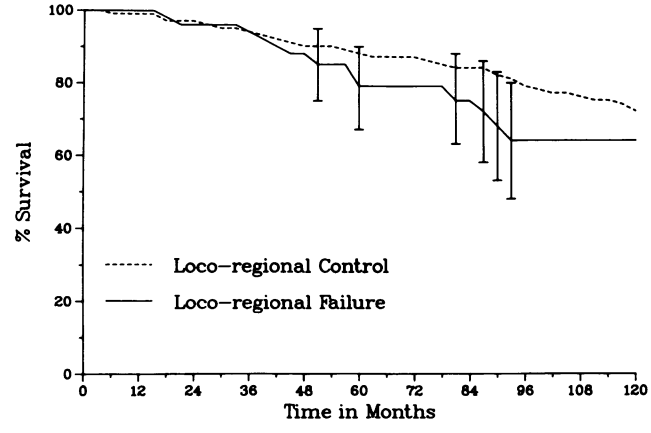


FIG. 3. Comparison of actuarial survival rates of patients whose breast cancer did and did not recur locoregionally. The vertical bars show the 95% confidence limits for the smaller group (with locoregional recurrence).

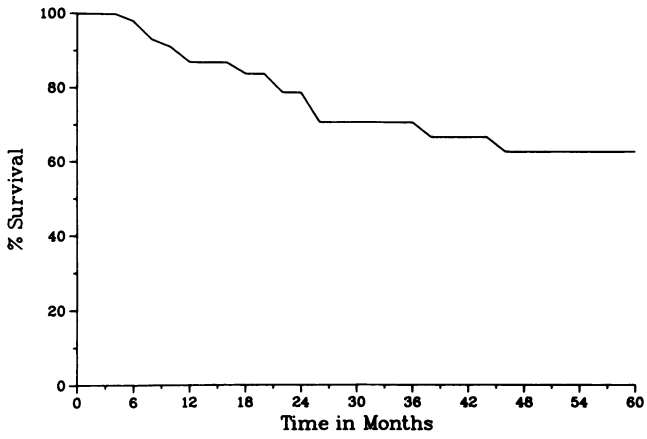


FIG. 4. Actuarial survival from the date of locoregional relapse (n = 49).

conservation therapy for stage 0, 21 for stage I, and 24 for stage II disease. None of the locoregional failures was *in situ*: 19 were equivalent to stage I, 14 to stage II, and 16 to stage III disease (Table 2).

Figure 5 shows the calculated survival predictions for these patients with locoregional failure, using equation 4. For comparison the calculated survival rates of the same group of patients as if their disease had not recurred is also plotted. The predicted difference in survival rate, due to locoregional failure, is 8% at 5 years and 20% at 10 years. Assuming that a prospective, randomized controlled trial of breast conservation therapy compared to mastectomy resulted in patterns of failure similar to those found in our patients (failure at similar intervals from treatment, recurrent disease of comparable extent, and a failure rate around 10%), the survival deficit in such a trial would be approximately 2% at 10 years because 90% of the patients carry only the risk related to the primary tumor.

The predicted 5-year survival rate from the date of locoregional failure is 61%; if these patients had not developed locoregional recurrence their calculated survival rate would be 83%, yielding a survival deficit of 22% (Fig. 6).

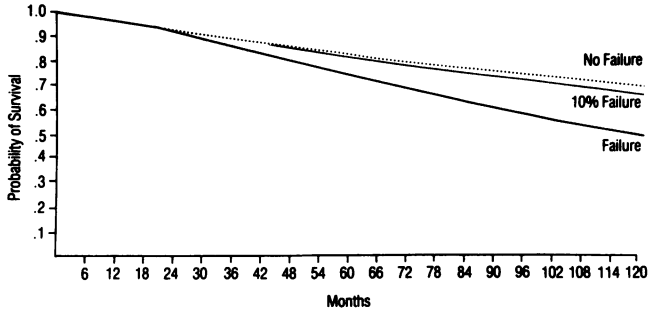


FIG. 5. Predicted survival curve for the patients developing locoregional failure (lowest line) compared to the curve calculated as if the same patients had not had such a recurrence (top line). The middle curve illustrates the prediction if only 10% of the patients develop locoregional failure.

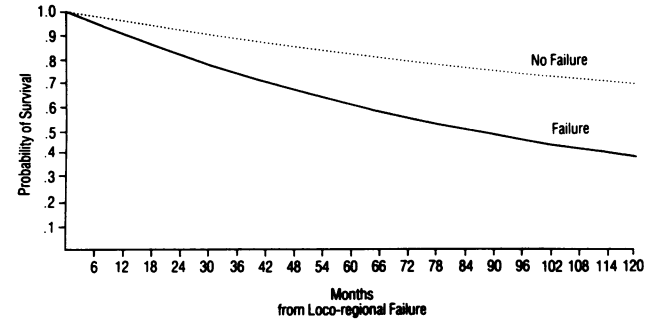


FIG. 6. Predicted survival from the date of locoregional failure (lower curve). The comparison is to predictions for the same patients as if they had not developed locoregional recurrence (upper curve).

## Discussion

Our hypothesis is that there is a higher risk of death from disease for patients whose tumors relapse in the treated breast or axilla after breast conservation surgery and irradiation. The calculations predict a survival deficit for those with locoregional recurrence relative to those with locoregional control of 8% at 5 years, when survival rates are calculated from the date of initial diagnosis (Fig. 5). The actual survival curves of patients who did and did not relapse locoregionally (Fig. 3) show a trend toward a lower survival rate for those whose disease recurred, compatible with these calculated predictions. Published curves based on patients treated elsewhere also show the same pattern.[8,23] When survival rate predictions are made from the date of locoregional relapse, a predicted additional 22% risk of death results in a 61% survival rate at 5 years (Fig. 6); the actual 5-year survival rate following recurrence in our patients is remarkably similar at 63% (Fig. 4). Because only a few patients suffer locoregional relapse, the predicted survival deficit in a randomized controlled trial comparing breast conservation therapy with mastectomy is less than 5% at 10 years. More than 10,000 patients would need to be accrued and monitored for more than 10 years to demonstrate a statistically significant difference in survival rate because the overall survival rate of patients treated by breast conservation therapy is dominated by the sustained low risk of the majority of the patients who do not have a locoregional recurrence.

Information on locoregional failure has been published from four prospective randomized trials comparing breast conservation therapy with mastectomy: two from Guy's Hospital, London;[15,26] one from Milan;[16,17] and the United States' National Surgical Adjuvant Breast Project's trial B-06.[14] Their results are summarized in Table 4.

The largest study is B-06, which contained about 600 patients in each of three arms: lumpectomy, lumpectomy with radiotherapy, and mastectomy. The survival rates of the three patient groups are the same. The group who had lumpectomy alone had a rate of locoregional recurrence

TABLE 4. *Results from Prospective Randomized Trials of Breast Conservation Therapy* Versus *Mastectomy*

| Trial | Treatment | No. of Patients | Years of Follow-up | Failures | | | |
|---|---|---|---|---|---|---|---|
| | | | | BR | CW | AX | SC |
| Guy's I[15] | WLE + XRT | 180 | >15 | 17 | 21 | 35 | 1 |
| | MAST | 192 | | | 28 | 3 | 3 |
| Guy's II[15] | WLE + XRT | 120 | >11 | 6 | 12 | 15 | 3 |
| | MAST | 138 | | | 11 | 2 | 5 |
| Milan[16,17] | QUART | 352 | 8.5 | 7 | 7 | | |
| | MAST | 349 | average | | 7 | | |
| B-06[14] | L | 636 | 7.75 | 175 | 46 | 46 | |
| | L + XRT | 629 | average | 39 | 7 | 28 | |
| | MAST | 590 | | | 48 | 23 | |

BR, breast; CW, chest wall; AX, axilla; SC, supraclavicular nodes; WLE, wide local excision; XRT, radiotherapy (doses used, areas treated and modality varied); MAST, mastectomy; QUART, quadrant excision, axillary dissection and radiotherapy; L, lumpectomy.

substantially higher than 10%: 175 failures in the breast, 46 in the chest wall, and 46 regional nodal relapses (42% overall at 8 years). Nevertheless patient numbers are insufficient for the study to be expected to show a significant survival difference. Although the numbers of patients included in this trial are larger than in any other, and the locoregional failure rate in the surgery-only arm is higher, even with further follow-up a survival difference due to locoregional failure is not likely to be detectable.

The study with the longest follow-up is the first Guy's trial, in which a total of 372 patients were randomized to wide local excision plus radiotherapy, or mastectomy. At the latest update, minimum follow-up was probably in excess of 15 years, by which time 17 breast recurrences and 35 axillary recurrences had developed, 29% overall (the axilla was not dissected and the radiotherapy dose used was low by current standards).[15] Again a statistically significant survival deficit would not be expected from our hypothesis, and none was found. The second Guy's trial, however, resulted in a significantly higher survival rate for those treated with mastectomy, and subsequent analysis has indicated that the difference was largely related to the higher survival rate for patients with stage I tumors treated by mastectomy.[13] This study, now at 11 years follow-up, had fewer patients than the first (total 258) but a more homogeneous patient population: accrual was restricted to patients with $T_{1-3A}$, $N_0$ tumors. It is nevertheless possible that, with arms containing less than 150 patients, there may have been important differences between the patient groups at randomization that led to differences between the survival curves. Such differences would become progressively more obvious during the follow-up and would lead to spurious statistical significance.[27,28]

The most recent update of the Milan trial, in which patients with $T_1$, clinical $N_0$ tumors were randomized to mastectomy (most had radical mastectomy) or quadrantectomy, axillary dissection and radiotherapy (QUART), has 349 and 352 patients in each arm, an average follow-up of 8.5 years, and 7 breast failures reported in the QUART arm. There is no significant survival difference between the treatment arms.

Thus no randomized prospective study comparing breast conservation therapy with mastectomy to date has the statistical power to demonstrate a survival deficit due to locoregional failure if it is of the magnitude of that associated with a comparable primary, and no reproducible survival difference has been demonstrated. Application of our model to the combined results of the four randomized controlled trials comparing breast conservation therapy with mastectomy would be of interest. However it would require information on the timing and extent of locoregional recurrence that is not available from the published reports.

Another approach to estimating the additional risk for patients with locoregional failure is to compare them with patients with metachronous bilateral breast cancer. Contralateral breast cancers are accepted as carrying independent risks of metastasis and death. The effect is assumed to be related to the stage of the second primary, so that the prognosis for patients with bilateral tumors is understood to be dominated by that of the more advanced tumor. A recent study[29] included a direct comparison of the survival rates of patients treated with breast conservation therapy whose disease recurred locally with those of patients who developed contralateral tumors. Although the timing and stage of contralateral primaries were different from those of ipsilateral recurrences, so that a close match would not be expected, the similarity of the patients' actuarial curves supports the thesis that an ipsilateral recurrence carries approximately the same survival hazard as a similar contralateral primary.

Those same primary tumor features that lead to locoregional failure may also lead to metastasis and death; our model cannot prove a direct effect of locoregional failure on survival. However, in the absence of a very large randomized controlled trial, a survival deficit due to locoregional recurrence cannot be discounted. On av-

erage, locoregional recurrences in our patients were at a higher stage than that of the initial primary disease. Therefore recurrence was predicted to more than double the hazard for an individual patient. This would be of clinical importance, underlining the importance of frequent screening for early detection and effective treatment of locoregional failures after breast conservation therapy.

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