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THE IMPORTANCE OF LOCAL CONTROL IN THE CONSERVATIVE TREATMENT OF BREAST CANCER

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The purpose of this study was to examine the meaning of local control, especially on survival, in breast cancer patients treated by lumpectomy with or without radiotherapy. We analyzed the survival results of four major published randomized trials that compare conservation surgery with or without radiation using three different statistical approaches: p-values, confidence intervals, and Bayesian techniques. All four trials report statistically significant increased local control and improved survival for the irradiated patients. Survival based on p-values and confidence intervals shows statistical significance for long-term follow-up of the NSABP-B06 trial, but not for the other trials, probably because of small sample sizes and short follow-up. At 10 years, the overall survival rates for the NSABP-B06 were 65% and 71% for lumpectomy alone or with radiation respectively. Interpreted in a Bayesian framework, the expected advantage in 10-year survival was 6% (the mean of NSABP-B06 10-year survival) with an 83% probability that the 10-year survival difference may lie between 2% and 10%. An 85% probability that 3% of patients will survive at 10 years because of irradiation translates into a 30% reduction in annual odds of death several years after treatment in stage I good prognosis patients and 15% in stage I poor prognosis patients. Analyses of the randomized trials comparing lumpectomy with or without radiation indicate a clear improvement in survival for the irradiated patients associated with increased local control. Combination of improved survival with the reduced psychological and economic costs associated with local recurrence argues well for the inclusion of radiation for many breast cancer patients.

Conservation surgery is increasingly the treatment of choice for many women diagnosed with breast cancer. Because local control and survival rates are comparable between conservation surgery and mastectomy, the added benefits to quality of life and potential decreased costs with conservation surgery have made this a major advancement in the treatment of breast cancer.

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Whether the addition of radiation to conservation surgery provides optimal treatment benefit remains controversial. Local control rates are significantly increased with the addition of radiation, and local control is associated with decreased risk of distant disease and mortality, and improved quality of life. The NSABP-B06 study found that patients who developed an ipsilateral breast tumor recurrence (IBTR) had a 3.41 relative risk of distant relapse compared to patients who did not recur (1). Other studies report a similar increase in distant disease and mortality in patients who relapse versus patients who do not (2–4).

Increased local control also helps to preserve the breast, since the standard treatment for a local failure after conservation surgery is salvage mastectomy. Because preservation of the breast is one of the major advantages of conservation surgery over mastectomy, increasing the

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chances that conservation surgery will succeed in preserving the breast is important. Results of the 10-year reanalysis of the NSABP-B06 study show a significant increase in mastectomies for node-negative patients initially treated by lumpectomy alone versus lumpectomy with radiation (84% versus 66%; $p = 0.006$). Mastectomies were more frequent and occurred earlier in the lumpectomy alone group, and if an ipsilateral recurrence occurred in the lumpectomy plus irradiation patients, these patients had a greater probability of breast retention (5). The potential increase in costs of salvage mastectomy is an additional reason for preventing local relapse.

Arguably, these benefits are sufficient for the use of radiation in the treatment of many breast cancer patients. Debate continues, however, over the different interpretations of the effect of improved local control on survival, which reflects the different views of the natural history of the disease. Arguments for or against the benefit of local control on survival have been based on a view of the disease as either systemic from initiation or as spread sequentially from the primary tumor through the lymph nodes to distant sites. More recent understanding of disease spread focuses on prognostic features of the primary tumor that may predict for either systemic or localized disease (6–8). Tumor size, lymph node involvement, and other prognostic features indicate at least three subgroups of patients: 1) patients with indolent disease in whom treatment would have no effect on survival; 2) patients in whom the disease can be cured if adequately diagnosed and treated, or patients in whom the disease has metastasized because of inadequate diagnosis and treatment; and 3) patients in whom the tumors are systemic at diagnosis.

Results of a recent study from Canada provide a good example of why controversy persists over the benefit of local control on survival. Whelan et al. (9) report a significantly greater 5-year cumulative rate of ipsilateral breast tumor recurrence (IBTR) for patients treated with lumpectomy alone versus lumpectomy with radiation ($p = 0.0001$). They also found that an IBTR predicted increased mortality ($p = 0.0006$). However, no significant difference in overall survival was found between irradiated and non-irradiated patients ($p = 0.45$). The lack of statistically significant survival results in this study, as well as in other studies, serve as the main argument against the need for local control by proponents of the systemic nature of breast cancer. Advocates for local control challenge this conclusion and ask why the reduction in local recurrence for the irradiated patients does not translate into an increased overall survival benefit if an IBTR predicts an increased mortality.

Material and Methods

To address this question, we searched the medical literature and found three other randomized trials that compare conservation surgery alone or with radiation—Milan III (10), Uppsala-Örebro (11), and NSABP-B06 (5) trials. In three of the four trials, we show the limitations of p-values to accurately interpret survival data because of small sample sizes and short follow-up. To illustrate the effect of small sample sizes and short follow-up on survival results, we constructed a simple statistical model based on exponentially distributed times to event: time to relapse and time to death with constant but different rates before and after relapse. We also used 95% confidence intervals to visually show the survival differences between the two treatments.

Since the ongoing problems with small sample sizes and short follow-up in breast cancer trials continue to impede statistical interpretation based on the commonly used p-values and, to a lesser extent, confidence intervals, we included the less conventional Bayesian approach that offers a way to combine the studies to increase the sample size (we omitted the Milan trial in this interpretation because quadrantectomy was used instead of lumpectomy). First, we imposed a non-informative normal prior distribution on the observed difference in 5-year survival of the Uppsala-Örebro study (i.e., we generated a normal distribution with the mean and standard deviation of the 5-year difference of the Uppsala-Örebro study). This distribution was then used as a prior distribution for the difference in 5-year survival in the Canadian study. We then used these combined studies as a prior distribution for the NSABP-B06 study. Our choice of the order to combine the trials was based on the chronological order in which the trials were conducted and published; however, the result of the combined studies is independent of the order in which the studies were entered. A recent article (12) provides additional description of the Bayesian method.

Results

As shown in Table 1, all four major randomized trials comparing conservative therapy with or without radiation report a statistically significant decrease in local failure and a trend in increased survival for the irradiated patients. In the Milan III, Canadian, and Uppsala-Örebro studies, at an average 5-year follow-up, the survival trend for the irradiated patients was not statistically significant, most likely because of small sample sizes and short follow-up. For these three studies to show a significant survival difference at the commonly used $p < 0.05$ based on the difference in lifetable curves of each study (i.e., 5 years), crude estimates demonstrate that the sample size of the Milan III would have to increase from 567 to 56 700 patients, the Canadian trial from 837 to 5 273 patients, and the Uppsala-Örebro trial from 381 to 2 400 patients.

Use of a model based on exponentially distributed time to relapse and time to death (with constant but different

Table 1

Comparison of local failure and overall survival rates of the four major published randomized trials comparing conservative surgery with or without radiation

	Criteria for inclusion	Treatment Number of patients evaluated)	Local recurrence (percentage)	Overall survival (percentage)	F/U
Milan III	Tumors <2.5 cm N0 N1 disease	QUAD = 273 QUART = 294	QUAD = 8.8% QUART = 0.3%	QUAD = 4% (12/273) QUART = 3% (9/294) (p = 0.85)	3.5 yrs
NSABP-06	Tumors < 4.0 cm Stage I or II disease	L = 520 L & RT = 515	*Risk ratio = 0.25 (0.18, 0.33) (p < 0.001)	L = 65 ± 2.1% L & RT = 71 ± 2.0% (p = 0.04)**	10 yrs
Canadian	Tumors <4.0 cm clear resection margins	L = 421 L & RT = 416	L = 30% (25, 36%) L & RT = 8% (5, 11%) (p < 0.001)	L = 86% (82, 90%) L & RT = 88% (85, 92%) (p = 0.45)**	5 yrs
Uppsala-Örebro	< 80 yrs old Unifocal tumor Tumors ⩽20 mm	L = 197 L & RT = 184	L = 18.4% L & RT = 2.3% (p = 0.0001)**	L = 90.3% (85.8, 94.8%) L & RT = 91.0% (86.4, 95.4%) (p = 0.44)**	5 yrs

F/U = follow-up; QUAD = quadrantectomy plus axillary dissection; QUART = quadrantectomy, axillary dissection, and radiotherapy; L = lumpectomy; RT = radiation therapy; ( ) = 95% confidence intervals.

* Based on data provided on patients who accepted randomized assignment; includes all trials with a total number of patients for L = 572 and for L plus RT = 568; no data available for results omitting the St. Luc study.

** p-values based on lifetable curves.

rates before and after relapse) to illustrate the effect of small sample size and short follow-up on survival results demonstrated the following; with an annual death rate of 0.035 without relapse, a death rate of 0.08 after relapse (corresponding to the relative hazard given in the Canadian study), and annual relapse rates of 0.05 and 0.007, we found 5-year survival probabilities between lumpectomy alone and with radiation of 82% and 84%, and 10-year survival probabilities of 65% and 70% (approximately the values found in the NSABP B06 protocol). At 15 and 20 years, the chance of survival would be 50% and 38% respectively for lumpectomy alone and 58% and 47% respectively for lumpectomy with radiation. To discover a difference of 5% between 65% and 70% at a significance level of 0.05 (2-sided test), the sample size needed for a power of 0.8 would be 1 416, for a power of 0.65, the sample size would have to be 1 000 (13).

The effect of longer follow-up on survival difference is demonstrated by a comparison of the 5- and 10-year results of the NSABP-B06 trial, which had the largest sample size and longest follow-up of all four trials. At 10 years, the survival rates were statistically significant for the irradiated patients at the commonly used $p < 0.05$; overall survival was 71% vs. 65% ($p = 0.04$), distant-disease-free survival was 62% vs. 55% ($p = 0.03$), and disease-free

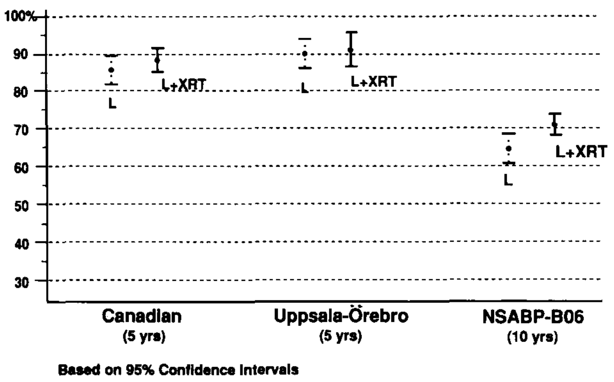

Fig. 1. Comparison of overall survival based on 95% confidence intervals between lumpectomy with or without radiotherapy at longest follow-up for the Canadian, Uppsala-Örebro, and NSABP-B06 trials.

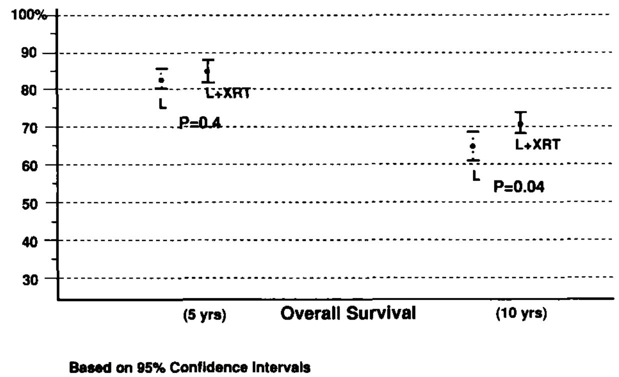

Fig. 2. Comparison of 5- and 10-year overall survival based on 95% confidence intervals between lumpectomy with or without radiotherapy: NSABP-B06 trial.

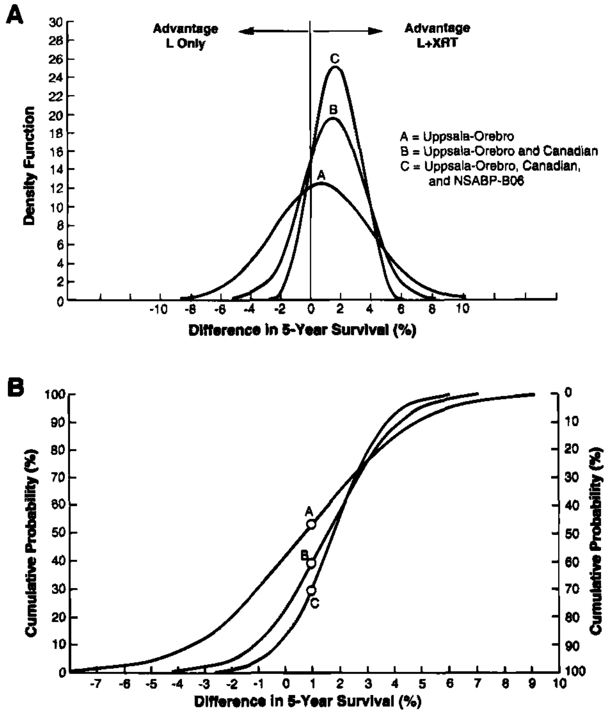

Fig. 3. Difference in 5-year survival between lumpectomy with or without radiation based on combining the Uppsala-Örebro, Canadian, and NSABP-B06 trials under a Bayesian approach: A) distribution of treatment difference and B) cumulative probability of an advantage for lumpectomy with radiation.

survival was 72% vs. 63% ($p < 0.01$). (We calculated significance at the commonly used alpha value of <0.05, whereas the authors interpreted their results according to the lower alpha of <0.01. Discussion of the statistical principle behind this adjustment goes beyond this paper, but under either interpretation, a definite improvement in survival over time is evident.) At 5-year follow-up, the difference between lumpectomy with and without radiation was not significant for overall survival (85% vs. 83%; $p = 0.4$) nor for distant-disease-free survival (76% vs. 71%; $p = 0.07$). Disease-free survival was significant both at 5- and 10-year's follow-up (72% vs. 63%; $p < 0.01$) (5).

To visually show the survival difference between treatments, we plotted 95% confidence intervals (Figs 1 and 2). The overall survival for lumpectomy with and without radiation at the longest follow-up for each trial based on 95% confidence intervals (CI) was 88% (CI 85%–92%) versus 86% (CI 82%–90%) for the 5-year results of the Canadian trial, 91% (CI 86.4%–95.4%) versus 90.3% (CI 85.8%–94.8%) for the 5-year results of the Uppsala-Örebro trial, and 71% (CI 68%–74%) versus 65% (CI 61%–69%) for the 10-year results of the NSABP-B06 (Fig. 1) (we omitted the Milan trial from these comparisons because quadrentectomy was used instead of lumpectomy). Overall survival between lumpectomy with and without radiation in the NSABP-B06 trial was 85% (CI 82%–88%) versus 83% (CI 80%–86%) at 5 years and 71% (CI 68%–74%) versus 65% (CI 61%–69%) at 10 years (Fig. 2).

Under a Bayesian approach, the three studies can be combined to increase the sample size (Fig. 3). As shown in Fig. 3A, the bell curve becomes narrower and higher with each added study indicating a decreasing margin of error and an increasing probability of a positive difference between lumpectomy with radiation over lumpectomy alone at 5-year survival. Five-year survival difference for the Uppsala-Örebro study was 0.7% (standard deviation of 3.2), 1.47% (standard deviation 2.05) for Uppsala-Örebro and Canadian studies combined, and 1.71% (standard deviation of 1.32) for all three studies. These numbers indicate the extreme unlikelihood that the 5-year survival difference between treatments is more than 6% or less than −2.6%. Chances are 86% that the treatment difference is positive for the irradiated patients at 5 years, but only 6.5% that the advantage is more than 4%. This means that there is a 79.5% chance that the positive 5-year survival difference between the irradiated and non-irradiated lumpectomy patients lies between 0% and 4%. Fig. 3B shows that the cumulative probability of a 1% or more survival difference at 5 years is 70% for all three studies combined (C), 60% for the combined Uppsala-Örebro and Canadian studies (B), and 50% for the Uppsala-Örebro study (A).

Fig. 4A displays the (posterior) distribution of the difference in 10-year survival of lumpectomy with or with-

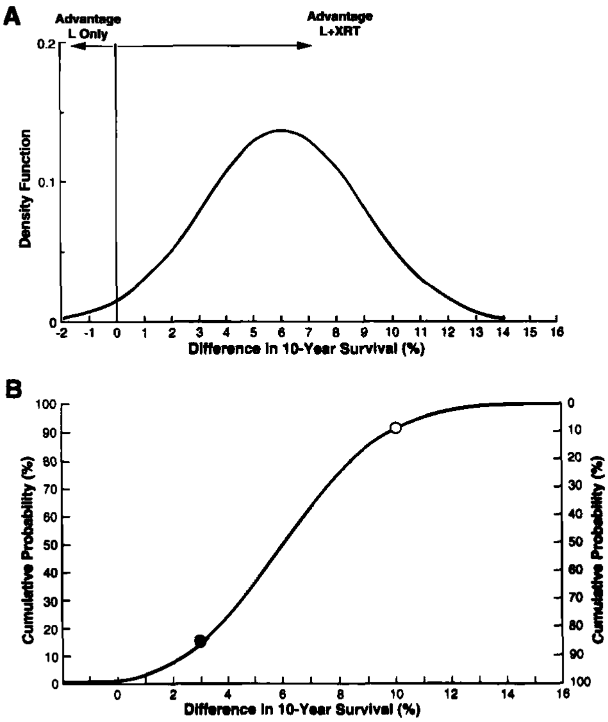

Fig. 4. Difference in 10-year survival between lumpectomy with or without radiation in the NSABP-B06 trial based on a Bayesian approach: A) distribution of treatment difference and B) cumulative probability of an advantage for lumpectomy with radiation.

out radiation. Fig. 4B provides more specific interpretation of the overall difference in survival distribution. For example, the probability that survival is less than 10% is 92% (○), whereas the probability of a difference of less than 3% is only 15% (●).

Discussion

Clear evidence for improved survival associated with local control is demonstrated by a closer examination of the four major randomized trials that compare conservative surgery with or without radiation. Statistically significant increased local control for the irradiated patients translated into an increased survival trend for all four trials. For three of these trials, interpretation of this survival trend based on p-values was limited by the common problems of small sample size and short follow-up. Only the NSABP-B06 trial, which had the largest sample size and longest follow-up, showed significant survival results. Comparison of the 5- and 10-year results of the NSABP-B06 trial emphasizes the importance of longer follow-up to detect survival differences. The statistically significant overall and distant-disease-free survival rates found at 10 years were non-significant at 5 years. Disease-free survival was significant both at 5- and 10-year follow-up (5). Confidence intervals provided slightly more information about the survival results, emphasizing again the importance of longer follow-up. The need for longer follow-up has been reported in other studies that show evidence of survival differences only after 10–12 years after treatment (14, 15).

To help overcome the limitations of small sample sizes and the limitations imposed by hypothesis testing (which aims at the rejection of the null hypothesis of no difference, and therefore provides only an either/or answer), we used a Bayesian analysis that provides a descriptive interpretation of treatment differences. Based on this analysis, we were able to cite specific examples of the differences in survival between the treatment groups. A further interpretation of the 10-year results of the NSABP-B06 trial is made by considering the mean of the study (Fig. 4), which indicates that 6% of patients can be expected to have a survival benefit with irradiation. The black dot indicates that the chances are 85% that more than 3 patients out of 100 will survive at 10 years because of irradiation (which translates into more than 30 patients out of 1 000) (Fig. 4B). In the standard approach to treatment comparisons by hypothesis testing with a 5% significance level, these numbers may not indicate statistical significance, but do indicate clinical importance for many individual patients. As reported in the Early Breast Cancer Trialists' Collaborative Group's study on systemic treatment of early breast cancer, a 30% reduction in the annual odds of death is associated with a reduction of 4 deaths per 100 women treated who have a 10–20% probability of dying from breast cancer in 10 years. The 20–30% probability of dying from breast cancer in 10 years can be reduced by 8 deaths of 100 women treated (Table 2) (16). Application of these calculations to the 3% survival improvement for patients treated with lumpectomy with radiation versus those treated by lumpectomy alone (as discussed above), a 30% reduction in the annual odds of death after many years can be expected for stage I good prognosis patients and 15% for stage I poor prognosis patients. Given that in the United States alone, 46 240 breast cancer patients are estimated to die this year, with an estimated 183 400 newly diagnosed cases, these small percentage reductions in death translate into improved survival for many patients (17).

Table 2

Absolute reductions in 10-year mortality produced by a persistent reduction of 30% or 15% in the annual odds of death

10-year risk of death from breast cancer	Possible example of early breast cancer patients at such risk	Approximate absolute benefit: difference in numbers alive several years later if 100 women have a persistent reduction in annual odds of death of	
		30%	15%
10–20%	Stage I, good prognosis	4	2
20–40%	Stage I, poor prognosis	8	4
40–80%	Stage II, any prognosis*	12*	6*

* These eventual absolute benefits apply chiefly to survival, where the annual risk reductions may well be persistent. Elsewhere, they may be less if the reduction in the annual risk is substantial for only the first few years.

Conclusion

Analyses of the three major published randomized trials comparing lumpectomy with or without radiation indicate a clear improvement in survival for the irradiated patients associated with decreased local failure. Combination of this survival trend with the reduced psychological and economic costs associated with local recurrence argues well for the inclusion of radiation for many breast cancer patients.

It is hoped that research underway will help define which patients can safely forego local treatment without a compromise to survival or quality of life (18). Until we can more precisely predict which patients will not recur, the proven benefit to local control, the reduction in psychological distress and economic cost, and the trend in increased survival advantage strongly support the benefit of radiation.

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Addendum

The data we used from the NSABP-B06 reanalysis to analyze the three survival outcomes (i.e., overall, disease-free, distant-disease-free) between lumpectomy alone and with radiation were based on eligible patients who accepted randomized treatment. This cohort included both positive and negative node patients. We used the full cohort in our original analysis because it allowed for a more statistically accurate analysis of the data than is allowed with a subset analysis. However, since the Canadian and Uppsala-Örebro trials included only node-negative patients, we reanalyzed the subset of node-negative patients only in NSABP-B06 trial data to evaluate any changes this may have on our original analysis.

Under this analysis, the overall survival at both 5 and 10 years for the node negative patients was nonsignificant between lumpectomy alone or with radiation ($p = 0.4$ versus $p = 0.24$ respectively). Disease-free and distant-disease-free survival were significant both at 5 and 10 years in favor of the irradiated patients ($p < 0.001$ and $p = 0.002$, disease-free; $p = 0.015$ and $p = 0.002$, distant-disease-free). The 95% confidence intervals (CI) for lumpectomy alone and with radiation at 5 years were 87% (CI 84%–91%) and 89% (CI 86%–92%) respectively. At 10 years the 95% confidence intervals were 74% (CI 70%–78%) and 78% (CI 75%–82%) respectively. These results indicate some differences with the cohort of eligible patients who accepted randomization, but have little impact on our previous conclusions that survival is improved for the irradiated patients.

Only a slight change was found from our original Bayesian analysis when we included only the node-negative patients from the NSABP-B06 trial. For all three studies combined, the 5-year difference was 1.68% (standard deviation of 1.36) instead of our original finding of a difference of 1.71% (standard deviation of 1.32). This slight change did not affect our previous analyses or conclusions.