

## Breast-Conserving Surgery With or Without Radiotherapy: Pooled-Analysis for Risks of Ipsilateral Breast Tumor Recurrence and Mortality

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For The Breast Conserving Surgery Project

**Background:** The objective of the study was to investigate whether radiotherapy or its omission after breast-conserving surgery has measurable consequences on local tumor growth and patient survival. **Methods:** We conducted a pooled analysis of published randomized clinical trials that compared radiotherapy versus no radiotherapy after breast-conserving surgery. The outcomes studied were ipsilateral breast tumor recurrence and patient death from any cause. The pooled relative risks (RRs) were estimated with a random-effects model. Heterogeneity was assessed using the Cochran Q test. **Results:** A search of the literature identified 15 trials with a pooled total of 9422 patients available for analysis. The relative risk of ipsilateral breast tumor recurrence after breast-conserving surgery, comparing patients treated with no radiotherapy or radiotherapy, was 3.00 (95% confidence interval [CI] = 2.65 to 3.40). Mortality data were available for 13 trials with a pooled total of 8206 patients. The relative risk of mortality was 1.086 (95% CI = 1.003 to 1.175), corresponding to an estimated 8.6% (95% CI = 0.3% to 17.5%) relative excess mortality if radiotherapy was omitted. **Conclusion:** Omission of radiotherapy is associated with

a large increase in risk of ipsilateral breast tumor recurrence and with a small increase in the risk of patient mortality. [J Natl Cancer Inst 2004;96:115–21]

The panel of the National Institutes of Health Consensus Development Conference on Treatment of Early-Stage Breast Cancer indicated in its 1990 statement (1) that breast-conserving surgery plus radiotherapy to the breast is an appropriate method of primary therapy for the majority of

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See "Notes" following "References."

DOI: 10.1093/jnci/djh013

Journal of the National Cancer Institute, Vol. 96, No. 2, © Oxford University Press 2004, all rights reserved.

women with stage I and II breast cancer and is preferable to total mastectomy because it provides survival equivalence while preserving the breast. Several trials, including recent updates with long-term follow-up, have confirmed this statement (2–8). Together with the recent increasing acceptance of sentinel node biopsy replacing up-front axillary lymph node dissection (9,10), the trend has evolved toward less aggressive surgery in early breast cancer.

The role of radiotherapy to the breast for treatment of early-stage breast cancer has recently been challenged, however, because routine radiotherapy after conservative surgery in early-stage breast cancer may be complicated by socioeconomic problems, limited radiotherapy resources, and treatment-related morbidity (11,12). Short-term effects to the skin are temporary, and possible chronic adverse effects include poor cosmetic results and increased risks of arm dysfunction and lymphedema in conjunction with extensive axillary lymph node dissection. Long-term toxic effects may include carcinogenesis and cardiac or lung damage. Radiotherapy prolongs the treatment duration, which could result in loss of income and additional costs that have to be borne by the patient or by the public health system. Some countries and isolated geographic areas have limited radiotherapy resources, which may need to be allocated to more urgent cancer care. Assessment of the consequences of omitting radiotherapy for patients diagnosed with early-stage breast cancer is therefore needed.

A recent review by Whelan et al. (13) addressed possible survival differences between patients receiving radiotherapy and those not receiving it. Five randomized clinical trials comparing patients receiving breast irradiation with those receiving no breast irradiation following breast-conserving surgery were analyzed in this study, and no difference in survival was detected in any of the five trials (13). In another review focusing on long-term results of radiotherapy, six trials comparing use of radiotherapy versus no radiotherapy were identified (14). No statistically significant difference in the annual death rates was shown.

These results may suggest that the omission of radiotherapy may not have an effect on patient survival. However, a study of the Surveillance, Epidemiology, and End Results (SEER)<sup>1</sup> Program database found that, among women who underwent axillary lymph node dissection, breast-conserving surgery with radiotherapy was associated with a reduced mortality hazard ratio of 0.728 compared with total mastectomy, whereas breast-conserving surgery without radiotherapy was associated with an increased mortality hazard ratio of 1.105 when compared with total mastectomy, implying a substantial survival disadvantage in patients who did not receive radiotherapy (15). Moreover, a subsequent study (16) directly comparing the omission of radiotherapy with the delivery of radiotherapy after breast-conserving surgery in patients aged 40–69 years found a 35% excess in relative mortality associated with the omission of radiotherapy.

Because of the discrepancy between the results of the literature reviews and those of the population-based studies, we decided to re-evaluate the risk of omitting radiotherapy by performing an independent pooled analysis of published studies of patients with early-stage breast cancer. The objectives were to evaluate the mortality risk from any cause and to confirm the risk of ipsilateral breast tumor recurrence.

## MATERIALS and METHODS

The literature search was aimed at identifying randomized trials of invasive breast cancer primarily treated by breast-conserving surgery (lumpectomy or local excision) that compared radiotherapy after surgery with no radiotherapy, with or without systemic treatment. No exclusion criteria were intended for the present analysis.

The search was performed by browsing and following links using Internet search engines (Google, AllTheWeb) and online literature databases (National Library of Medicine MEDLINE, ISI Web of Science). It was complemented by browsing references of original articles, review articles, and conference proceedings. No attempt was made to restrict the search criteria, although some combinations of words were used preferentially during the search: breast conserving, conservation surgery, or radiotherapy.

The search identified 18 randomized trials, with a total of 10 149 patients. Eleven trials, with a pooled total of 6422 patients, have been published as full articles (Table 1): National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 (3), Uppsala-Orebro (17), St. George's (18), Ontario (19), Scottish (20), Tokyo (21), St. Petersburg 85–96 (22), Milan III (23), NSABP B-21 (24), Tampere (25), and Swedish Breast Cancer Group (SweBCG) 91-RT (26). Four trials (3106 patients total) have been published as abstracts: Cancer Research Campaign (CRC)-UK (27), Toronto (28), British Association of Surgical Oncology (BASO)-II (29), and Cancer and Leukemia Group B (CALGB)-9343 (30).

Reports were unavailable for three of the 18 trials: German Breast Center Study Group (GBSG)-5 (31), 361 patients, analysis pending (Sauerbrei WF: personal communication); Postoperative Radiotherapy in Minimum-risk Elderly (PRIME) study, still ongoing, projected accrual of 240 patients (32); and European Organization for Research and Treatment of Cancer (EORTC)-10932 trial (33), closed prematurely after accrual of 20 patients because of low accrual rate (Therasse P: personal communication). These three trials are mentioned for information, but because data reports were unavailable they were not considered for this analysis. All 15 published trials were closed before 2001 and were included in the pooled analysis (Table 1).

For local recurrence analysis, recurrence or relapse was defined as ipsilateral breast tumor recurrence presenting as a first event. The estimates of ipsilateral breast tumor recurrence were based on published results for 13 trials and on unpublished updated figures for one trial (St. Petersburg) and were computed using the published relative risk of ipsilateral breast tumor recurrence in one trial (CRC-UK).

For survival analysis, the endpoint was death from any cause. Thirteen of the 15 published studies reported mortality data. Three were in abstract form (two with <5 years of follow-up). All 10 of the studies presented in full articles had more than 5 years of follow-up (Table 1).

The summary statistic used the relative risk of death. The reference for calculation of relative risks was the group of patients assigned to radiotherapy. The intention-to-treat assignment was applied. If the numbers of deaths were not available, then survival graphs or survival rates were used to estimate the numbers of deaths. If the survival graphs or rates were not available, then the published hazard ratio was used.

**Table 1.** Clinical trials studying patients with early stage breast cancer treated with breast-conserving surgery with or without radiotherapy

Trial (ref.)	Years of study	No. of patients	Median follow-up (y)	Mean age (range)	Tumor size, cm	Resection margins; other criteria	Node dissection level	Node-positive %	Systemic therapy	% local relapse		Relative risk of death (95% CI)*
										No RT	RT	
NSABP B-06 (3)	1976–1984	1137†	20.7	53‡ (≤70)	≤4	Free margin	I–II	37	Node positive	39.2	14.3	1.07 (0.96 to 1.20)
Uppsala-Orebro (17)	1981–1988	381	8.8	60 (<80)	≤2	2 cm normal tissue; no tumor transection during surgery	I–II	None	None	24	8.5	0.98§ (0.67 to 1.42)
St. George's (18)	1981–1990	418	6.1	51# (28–70)	≤5	Tumor involved margin in 6%	I	38	All	35	13	1.15¶ (0.74 to 1.79)
Ontario (19)	1984–1989	837	7.6	56‡ (≥50)	≤4	0.5–1 cm normal tissue	I–II	None	None	33.5	10.6	1.12 (0.87 to 1.45)
Scottish (20)	1985–1991	585	5.3	57# (28–70)	≤4	1 cm normal tissue, re-excision accepted	Sampling or I–III	23**	All	24.5	5.8	1.01 (0.69 to 1.49)
Tokyo (21)	1985–1993	113	4.6	51# (<80)	≤5	Free margin required	I–II	40††	All	9.4‡‡	7.1‡‡	1.18 (0.84 to 1.65)
St. Petersburg§§ (22)	1985–1996	360	9.9	68 (>50)	≤2.5	1–2 cm normal tissue	I–II	20	All	14.2	5.8	1.03 (0.78–1.36)
CRC UK (27)	1986–1995	518	9.7	60 (<70)	≤2.5	Tumor involved margin in 23.4%	I–II	31	Almost all (95%) positive	21.2	6.6	1.18*** (0.84 to 1.66)
Milan III (23)	1987–1989	579¶¶	9.1	52## (≤70)	≤1	Free margin required	I–III	None	Node positive	23.5	5.8	0.91 (0.51 to 1.63)
NSABP B-21 (24)	1989–1998	673†††	7.2	59‡	≤1	Free margin required, re-excision allowed	I–II	None	Tamoxifen	13.5	2.7	1.85§§§ (0.46 to 7.48)
Tampere (25)	1990–1995	152	6.7	55# (>40)	<2	1 cm normal tissue	I–II	None	None	18.1†††	7.5†††	1.15     (0.74 to 1.79)
SweBCG (26)	1991–1997	1187	7	60 (<76)	≤5	No tumor cells in resection margins	I–II	None	In 9% of patients	13.3	4.4	1.40¶¶¶ (0.81 to 2.45)
Toronto (28)	1992–2000	769	3.4	68 (>50)	≤5	Grade I; clear margin required	Not if age >65	None	Tamoxifen	5.7	0.5	1.05 (0.57 to 1.92)
BASO II (29)	1992–2000	1172	2.9	60 (<70)	≤2	Estrogen receptor positive	Not required	None	Randomized tamoxifen	3.6	1.3	
CALGB 9343 (30)	1994–1999	647	2.3	60 (≥70)	≤2		Not required	None	Tamoxifen	1.3	0	

\*Relative risk of death from any cause in no radiotherapy (RT) versus RT (RT is reference group) and 95% confidence interval (CI) (35). NSABP = National Surgical Adjuvant Breast and Bowel Project; CRC-UK = Cancer Research Campaign, United Kingdom; SweBCG = Swedish Breast Cancer Group; BASO II = British Association of Surgical Oncology; CALGB = Cancer and Leukemia Group B.  
†Three-arm trial. Data are based on the lumpectomy arms: no RT (304 deaths/570 patients) versus RT (283 deaths/567 patients).  
‡Mean was estimated from earlier reports, assuming a normal population standard deviation of 13.6.  
§Estimated 10-year survival: no-RT group = 78%; RT group = 77.5%.  
||Allocation changed from no RT to RT for 16 patients with involved margin.  
¶Estimated from relapse-free survival, assuming identical number of deaths from relapse.  
#Estimated median.  
\*\*Premenopausal women with involved axillary lymph nodes were not eligible.  
††Distribution of patients with involved lymph nodes: 30 of 85 in no-RT group; 15 of 28 in RT group.  
‡‡Regional relapses, metastases, and deaths from any nonlocal cause were censored.  
§§Updated data (August 2002), courtesy of Dr. Semiglazov.  
|||Locoregional relapse computed from (27) that reported a relative risk of 0.31 in RT versus no-RT group.  
¶¶Twelve patients with involved margins were excluded after randomization.  
##Estimated from percentage distribution of patients' ages.  
\*\*\*Crude estimate, number of deaths: no-RT group = 57 of 273; RT group = 52 of 294.  
†††Three-arm randomization. Data are based on the tamoxifen arm (20 deaths/334 patients) versus the tamoxifen + RT arm (22 deaths/334 patients).  
‡‡‡Locoregional relapse.  
§§§Crude estimate in 2001, number of deaths: no-RT group = 5 of 72; RT group = 3 of 80 (data courtesy of Dr. K. Holli, University of Tampere).  
||||Five-year survival: no-RT group = 93%; RT group = 94%.  
¶¶¶Estimated 4-year survival: no-RT group = 92.8%; RT group = 94.7%.

The pooled relative risks were estimated by a random-effects model applied to the log relative risks (34). Heterogeneity was assessed using the Cochran Q test (34). All computations were performed using EasyMA software (35).

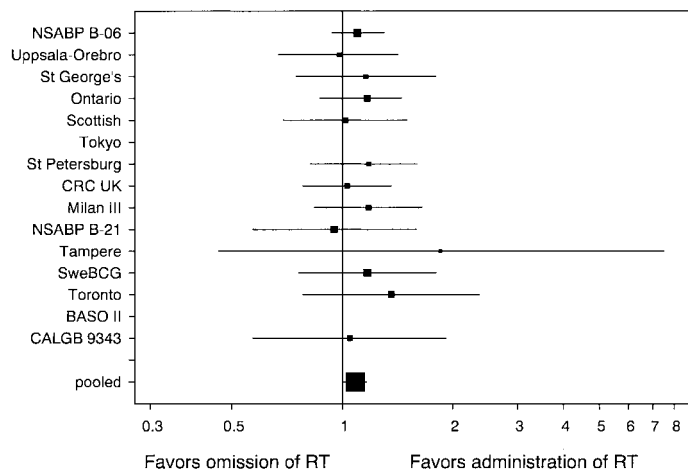
Because abstracts are not exposed to the same scrutiny as full articles, and interpreting ipsilateral breast tumor recurrence and mortality needs a relatively long follow-up, a second analysis was performed on a subset of nine trials (referred to as “9-trials subset” further in the text) that excluded studies published as abstracts (27–30), studies with less than 5 years of follow-up (21), and the one study that did not report results by treatment assignment (the data were presented incompletely in the original publication and reported only actual assignment) (18).

In an effort to improve data quality and identification of trials, earlier drafts of this article, with the corresponding calculation spreadsheets, were repeatedly made available electronically to the authors of trials and reviews and to the editors of journals in which reviews were published.

## RESULTS

Table 1 summarizes the characteristics of the trials included in this study. Mortality estimates were calculable for 13 trials, for a pooled total of 8243 randomly assigned patients, of whom 8206 were analyzed in the original reports: 4097 patients and 824 deaths in the no-radiotherapy arms versus 4109 patients and 755 deaths in the radiotherapy arms. Recurrence estimates were calculable in all 15 trials, for a pooled total of 9528 patients, of whom 9422 were analyzed: 4731 patients of whom 875 had ipsilateral breast tumor recurrence in the no radiotherapy arms versus 4691 patients of whom 279 had ipsilateral breast tumor recurrence in the radiotherapy arms.

The pooled relative mortality risk of no radiotherapy versus radiotherapy estimated from the 13 trials with survival or mortality data is 1.086 (95% confidence interval [CI] = 1.003 to 1.175), that is, an 8.6% relative excess mortality if no radiotherapy is administered. The test of heterogeneity was not statistically significant. In all but two trials, the relative mortality risk was larger than 1 (Fig. 1). Of the two negative trials, one reported 15 of 172 patients (8.7%) allocated to radiotherapy who



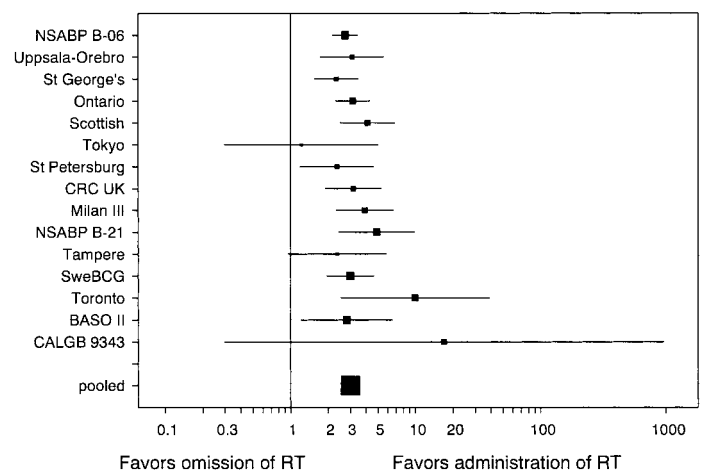
**Fig. 1.** Omission versus administration of radiotherapy (RT) after breast-conserving surgery. Plot of relative risk of death from any cause (1 = no difference) and 95% confidence intervals. The size of each box is scaled as a square-root function of trial size.

did not receive radiotherapy, but there was full compliance in the surgery-only arm (17). The other trial provided no compliance figures (24).

Omission of radiotherapy was associated with an increased rate of relapse, whether or not patients received systemic treatment (Table 1). The pooled relative risk of ipsilateral breast tumor recurrence with no radiotherapy versus radiotherapy based on all 15 trials was 3.00 (95% CI = 2.65 to 3.40) (Fig. 2). There was a statistically significant heterogeneity across studies, with substantial variations in relative risks. In the 11 studies with a median of more than 5 years of follow-up (Table 1), the observed average percentage of local relapse ranged from 1.4% to 5.7% per year when radiotherapy was omitted and from 0.4% to 2.1% per year when radiotherapy was administered. The individual relative risks estimated in these trials varied from 2.32 (95% CI = 1.56 to 3.45) to 4.89 (95% CI = 2.45 to 9.76). In the four studies that had less than 5 years of follow-up, the percentages of relapse were small (Table 1). The corresponding relative risks presented more variability, as might be expected from the shorter follow-up, ranging from noncalculable (30) to 1.22 (95% CI = 0.3 to 5.02) (21), 2.82 (95% CI = 1.22 to 6.53) (29), and 9.92 (95% CI = 2.53 to 38.79) (28) (Fig. 2). The reanalysis performed on the 9-trials subset found relative risks of mortality and ipsilateral breast tumor recurrence of 1.083 (95% CI = 0.993 to 1.180) and 3.09 (95% CI = 2.69 to 3.56), respectively.

## DISCUSSION

The gold standard is the individual patient data meta-analysis (36). A literature-based pooled analysis depends on information in the published reports. It is subject to publication bias or to lack of transparency in patient allocation. The use of the total number or proportion of deaths on each arm may be inefficient as compared with analyses using individual patient's survival times. These limitations apply to the present study. However, resources needed to collect individual patient data might prevent or considerably delay the communication of results. A pooled analysis based on data extracted from the literature may, in some



**Fig. 2.** Omission versus administration of radiotherapy (RT) after breast-conserving surgery. Plot of relative risk of ipsilateral breast tumor recurrence (1 = no difference) and 95% confidence intervals. The size of each box is scaled as a square-root function of trial size. Due to the scale, the 95% confidence interval for the pooled relative risk is smaller than the size of the corresponding box.

cases, be a practical alternative as a precursor to a larger project (37,38).

With the caveat that the pooled estimates might differ from those obtained in an individual patient data meta-analysis, our results show that omission of radiotherapy is associated with a threefold increase in the risk of ipsilateral breast tumor recurrence. Almost all investigators in the included studies reported that radiotherapy could not be omitted. Fisher and Anderson (39) questioned the utility of a radiation boost (a dose of radiation to the tumor bed in addition to conventional doses already delivered to the whole breast) but never dismissed the requirement for radiation. Fisher et al. (40) performed a systematic analysis of the NSABP B-06 trial, using modern statistical tools to examine 31 pathologic and six clinical features in 1039 evaluable patients and concluded that the use of local irradiation after lumpectomy appeared to supersede all other prognostic factors (40). These investigators explicitly noted that a formal test of interaction failed to reveal any pathologic or clinical feature that might have allowed for the omission of local irradiation of the breast after lumpectomy (40). Other investigators (19,20,25,27) have also noted that no particular group can be considered to be at low risk for locoregional relapse of breast cancer.

We did not attempt any subgroup analysis, for the following reasons. First, the current published average of 6 years for follow-up is too short a time period for enough events to have occurred, and the group results barely reached statistical significance (loss of statistical significance was noted when the data were reanalyzed using the 9-trials subset). Second, the diagnosis of recurrence depends on the pattern of surveillance, which could vary between subgroups.

Although the effect of radiotherapy in reducing the risk of recurrence is undisputed (14), no statistically significant differences in overall survival were found in any individual trial (Table 1). Results of the analysis on the 9-trials subset suggest that the relative risk estimate of mortality is robust. However, the lack of statistical significance still casts doubt on the reality of a survival effect. Is there a favorable effect or not? And if there is, why? A literature search found several reports from registries and practice surveys that provided survival results for breast-conserving surgery: Switzerland Geneva (cancer registry) (41), Canada Ontario (patterns of surveillance) (42), U.K. Northern & Yorkshire (cancer registry) (43), Sweden (population practice survey) (44), U.S. SEER (cancer registries) (15), U.S. National Cancer Data Base (hospital registries) (45), U.S. Health Maintenance Organization (HMO) Washington State (health organization) (46), and Germany survey of practice outcome follow-up of the German Breast Cancer Study Group's trial (GBSG-1) (47). All showed a survival advantage for breast-conserving surgery with radiotherapy as compared with other local treatment modalities. Observational studies are difficult to interpret, but all have provided evidence of a favorable effect of radiotherapy on survival after breast-conserving surgery (14,41-47). They corroborate the trend for better survival observed in this pooled analysis of randomized clinical trials.

A reduction in the rate of ipsilateral breast tumor recurrence seems insufficient to explain the more favorable survival in patients receiving radiotherapy after conservative surgery. The probability of local recurrence has been found to be higher in patients who received breast-conserving treatment as compared with that in patients who received radical mastectomy (4). If local recurrence was a major factor, then the best survival should

have been observed after radical mastectomy, which is not the case (4). The discrepancy between recurrence and survival may be due to a different impact of in-breast recurrence and chest wall recurrence. In the NSABP B-06 trial, which was a three-arm trial of lumpectomy versus lumpectomy plus radiotherapy versus mastectomy, Fisher et al. (3) reported rates of ipsilateral breast tumor recurrence when comparing radiotherapy with no radiotherapy but used chest wall recurrences when comparing lumpectomy with mastectomy. The respective rates of chest wall recurrences were 2.7% in the lumpectomy plus radiotherapy group versus 8.8% in the lumpectomy group versus 10.2% in the total mastectomy group. Thus, ipsilateral breast tumor recurrence and chest wall recurrences do not appear to have the same clinical significance. Furthermore, the pattern of radiation may be different after mastectomy versus after lumpectomy. Radiotherapy given after mastectomy usually includes the axilla or supraclavicular fossa and often the internal mammary chain in addition to the chest wall. In contrast, radiotherapy given after breast-conserving surgery often involves treatment to the breast alone (14). One possible hypothesis for explaining the survival differences is that the radiotherapy administered in lumpectomy trials irradiated less lung or heart than the radiotherapy administered with mastectomy yet was more efficient than total mastectomy alone in reducing cancer recurrences in the chest wall, without being offset by an excess mortality from other causes, as was observed with radiotherapy after mastectomy (14).

In addition, the survival advantage observed with radiotherapy is seen from trials that generally specified clear margins (Table 1). Clear margins were similarly specified in previous trials that demonstrated the equivalence between breast-conserving treatment and mastectomy (2-8). Outcome results may be different in case patients showing involved margins with a radiotherapy regimen that was designed assuming complete resection.

In summary, the present study confirms that radiotherapy should not be omitted after breast-conserving surgery, except for medical contraindications such as systemic vascular disease or a previous history of irradiation (48). Although the mortality risk may seem small, in daily practice in the general population it may translate into a considerable survival disadvantage for patients in whom radiotherapy is omitted. On an individual level, it is less obvious whether all patients should receive radiotherapy. Decision making requires an assessment of absolute risks, and the decision may depend on the histopathologic characteristics of the tumor and on a woman's comorbidities and life expectancy. For example, even if we accept that the mortality increase of 8.6% applies to all women, a 65-year-old woman with a 1-cm estrogen receptor-positive tumor and negative lymph nodes would have a minuscule improvement in survival due to radiotherapy. According to the SEER data, her chances of survival at 5 years and 10 years are 95% and 85%, respectively (49). With an estimated 8.6% relative excess mortality without radiotherapy (assuming that this relative excess does not decrease over time, and assuming the same controlled conditions in daily practice as in clinical trials), the absolute survival benefit with radiotherapy is 0.5% and 1.5%, respectively. Therefore, the issue of adjuvant radiotherapy or not remains open; alternatives, such as a partial-breast irradiation, should continue to be researched (50,51).

In conclusion, this pooled analysis of the data available in the literature finds that omission of radiotherapy after breast-

conserving surgery was associated with a threefold increase of ipsilateral breast tumor recurrence and was associated with a marginally statistically significant excess mortality risk of 8.6% (95% CI = 0.3% to 17.5%) relative to the delivery of radiotherapy.

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## NOTES

<sup>1</sup>*Editor's note:* SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

The Breast Conserving Surgery Project includes Vincent Vinh-Hung (data collection and statistical analyses), Claire Verschraegen (critical review of the data and redaction of the manuscript), Guy Storme, and Jan Van de Steene (redaction of the report).

We are grateful to Kaija Holli, Patrick Therasse, Vladimir F. Semiglazov, Dirk Van den Berge, Valeri N. Verovski, Mia Voordeckers, and many others who encouraged, helped, commented, or contributed to this report. We are also grateful to Michel Cucherat for making available the EasyMA software.

Manuscript received May 15, 2003; revised November 12, 2003; accepted December 5, 2003.