Long-term community-based results of breast-conserving therapy in early-stage breast cancer

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Background Multicenter clinical trials conducted primarily at academic centers have shown that breast-conserving therapy (BCT) and mastectomy lead to equivalent overall survival (OS) for women with early-stage breast cancer.
Objective To determine rates of BCT and OS after conservation therapy in a large urban community practice, compare them with national rates, and identify risk factors for survival.
Methods We identified 1,172 T1-2, N0 breast cancer patients diagnosed during 1997-2007 in our hospital tumor registry and compared the rates of BCT and adjuvant radiotherapy with a similar population in the SEER [Surveillance, Epidemiology, and End Results] database (N = 232,898) for the same treatment period. Cox proportional hazards models were used to assess the influence of age at diagnosis, tumor grade, biomarker status, margin status, and receipt of hormones, radiation, or chemotherapy on OS after BCT.
Results The rate of breast-conserving surgery (BCS) was higher in our practice compared with the national average (90.9% and 66.4%, respectively). The rate of adjuvant radiation after BCS in our practice was 93.7%; survival estimates were higher for patients treated with adjuvant radiation across all age groups, compared with the national estimates (92.5% and 72.9%). Younger age and receipt of radiation were associated with improved survival.
Limitations Retrospective study design; confounding factors such as comorbidities were not considered.
Conclusions We had high rates of BCT and adjuvant radiation in early-stage breast cancer patients in our community practice, which resulted in excellent survival rates that compared favorably with those in large academic centers and emphasizes the role of appropriate use of adjuvant radiation.
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Breast-conserving therapy (BCT) – the use of breast-conserving surgery (BCS) followed by whole breast radiation therapy – is considered the standard of care for women with early-stage breast cancer.[1] This recommendation is based on a significant body of evidence that shows that BCT is equivalent to mastectomy as local treatment for most women with stage I or II breast cancers in terms of overall survival (OS), even with very long-term follow-up.[2-6] The EORTC 10801 trial, which compared BCT with modified radical mastectomy in 448 patients with early-stage breast cancer, reported that the 20-year overall survival was comparable between the 2 treatment groups (44% vs 39%, respectively), with no significant differences for time to death (hazard ratio [HR], 1.11).[5] Although the EORTC study and others showed a slight increase in the risk of local recurrence with BCT, present-day studies have reported local recurrence rates after BCT that are much lower than in previous decades. A more recent analysis reported lower all-cause mortality with BCT when compared with unilateral mastectomy, and no survival advantage of bilateral mastectomy over BCT.[7]

Findings from large randomized trials confirm the importance of adjuvant radiation after BCS on local tumor control in early-stage breast cancer. A meta-analysis of 17 randomized trials conducted by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) confirmed that the addition of radiotherapy to surgery resulted in significant reductions in local recurrence rates.[8,9] In that meta-analy-

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sis, adjuvant radiotherapy significantly reduced the 10-year risk of any first recurrence (locoregional or distant) from 35% to 19% ($2P < .00001$). Moreover, radiotherapy compared with no radiotherapy (with or without systemic therapy) reduced local recurrence in all women with early-stage breast cancer, regardless of age or tumor characteristics.[3,9]

Despite significant reductions in locoregional recurrence, individual trials have shown that the addition of radiation therapy to BCS did not translate into a survival benefit.[4,10] Consistent with these results, meta-analyses from the EBCTCG trials also did not show long-term reduction in all-cause mortality. A modest but statistically significant reduction in breast cancer mortality was shown, with a 15-year absolute risk reduction from 25% to 21% ($2P = .00005$).[9] Improvements in local control of between 10% and 20% were found to be associated with statistically significant differences in breast cancer survival at 15 years.[9] Overall, it was estimated that about 1 breast cancer death was avoided by year 15 for every 4 recurrences avoided by year 10. Yet, increase in deaths due to other causes offsets any benefit achieved from decreased deaths due to breast cancer.[4] It is important to note that several aspects of breast cancer care, such as screening, surgery, pathology, radiotherapy, and systemic therapy, have changed considerably since these pivotal trials. It is, therefore, reasonable to anticipate that the clinical outcomes in present-day trials will surpass those from the historical trials.

Our study was conducted to evaluate the present-day rates of BCT and OS after BCT for women with early-stage breast cancer in a large community hospital setting; to compare those rates with national averages; and to identify the clinical factors associated with survival among patients who underwent BCT in our community populations. The rationale for conducting the study was multifold. First, most of the available reported data were obtained from randomized clinical trials that had been conducted mostly in academic centers or large regional care centers. Our study assessed whether the results are clinically relevant in a real-world, community hospital setting, using the Surveillance, Epidemiology, and End Results (SEER) database as a substantial normative source for benchmarking. Furthermore, because the pivotal randomized studies were conducted in the 1980s, our study also evaluated the validity of reported outcomes in a present-day community setting given the many advances in treatment over the past 3 decades.

Methods

We used the tumor registry at Providence St Joseph Medical Center in Burbank, California, to identify T1-2, N0 breast cancer patients diagnosed during January 1, 1997-December 31, 2007. All identified patients had been treated by physicians belonging to a single medical group, Valley Radiotherapy Associates in Los Angeles. The standard of care at the local practice was to offer BCS followed by radiation therapy as a primary local treatment, with re-excision as necessary, in patients with early-stage breast cancer. Radiation therapy included whole-breast irradiation (45-50.4 Gy) plus a boost, typically delivered by electrons, to the lumpectomy cavity (10-20 Gy).

Rates of BCS and adjuvant radiation after BCS stratified by age at diagnosis of patients in the local registry were compared with those of the same age, stage, and treatment period identified through SEER. The effects of surgical margin status, biomarker status (estrogen receptor [ER], progesterone receptor [PR], and human epidermal growth factor receptor 2 [HER2] amplification), and adjuvant systemic treatment (hormone therapy or chemotherapy) on rates of adjuvant radiation after BCS were also analyzed. For survival analyses, to allow for adequate follow-up, only those patients who had definitive BCT and at least 8 years of actual or potential follow-up were included; median follow-up was 10.6 years. Earlier published data from this same community setting reported on a shorter time period and hence a smaller number of patients.[7] Overall survival estimates for those who received BCT in our study were calculated using our data and the comparable data set from SEER. We determined the influence on OS of the following disease and treatment characteristics: age at diagnosis, race, surgical margin status, tumor histopathology, tumor grade, biomarker status (ER, PR, or HER2), and adjuvant treatment (radiation therapy, hormone therapy, or chemotherapy). We were not able to conduct an analysis of local recurrence or distant metastases for patients from the local tumor registry because of inadequate or incomplete reporting of data.

Pearson's chi-square test or the Fisher exact test was used to examine relationships between categorical variables. If the large sample assumptions were not met for the chi-square test, then we used the Fisher exact test. The Kaplan-Meier product-limit estimate of the survival curves was used to compare OS between simple strata. The effect of specific variables on OS while adjusting for additional variables in the model were examined by Cox proportional hazards models.

Results

We identified 1,172 patients in our local tumor registry who were diagnosed with T1-2, N0 breast cancer during 1997-2007 and who underwent mastectomy or BCS. A search of the SEER database using similar criteria led to the identification of 232,898 patients with breast cancer.

A comparison of the rates of surgical procedures for early-stage breast cancer in the local registry and the SEER database showed that fewer patients in our community practice underwent mastectomy compared with the national average (9.1% vs 33.6%, respectively; Table 1) and that conversely, a greater proportion of patients in the local practice underwent BCS (90.9% vs 66.4%) and received radiation therapy (85.2% vs 49%) compared with the SEER dataset.

The baseline characteristics and demographics of the 1,065

patients from the local tumor registry who had undergone BCS and who had at least 8 years of follow-up are shown in Table 2. The median age of the patients was 59 years. A majority of patients had T1 (85.6%) and grade 1-2 disease, indicating that our study included a relatively low-risk population. About half of the overall population received adjuvant hormone therapy and about a quarter of the patients received systemic adjuvant chemotherapy. Whole-breast radiation therapy was administered at a median dose of 5040 cGy. The majority of patients (81.2%) were given a boost to the lumpectomy cavity with a median boost dose of 1400 cGy.

An analysis of patients who underwent BCS showed that 93.7% of those in the local registry also had adjuvant radiation, compared with 74.4% of those in the SEER dataset (Table 3). Subgroup analyses by age showed that the rates of adjuvant radiation were generally lower for patients who were aged 70 years or older, compared with those who were younger than 50 years in both the local registry (87.4% vs 96.6%, respectively) and the SEER datasets (65.6% vs 76.3%, respectively). Nevertheless, the rates of radiation remained substantially higher in the local registry than in the SEER database (87.4% vs 65.6%) in the elderly subgroup (Table 3). There were no significant differences in the administration of adjuvant radiation by other prognostic factors studied, including margin status, biomarker status, or adjuvant systemic treatment (data not shown). At least 95% of patients who were treated with adjuvant chemotherapy or hormone therapy also received adjuvant radiation (data not shown).

A comparison of 10-year survival estimates in the overall SEER dataset showed that the addition of adjuvant radiation therapy to BCS was associated with improved survival compared with mastectomy (82.4% vs 72.1%; Table 4). This association with improvement in survival was also seen in all age groups. A similar analysis could not be conducted for the local tumor registry because of the low incidence (<10%) of mastectomy in our practice.

An analysis of the SEER dataset and the local tumor registry data showed that 10-year survival estimates were consistently greater for patients treated with adjuvant radiation after BCS across all age groups (Table 4). As expected, elderly patients (≥70 years) showed significantly lower survival rates, compared with patients who were younger than 50 years, whether they received radiation therapy or not (Table 4). However, among elderly patients, those who were treated with adjuvant radiation showed significantly greater 10-year OS estimates than those without adjuvant radiation (77.5% vs 50.5%, $P < .0001$). Similar trends were observed for other age groups, although they did not reach statistical significance (Table 4).

A Cox proportional hazards regression model indicated that in our study population, age at diagnosis and the administration of radiation therapy were the only significant predictors of OS. Other factors, including race; surgical margin status; tumor histopathology; tumor grade; ER-, PR-, or HER2-status; adjuvant hormone therapy; or adjuvant chemotherapy, did not show an effect on survival

TABLE 1 Rates of mastectomy and breast-conserving surgery in the local tumor registry and SEER database

Procedure	SEER database, n (%) (N = 232,898)	Local tumor registry, n (%) (N = 1,172)
Mastectomy	78,189 (33.6)	107 (9.1)
BCS		
Total	154,709 (66.4)[a]	1,065 (90.9)
With radiation	114,053 (49.0)	998 (85.2)
Without radiation	39,306 (16.9)	67 (5.7)

BCS, breast-conserving surgery; SEER, Surveillance, Epidemiology, and End Results

[a]Inadequate data on 1,350 patients who had undergone BCS.

TABLE 2 Characteristics of patients in local tumor registry

Characteristic	Value (N = 1,065)
Median age, y (range)	59 (25-95)
Margins, n (%)	
Positive/focal positive	18 (1.7)
Negative	1035 (97.1)
Unknown	12 (1.1)
Biomarker status, n (%)	
HR-positive, HER2-positive	158 (14.8)
HR-positive, HER2-negative	407 (38.2)
Triple negative	154 (14.5)
Unknown/missing values	346 (32.5)
Adjuvant treatment, n (%)	
Hormone therapy	
Yes	524 (49.2)
No	540 (50.7)
Unknown	1 (0.01)
Chemotherapy	
Yes	284 (26.7)
No	781 (73.3)
Median dose, cGy	
Whole-breast	5040
Boost dose to lumpectomy cavity	1400
% of patients receiving boost dose	81.2

HR, hormone receptor; HER2, human epidermal growth factor receptor 2

TABLE 3 Rates of radiation after breast-conserving surgery in the local tumor registry and SEER database

	SEER database, n (%) (N = 232,898)		Local tumor registry, n (%) (N = 1,172)	
Age group, y	BCS without radiation	BCS with radiation	BCS without radiation	BCS with radiation
All patients	39,306 (25.6)	114,053 (74.4)	67 (6.3)	998 (93.7)
<50	7,192 (23.7)	23,110 (76.3)	8 (3.4)	229 (96.6)
50-69	14,566 (20.4)	56,842 (79.6)	28 (4.8)	553 (95.2)
≥70	14,269 (34.4)	27,220 (65.6)	31 (12.6)	216 (87.4)

BCS, breast-conserving surgery; SEER, Surveillance, Epidemiology, and End Results

TABLE 4 10-year survival estimate by age with and without radiation

	10-year survival estimate, % (95% confidence interval)				
	SEER database (N = 232,898)			Local tumor registry (N = 1,172)	
Age group, y	Mastectomy	BCS without adjuvant radiation	BCS with adjuvant radiation	BCS without adjuvant radiation	BCS with adjuvant radiation
All patients	72.1 (71.7-72.5)	66.5 (65.8-67.1)	82.4 (82.2-82.8)	72.9 (60.5-82.0)	92.5 (90.7-94.0)
<50	89.2 (88.6-89.8)	89.2 (88.2-90.0)	92.2 (91.8-92.6)	87.5 (38.7-98.1)	98.3 (95.4-99.3)
50-69	82.8 (82.3-83.4)	82.2 (81.3-83.0)	88.3 (88.0-88.7)	92.9 (74.4-98.2)	96.0 (94.0-97.4)
≥70	47.6 (46.7-48.4)	39.4 (38.2-40.5)	62.7 (61.8-63.5)	50.5 (31.8-66.6)	77.5 (71.3-82.5)

BCS, breast-conserving surgery; SEER, Surveillance, Epidemiology, and End Results

in this low-risk population in which a minority of patients received chemotherapy.

Discussion

In our study, a higher percentage of patients in the local registry underwent BCS compared with those in the SEER database (90.9% vs 66.4%, respectively). Consistent with the current standard of care, a greater majority of the patients in the local registry who received BCS also went on to receive radiation therapy than did patients in the SEER database (93.7% vs 74.4%). These results demonstrate that high rates of BCS with adjuvant radiation can be achieved in community settings for appropriate early-stage breast cancer patients.

We also report 10-year survival rate estimates of 92.5% with the local registry database and 82.4% for the comparable SEER dataset for those patients who received adjuvant radiation therapy. Those estimates are favorable even when compared with present-day clinical trial results mainly from academic centers or cooperative groups; for example, the Ontario Clinical Oncology Group trial showed 10-year overall survival rates of about 84%.[12] Our study also reported an absolute difference in OS of 19.6% and 15.9% associated with receipt of adjuvant radiation for the local registry and SEER populations. In contrast, the NSABP-B06 trial reported no significant differences in OS between cohorts treated with and without adjuvant radiation therapy.[13,14] Meta-analyses of the EBCTCG trials also did not show long-term improvements in OS with the addition of radiation therapy; however, a significant improvement in breast cancer mortality was reported.[8,9,15] For example, Darby and colleagues reported that radiation therapy reduced the 15-year risk of breast cancer death from 25.2% to 21.4% for an absolute reduction of 3.8%. The substantially higher survival rates observed in our study may be attributed to the generally favorable group of patients with early-stage, node-negative disease reported in this study; 86% of patients had T1 tumors, the majority had grade 1-2 disease, and most patients were older than 50 years. In addition, these findings likely reflect some selection bias in which healthier patients were more likely to receive adjuvant radiation. Sicker patients may have refused treatment (either radiation or systemic therapies), may have been ineligible for these treatments, or may not have been offered these options by their physicians.

The effect of selection biases on treatment outcomes may

be particularly relevant for older patients. Our results also show that patients who were 70 years or older benefited from radiation, although again the effect of confounders such as presence or absence of comorbidities is unknown. These findings are consistent with the current recommendations of the National Comprehensive Cancer Network regarding the treatment of elderly patients, which state that "advanced age alone should not preclude the use of effective cancer treatment that could improve quality of life or extend meaningful survival."[16] Instead, they recommend that treatment decisions in elderly patients should be made after considering physiological age rather than biological age, the Fitness or Frailty index, and comorbidities.

In our analysis, age and the use of adjuvant radiation were the only significant predictors of survival. Although there is evidence supporting the survival benefits of adjuvant systemic therapies, such as hormone therapy for hormone-receptor–positive patients, and trastuzumab for HER2-positive patients, and chemotherapy for high-risk patients, our results can be explained by the study population and the timing of our study. As we have already noted, the study population from the local registry included a notable proportion of patients with a low risk of recurrence, who were not likely to have a significant benefit from chemotherapy.[17,18] Furthermore, the study period predated the widespread use of multigene assay testing to differentiate a population at higher risk for distant recurrence among early-stage, node-negative patients, as well as the US Food and Drug Administration's approval of trastuzumab for HER2-positive, node-negative patients. Although we did not have complete biomarker data for all treated patients, consistent with the needs of this low-risk population, only about 25% of patients were treated with chemotherapy, which is consistent with a population deemed to be of favorable risk.

Recently, there has been discussion about omitting radiation therapy in select patients with a lower risk of local recurrence.[10,19] In our local practice, 6% of patients who underwent BCS did not receive radiation therapy; in contrast, a third of the patients in the SEER database who underwent BCS did not receive radiation therapy. Although the reasons for this difference are not immediately apparent, there is evidence in the literature that select patients may not derive additional benefit with radiation therapy. In the CALGB 9343 study that evaluated the benefit of adjuvant radiation therapy after BCS and tamoxifen in elderly patients (≥70 years), investigators observed a modest 8% reduction in the rate of locoregional recurrence with the addition of radiation therapy to hormone therapy, which did not translate into an OS advantage.[10] In the PRIME 2 study of 1,326 patients aged 65 years or older and with hormone-receptor–positive breast cancer, there was a 3% absolute reduction in the risk of recurrence with the addition of radiation therapy, and an OS rate of about 96% in both groups.[19] Although these results suggest that radiation therapy may be omitted for elderly patients with ER-positive early-stage breast cancer who are receiving hormone treatment, we are also reminded that factors such as patients' overall health and longevity (physiological age), as well as tumor biology, remain important considerations in determining the group of patients for whom omission of radiation treatment is appropriate.

Our analysis also showed that 9.1% of patients with early-stage breast cancer in the local registry underwent mastectomy. That mastectomy rate is substantially lower than the national average and does not reflect the current trend of increasing rates of mastectomies among patients who are eligible for BCS or BCT.[19,20] A retrospective cohort study of the National Cancer Data Base, which included 1.2 million adult women treated at accredited centers during 1998-2011, reported an overall mastectomy rate of 35.5%, with a 34% increase of adjusted odds from 2003 to 2011.[20] Furthermore, rates of increase were highest in low-risk patients, that is, those who were node negative or had in situ disease. The analysis also reported that bilateral mastectomy rates increased from 1.9% in 1998 to 11.2% in 2008. An independent analysis of SEER data including more than 250,000 women who were diagnosed with early-stage breast cancer during 2000-2007 showed a reversal in a previously declining national rate of mastectomy, from a low of 35.6% in 2005 to 38.4% in 2008.[21] Those rates are consistent with the 33.6% rate obtained from our analysis of the SEER data that represent a similar time frame and a comparable patient group to our study. As shown by Mahmood and colleagues, rates of mastectomy are influenced by patient factors, such as age and marital status, as well as geographic region, reflecting physician biases, at least in part.[21]

Despite that trend, most of currently available evidence suggests that BCT and mastectomy have comparable outcomes in terms of survival.[3,5,6,15] A meta-analysis of several large prospective randomized trials showed no significant differences in OS at 10 years with mastectomy compared with BCT.[15] A 20-year follow-up of a randomized trial comparing total mastectomy, BCS, and BCS plus irradiation for the treatment of invasive breast cancer showed no significant differences between treatment groups with respect to OS, disease-free survival, distant disease-free survival.[4] After a median follow-up of 20 years, the survival rate among women who underwent breast-conserving surgery has been found to be the same as that among women who underwent radical mastectomy[6] or modified radical mastectomy.[5] In fact, there is some evidence to suggest that BCT may be associated with better outcomes compared with mastectomy, particularly in certain patient subgroups.[22] A review of the records of women diagnosed with early-stage breast cancer during 1990-2004 in the California Cancer Registry showed better survival estimates in patients who underwent BCT compared with mastectomy, irrespective of age and

hormone-receptor status.[23] Another study reported a lower risk of all cause mortality with BCT compared with unilateral mastectomy (16.8% vs 20.1%).[7] An observational study with a dataset of 37,207 patients with early-stage breast cancer from the Netherlands Cancer Registry recently reported improved 10-year survival in patients who underwent BCS plus radiation therapy, compared with those who underwent mastectomy alone (76.8% vs 59.7%). We speculate that radiation may have played an important role in the observed difference, although the investigators in that study acknowledged that other unmeasurable factors could have confounded the results despite their multivariable adjustments. Nonetheless, this report from the Netherlands substantiates the importance of BCT as an excellent if not preferable treatment option for women with early stage breast cancer.[24] These results are consistent with our results from the analysis of SEER data over our study time period, which showed that BCT was associated with improved survival outcomes compared with mastectomy; however, adjustments for confounding factors were not conducted in our study.

In conclusion, despite recent national trends toward more mastectomies, this community-based study lends additional support to the continuing use and the expected excellent results of BCT, including the added value of adjuvant radiation therapy, in early-stage breast cancer patients. In our community-based, favorable-risk study population, the appropriate use of adjuvant radiation is associated with excellent outcomes in all age groups studied.

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