

Survival Comparisons for Breast Conserving Surgery and Mastectomy Revisited: Community Experience and the Role of Radiation Therapy

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Objectives: Evidence suggests superiority of breast conserving surgery (BCS) plus radiation over mastectomy alone for treatment of early stage breast cancer. Whether the superiority of BCS plus radiation is related to the surgical approach itself or to the addition of adjuvant radiation therapy following BCS remains unclear.

Materials and Methods: We conducted a retrospective cohort study of women with breast cancer diagnosed from 1994–2012. Data regarding patient and tumor characteristics and treatment specifics were captured electronically. Kaplan-Meier survival analyses were performed with inverse probability of treatment weighting to reduce selection bias effects in surgical assignment.

Results: Data from 5335 women were included, of which two-thirds had BCS and one-third had mastectomy. Surgical decision trends changed over time with more women undergoing mastectomy in recent years. Women who underwent BCS versus mastectomy differed significantly regarding age, cancer stage/grade, adjuvant radiation, chemotherapy, and endocrine treatment. Overall survival was similar for BCS and mastectomy. When BCS plus radiation was compared to mastectomy alone, 3-, 5-, and 10-year overall survival was 96.5% vs 93.4%, 92.9% vs 88.3% and 80.9% vs 67.2%, respectively.

Conclusion: These analyses suggest that survival benefit is not related only to the surgery itself, but that the prognostic advantage of BCS plus radiation over mastectomy may also be related to the addition of adjuvant radiation therapy. This conclusion requires prospective confirmation in randomized trials.

Keywords: Breast neoplasms/surgery; Breast neoplasms/radiotherapy; Mastectomy/statistics; Breast conservation; Risk factors; Survival

Early trials demonstrated equivalent long-term survival rates for patients with early stage invasive breast cancer treated by mastectomy or breast conserving surgery (BCS).¹ In lieu of clinical trial results demonstrating the superiority of BCS with radiation compared to BCS alone, the default treatment approach for breast conserving therapy includes BCS followed by radiation therapy, with physicians infrequently opting to perform BCS alone.² In randomized controlled trials, BCS plus radiation has been shown to be at least equivalent, or even superior, to mastectomy.^{3,4} What

remains unclear is the relative importance of the surgical procedure itself. In other words, is mastectomy a superior procedure in terms of outcomes, or is the extent of surgery overshadowed by other adjuvant therapy?

In 1991, a National Institutes of Health consensus statement recommended BCS plus radiation as an appropriate alternative primary therapy to mastectomy for the majority of women with early stage breast cancer in whom breast conservation is not contraindicated.⁵ This approach was

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rapidly adopted and largely replaced mastectomy as the initial surgical procedure most commonly performed for management of a primary breast tumor.⁶⁻⁸ In recent years, however, mastectomy rates appear to have increased for a variety of reasons, including larger tumor size, multicentric breast cancer, family history, race, younger age at diagnosis, pre-operative magnetic resonance imaging utilization, socioeconomic status, distance from a radiation facility, patient preference, provider preference, surgeon volume and specialty training, and availability of and advances in reconstructive surgery.^{7,9-24} These factors and the lack of a well-accepted distinction between the effect of the surgical approach itself and associated adjuvant therapy on outcomes have resulted in patients receiving widely variable surgical approaches, as ideas about surgical impact may have been merged with choices regarding use of adjuvant therapies, including radiation therapy, chemotherapy, and endocrine therapy.

Experimentally, determining the efficacy of surgical approaches in the context of other adjuvant therapies is difficult. Adjuvant therapy use is closely monitored in randomized controlled trials, and randomization of a woman to BCS alone rather than BCS plus radiation in the context of well-established guidelines for radiation use would be unethical.²⁵ Instead, well-conducted observational studies from community practice, where patterns of surgical treatment and adjuvant therapy administration vary widely, can be used to determine the utility of these surgical approaches. A recently published population-based study by Hwang et al²⁶ demonstrated that among women with early stage breast cancer, BCS plus radiation was associated with improved survival compared to mastectomy, but it excluded women who underwent BCS alone (ie, without radiation) and women who underwent mastectomy and received radiation. Therefore, it is difficult to determine whether the advantage observed was related to the surgical approach itself or to the use of radiation therapy after surgery, prompting us to examine a population of women surgically treated for breast cancer in a community practice setting to evaluate surgical outcomes following BCS or mastectomy, independent of subsequent receipt of radiation therapy, chemotherapy, or endocrine therapy.

Materials and Methods

Study design and resources

We conducted a retrospective cohort study of women diagnosed with breast cancer at the Marshfield Clinic from 1994–2012. Marshfield Clinic is the largest, physician-owned, private group medical practice in Wisconsin and one of the largest in the United States, including an extensive regional oncology practice providing care to residents of central, northern, and western Wisconsin and Michigan's Upper Peninsula in collaboration with regional hospitals. Data were captured electronically using the Marshfield Clinic/St. Joseph's Hospital Cancer Registry as the main source of information for breast cancer diagnosis and

treatment. Marshfield Clinic/St. Joseph's Hospital Cancer Registry, initiated in 1960, is accredited by the American College of Surgeons Commission on Cancer, and meets the Association of Community Cancer Center standards for cancer programs. Data are entered into the Cancer Registry manually and verified for accuracy. Additional data were collected electronically using the Marshfield Clinic comprehensive electronic medical record (EMR), which includes extensive information pertaining to clinical encounters, diagnoses, medication use, procedures, laboratory results, and pathology reports. This study was approved by the Marshfield Clinic Institutional Review Board with waiver of informed consent.

Data collection

The Marshfield Clinic/St. Joseph's Hospital Cancer Registry was queried for female patients diagnosed with stage 0–IV breast cancer at any of the cancer center sites contributing data to the Cancer Registry using International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) codes C50.0–C50.9 with first date of diagnosis between January 1, 1994 and December 31, 2012. Cancer Registry data prior to 1994 did not include the specific type of surgery. Data captured from the Cancer Registry included age, gender, insurance type, tumor characteristics (diagnosis date, morphology, grade, and estrogen receptor [ER], progesterone receptor [PR], and human epidermal growth factor receptor 2 [HER2] expression), stage of cancer at diagnosis (by tumor size, nodal status, and presence of metastases), treatment specifics (type of definitive surgery, endocrine therapy, radiation therapy, and chemotherapy), and date of death. The Cancer Registry began collecting data for ER and PR status in 2004 and HER2 expression in 2010. Surgical designations of lumpectomy, excisional biopsy, partial mastectomy, re-excision, and segmental mastectomy were considered BCS if they were not followed by an additional surgical designation indicative of mastectomy. Surgical designations of mastectomy, modified radical mastectomy, radical mastectomy, subcutaneous mastectomy, and total (simple) mastectomy, all with or without implants, reconstruction, or contralateral breast mastectomy, were considered mastectomy.

Statistical analysis

Univariate analysis of relevant demographic and clinical characteristics (eg, age, stage) was performed to compare patients who underwent BCS versus mastectomy using the Wilcoxon rank sum test. Although previous studies relied on Cox proportional hazards modeling to compare survival between groups,²⁶ we found significant violation of the proportional hazards assumption; therefore, we did not analyze our data in this manner. Instead, survival time was weighted by the inverse probability of treatment (IPT) generated from a propensity score and took into account variables related to surgical decisions or treatment variables that are influenced by the surgical approach.²⁷ Two separate statistical analyses were performed. In the first, we compared BCS to mastectomy (regardless of radiotherapy status), and

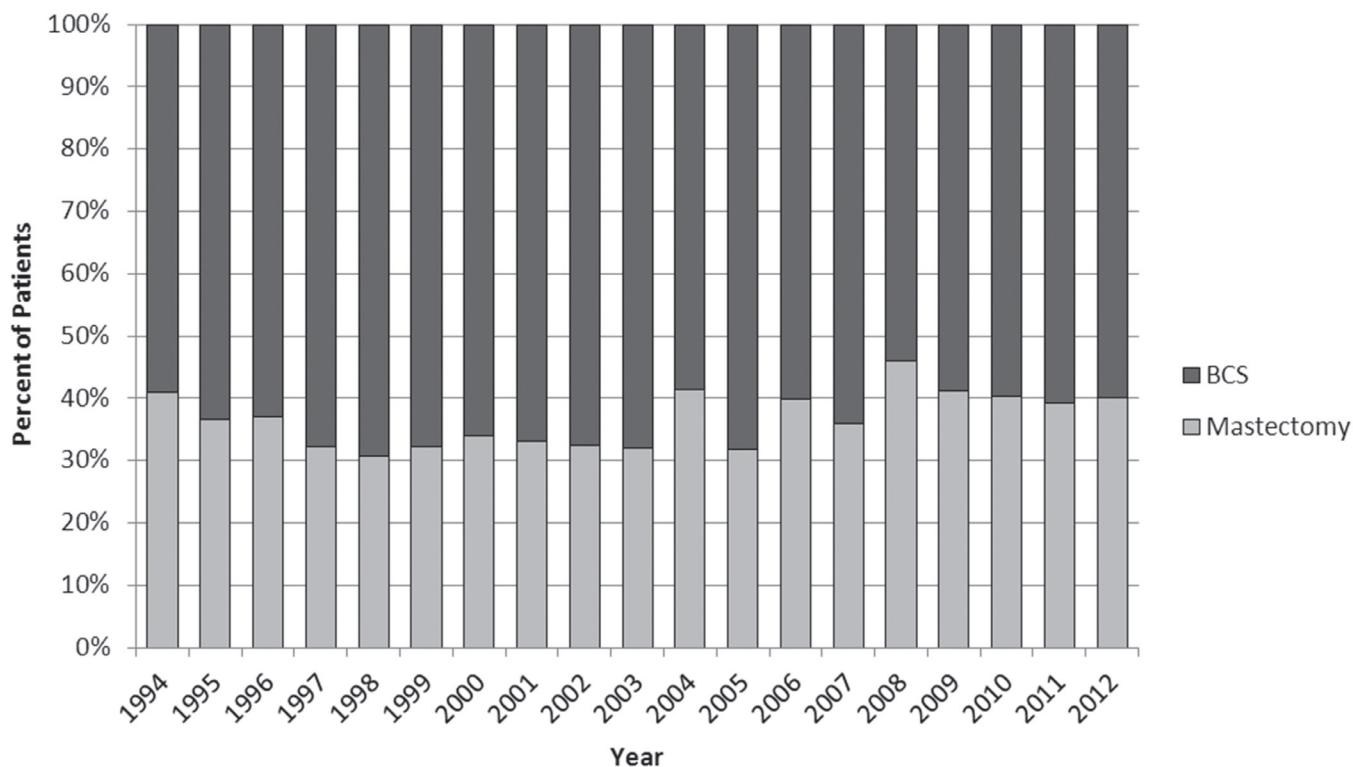


Figure 1. Surgical trends over study period. Light gray shading indicates the proportion of women who underwent mastectomy and dark gray shading indicates the proportion of women who underwent breast conserving surgery (BCS).

in the second, we compared BCS plus radiotherapy with mastectomy alone (no radiotherapy). In survival analyses, women with stage 0 and stage IV cancers were excluded as radiation therapy is unlikely to alter survival outcomes in such women.

The propensity score for the first analysis (BCS vs mastectomy) was computed as the probability of receiving a mastectomy and was estimated for each patient by fitting a multiple logistic regression model, including year of diagnosis (1994–2012), stage of breast cancer (I–III), age, grade of tumor (1–3), adjuvant treatment (chemotherapy [Y/N], radiation therapy [Y/N] and hormonal therapy [Y/N]), and three interaction variables (radiation treatment with age or stage; chemotherapy with grade). Model discrimination was excellent as assessed with the c-statistic ($c=0.944$; $P<0.001$). To investigate the link function for this model, we generated a covariate equal to the square of the linear predictor for that model using the Stata linktest. A refitted model with this new covariate demonstrated fit as the covariate was insignificant. The Hosmer Lemeshow (H-L) statistic was not used to demonstrate fit because as the sample size gets large, the H-L statistic can find smaller and smaller differences between observed and model-predicted values to be significant, as was the case with this dataset.

A second propensity score was developed for analysis of BCS plus radiation vs mastectomy alone (i.e., without radiation) to represent the probability of undergoing mastectomy alone

and was estimated for each patient by fitting a multiple logistic regression model, including year of diagnosis (1994–2012), stage of breast cancer (I–III), age, grade of tumor (1–3) and adjuvant treatment (except radiation therapy) (chemotherapy [Y/N] and hormonal therapy [Y/N]). The model discrimination was good ($c=0.634$; $P<0.001$), and the fit as assessed by the square of the linear predictor was also good, as this covariate was insignificant.

The IPT weights were computed from these propensity scores by:

$$w_i = \frac{Z_i}{e_i} + \frac{1-Z_i}{1-e_i}$$

where Z_i is the indicator variable for extent of surgery and $e_i = \Pr(Z_i = 1 | X_i)$ is the propensity score conditional on observed baseline covariates (X_i).²⁸ The final weight was then trimmed by replacing values greater than the 99th percentile with the 99th percentile value in each category (mastectomy [Y/N]).²⁹

Overall survival curves were estimated using Kaplan-Meier analysis with survival time set using IPT weights,²⁷ which reduces the effect of observed confounding in assignment for extent of surgery (BCS vs. mastectomy) when strong selection bias exists. In both analyses (BCS vs mastectomy; BCS plus radiation vs mastectomy alone), patients with stage I–III breast cancer were analyzed and the effects of selection based on adjuvant therapy use and other covariates were accounted

Table 1. Descriptive statistics of patients and cancer; women who underwent BCS were significantly different from those who underwent mastectomy with respect to all variables examined.

Patient Characteristics	BCS (N=3,340) N (%)	Mastectomy (N=1,995) N (%)	Total (N=5,335) N (%)	P value
Age ^a	63 (52-72)	60 (49-73)		<0.0001
Surgery Type	3340 (62.6.2%)	1995 (37.4%)	5335 (100.0%)	<0.0001
Breast Cancer Stage				
Stage 0	794 (24.0%)	330 (16.8%)	1124 (21.3%)	<0.0001
Stage I	1762 (53.2%)	675 (34.4%)	2437 (46.2%)	
Stage II	672 (20.3%)	650 (33.1%)	1322 (25.1%)	
Stage III	65 (2.0%)	266 (13.5%)	331 (6.3%)	
Stage IV	18 (0.5%)	43 (2.2%)	61 (1.2%)	
Chemotherapy	930 (27.9%)	922 (46.3%)	1852 (34.7%)	<0.0001
Endocrine Therapy	2233 (67.4%)	1181 (59.6%)	3414 (64.5%)	<0.0001
Radiation Therapy	2739 (82.2%)	327 (16.4%)	3066 (57.6%)	<0.0001
Grade				
1	822 (24.6%)	324 (16.2%)	1146 (21.5%)	<0.0001
2	1138 (34.1%)	672 (33.7%)	1810 (33.9%)	
3	896 (26.8%)	765 (38.3%)	1661 (31.1%)	
NA	484 (14.5%)	234 (11.7%)	718 (13.5%)	
ER/PR Status				
Positive	1490 (44.6%)	927 (46.5%)	2417 (45.3%)	<0.0001
Negative	224 (6.7%)	256 (12.8%)	480 (9.0%)	
NA	1626 (48.7%)	811 (40.7%)	2437 (45.7%)	
Deceased	556 (16.6%)	462 (23.2%)	1018 (19.1%)	<0.0001
Median Follow-up ^b	74 (33-134)	57 (29-109)		<0.0001

Abbreviations: BCS, breast conserving surgery; NA, not available; IQR, interquartile range; ER/PR, estrogen receptor/progesterone receptor.

^aYears (IQR)

^bMonths (IQR)

for statistically using IPT weighting. Finally, a sensitivity analysis using flexible parametric proportional hazards modeling³⁰ was undertaken to confirm the robustness of the weighted analysis. This was done using the *stpm* module in Stata. Akaike Information Criterion (AIC) values for several spline survival models were similar so the default Weibull model distribution of survival times (with one degree of freedom within *stpm*) was used. All tests of significance were two-tailed, and a *P* value of ≤ 0.05 was considered significant. All statistical analyses were performed with Stata software, version 11 (StataCorp, College Station, TX).

Results

A total of 5,737 breast cancer surgeries were identified system-wide between 1994 and 2012. Of these, 402 represented duplicate patients with synchronous or meta-synchronous primary breast cancer diagnoses. For such patients, the date of the first diagnosis was assessed, and the second primary cancer was excluded from analysis. For analysis purposes, 5,335 women were included in this study, of which 62.6% underwent BCS and 37.4% underwent mastectomy. Median follow-up time was 67 months (IQR 32-126 months), with unweighted mortality rates of 24.72 and 40.37 per 1,000 person-years for the BCS and mastectomy

groups, respectively. From 1994 to 2003, the proportion of women undergoing mastectomy decreased. However, a reversal in this trend and an increase in the proportion of women undergoing mastectomy was noted from 2004 to 2012 (figure 1).

Adjuvant radiation therapy is routinely recommended following BCS,³¹ but was not received in 17.8% of patients following BCS. In contrast, guidelines for use of adjuvant radiation therapy following mastectomy vary,³² and radiation was received by only 16.4% of women in the mastectomy group. Of women treated with BCS who did not receive radiation therapy, most were early stage (43.8% stage 0, 42.6% stage I, 10.3% stage II, 1.7% stage III, and 1.7% stage IV). Of women treated with mastectomy who received radiation, 1.8% had stage 0, 5.8% had stage I, 31.1% had stage II, 54.8% had stage III, and 6.5% had stage IV breast cancer. The remaining women who underwent BCS without adjuvant radiation therapy did so based on decision making that is typical in the community practice setting, including considerations such as tumor size, age, comorbidity status, patient preference, treating physician preference, and the primary care provider (oncology, radiation oncology consult, or surgery).

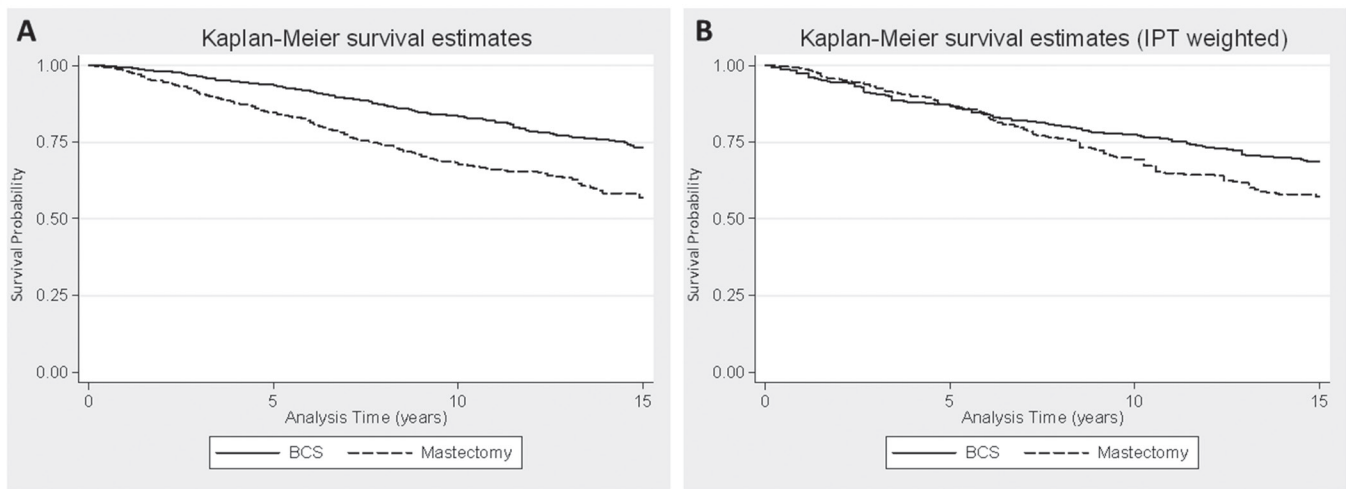


Figure 2. Kaplan-Meier curves for (A) unweighted overall survival and (B) inverse probability of treatment (IPT) weighted overall survival for patients with locally invasive (stage I-III) breast cancer who underwent breast-conserving surgery (BCS) versus mastectomy.

In addition to use of adjuvant radiation therapy, women who underwent BCS were significantly different from those who underwent mastectomy with respect to all other variables examined (Table 1). Women who had BCS were significantly older, more likely to be diagnosed with early stage breast cancer (stage 0-II vs III-IV) and tumors of lower grade (1-2 vs 3), less likely to receive chemotherapy, and more likely to receive hormonal therapy, as their breast cancer was more likely to be endocrine receptor positive, compared to those who had mastectomy.

We first compared the effects of surgical approach on survival in all subjects with stage I-III breast cancer, regardless of adjuvant therapy use. Subjects with stage 0 and stage IV cancer were excluded as local therapy is unlikely to have any effect on overall survival in such patients. All other covariates, including radiation therapy, were addressed through the use of a propensity score and IPT weighting, as described in the methods. Kaplan-Meier survival curves were generated for

each surgical category (figure 2), and Kaplan-Meier survival functions were calculated at 3-, 5-, and 10-years (figure 3). Without IPT weighting, 3-, 5-, and 10-year overall survival for BCS vs mastectomy was 95.0% vs 90.9%, 90.5% vs 84.2%, and 78.4% vs 62.8%, respectively (figure 3A). After IPT weighting to account for treatment selection bias, 3-, 5-, and 10-year survival for BCS vs. mastectomy was 90.3% vs 92.8%, 84.7% vs 86.8%, and 72.4% vs 65.1%, respectively (figure 3B). The unweighted analysis appears to exaggerate differences as time accrues, but this was corrected by the weighted analysis. This is demonstrated in figure 2A, where ignoring treatment selection bias (confounding) gives the impression that BCS has better survival outcomes. However, once the IPT weights are in place (figure 2B), there is no significant difference across surgical categories. Results from flexible parametric proportional hazards modeling were similar with a mastectomy hazard ratio (HR) of 0.93 (95% CI 0.75 – 1.14).

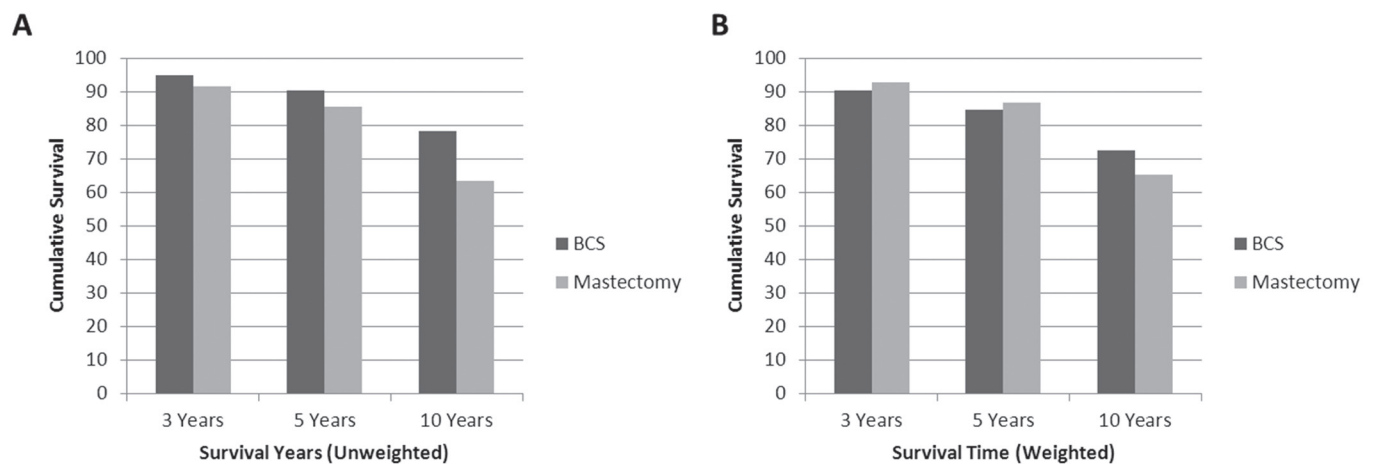


Figure 3. Kaplan-Meier survival estimates for (A) unweighted overall survival and (B) inverse probability of treatment (IPT) weighted overall survival for patients with locally invasive (stage I-III) breast cancer who underwent breast-conserving surgery (BCS) versus mastectomy at 3-, 5-, and 10-years.

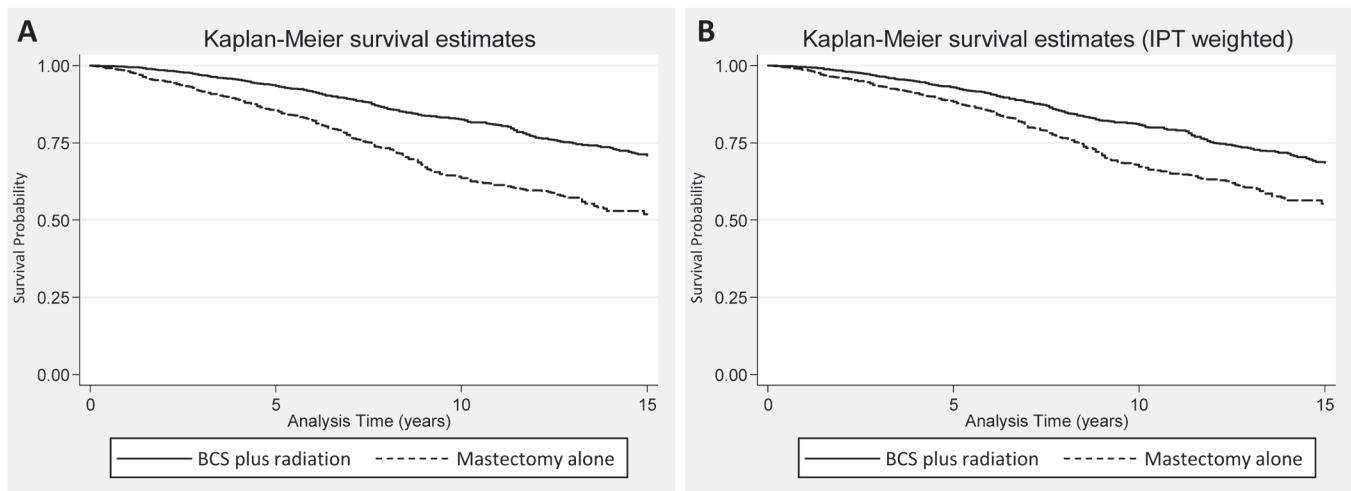


Figure 4. Kaplan-Meier curves for (A) unweighted overall survival and (B) inverse probability of treatment (IPT) weighted overall survival for patients with locally invasive (stage I–III) breast cancer who underwent breast conserving surgery (BCS) plus radiation versus mastectomy alone.

We then compared overall survival in women with stage I–III breast cancer who underwent BCS plus radiation vs mastectomy alone by excluding subjects who had BCS and did not receive radiation therapy, and women who had mastectomy and did receive radiation therapy, as in the study by Hwang et al.²⁶ This comparison allowed us to take the radiation therapy component of breast conserving therapy into consideration. Kaplan-Meier survival curves were generated for each treatment category (figure 4), and Kaplan-Meier survival functions were calculated at 3-, 5-, and 10-years (figure 5). Without IPT weighting, 3-, 5-, and 10-year overall survival for BCT vs mastectomy was 96.9% vs 91.6%, 93.5% vs 85.4%, and 82.6% vs 63.5%, respectively (figure 5A). After IPT weighting to account for treatment selection bias, 3-, 5-, and 10-year survival for BCS plus radiation vs mastectomy was 96.5% vs 93.4%, 92.9% vs 88.3%, and 80.9% vs 67.2%, respectively (figure 5B). Even after accounting for factors related to treatment selection, BCS plus

radiation appears to result in better overall survival than mastectomy alone. Again, flexible parametric proportional hazards modeling revealed a mastectomy alone HR of 1.60 (95% CI 1.36 – 1.89) consistent with the weighted Kaplan-Meier results.

Discussion

At least one trial has demonstrated equivalent long-term survival rates for patients with early stage invasive breast cancer treated by BCS alone or mastectomy.¹ However, several studies have demonstrated reduced local recurrence and better survival rates with combination BCS and radiation therapy than BCS alone,³³⁻³⁶ and current recommendations for breast conserving therapy include lumpectomy followed by radiation therapy.³¹ Several groups have demonstrated in randomized controlled trials that this approach (BCS plus radiation) is at least equivalent, or even superior, to mastectomy.^{3,4} In the community-treated population examined

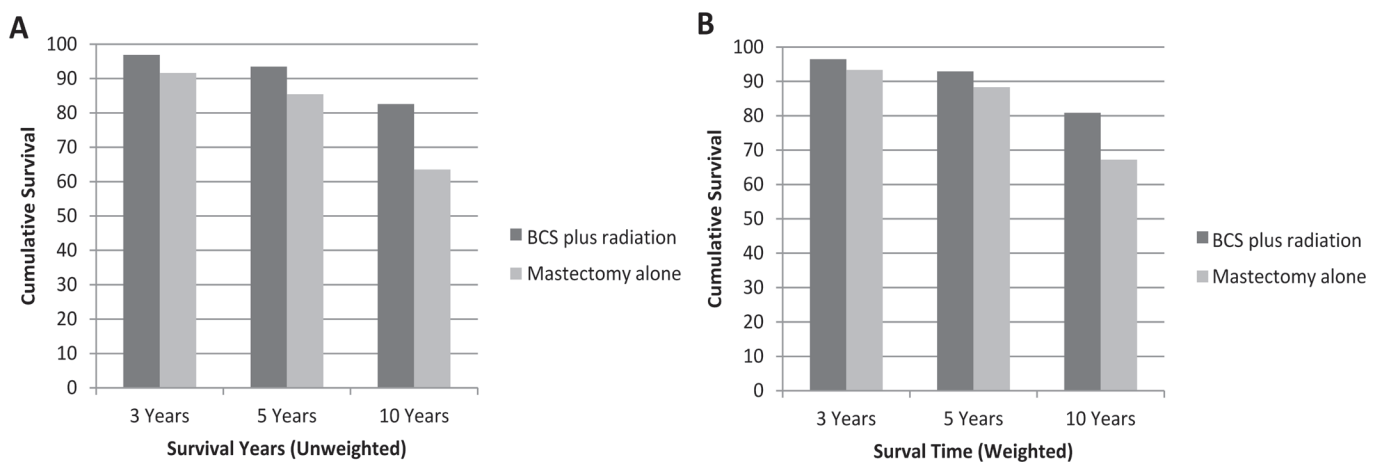


Figure 5. Kaplan-Meier survival estimates for (A) unweighted overall survival and (B) inverse probability of treatment (IPT) weighted overall survival for patients with locally invasive (stage I–III) breast cancer who underwent breast conserving surgery (BCS) plus radiation versus mastectomy alone at 3-, 5-, and 10-years.

here, the benefit of breast conserving therapy over mastectomy appears to be related to the combination of BCS and adjuvant radiation therapy rather than the surgical procedure itself. Additionally, BCS plus radiation appears to be superior to mastectomy alone suggesting that radical surgery may not provide additional benefit to women who have breast cancer with respect to overall survival.

We and others have demonstrated an increase in mastectomy utilization in recent years.^{7,9-22,26,37} While randomized controlled trials and meta-analyses are considered the gold standard for clinical evidence, results and recommendations may not always translate or apply in the same way to community practice where non-selective patient care occurs in environments very different from the controlled, clinical trial environment. Before adjustment, our results were similar whether we compared BCS and mastectomy or BCS with radiation and mastectomy without radiation, likely because the BCS group was affected by selection of adjuvant therapies post-procedure that were consequences of selection of the surgical procedure itself. A clear example is the addition of radiation therapy to a greater extent after BCS (82.2%) than after mastectomy (16.4%). In observational studies, the lack of random treatment assignment frequently results in differences between treated and untreated subjects. IPT-weighting was performed in our study to remove or minimize the effects of confounding due to differences in the distribution of observed and measured baseline covariates between treatment groups when estimating the effects of the treatments. Weighting by the inverse probability of treatment markedly reduced the effects of this confounding on surgical outcomes resulting in survival rates that focus on the differences due predominantly to extent of surgery (figure 2B). A recent population-based study by Hwang et al²⁶ demonstrated that BCS plus radiation resulted in greater disease-specific and overall survival in women with early stage breast cancer compared to those who underwent mastectomy without adjuvant radiation therapy. Our findings support this conclusion and suggest that the superiority of BCS plus radiation over mastectomy may be more related to the addition of radiation therapy than to surgery extent alone. Adjuvant radiation therapy following surgery is clearly important for prognosis, and this and other forms of adjuvant therapy, including chemotherapy and endocrine therapy, will be the focus of subsequent analyses.

In women with early stage breast cancer, mortality is more often attributable to cardiovascular disease than to breast cancer itself.³⁸ Interestingly, radiation to the chest has known cardiac complications.³⁹ However, exposure to radiation appears to have actually reduced overall mortality in practice suggesting that the cardiac risks posed by radiation therapy are outweighed by the benefits.

The patient characteristics associated with a higher likelihood of mastectomy in our study were similar to those previously described in the community and in clinical studies.^{7,9-11,37}

Mastectomy was more often utilized in younger women with advanced stage breast cancer and was associated with more chemotherapy use, less endocrine therapy use, less radiation use, higher tumor grade, and hormone receptor negativity compared to those who had BCS. Differences in the use of adjuvant therapy by surgery type is of particular interest, as the data presented here suggest that use of adjuvant radiation therapy following BCS is associated with better survival outcomes than mastectomy alone. The importance of adjuvant therapy and the role of mastectomy in breast cancer treatment in the absence of clear indications may, therefore, warrant further examination.

Our study has limitations inherent to any retrospective study, namely the use of data as reported and documented. We do not consider this a major limitation in this particular study, as our objective was to describe a community practice experience with non-selective care of patients using information that was not derived from a more controlled clinical trial environment. We did not differentiate between breast cancer-specific mortality and overall mortality, due to lack of accurate data. Finally, while many of the factors likely to contribute to confounding (treatment selection bias) were accounted for via IPT-weighting, additional factors that may have influenced selection of surgery type or radiotherapy remain unaccounted for, including patient preference, race, comorbidity, family history of breast cancer, geographical location, insurance type, surgeon preference and training, and the availability of a prospective, multidisciplinary care plan through a tumor board, and thus these findings require prospective confirmation. However, our multidisciplinary care plan developed through a tumor board takes into consideration all of these factors for planning both surgical treatment and subsequent selection of adjuvant treatment. Nevertheless, there is no guarantee that these results are not indeed the consequence of residual confounding by indication.

Conclusions

Evaluation of the community practice experience allows examination of outcomes following non-selective patient care using information derived from a less-controlled clinical environment. We found no difference in overall survival by breast cancer surgery type when the effects of adjuvant radiation therapy and other covariates were eliminated using statistical methods. However, comparison of BCS plus radiation to mastectomy alone revealed a significant survival benefit with breast conserving therapy, suggesting that the prognostic differences reported here and by others may be related to use of adjuvant radiation therapy after BCS rather than to the extent of surgery itself. Given the limitations inherent in this type of study design, prospective confirmation of this finding is necessary.

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