Twenty-five year results of the national cancer institute randomized breast conservation trial

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Abstract

Breast conservation therapy (BCT) consisting of lumpectomy and postoperative radiation has become an accepted alternative to mastectomy (MRM) for the treatment of early stage breast cancer. We currently report the 25 year outcomes of a single institution, prospective, randomized clinical trial at the National Cancer Institute. 237 women with pathologically confirmed invasive breast tumors 5 cm or less were accrued between 1979 and 1987 and randomized to receive either

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BCT or MRM. Overall survival was the primary endpoint. Patients with node positive disease were included and treated with doxorubicin and cyclophosphamide. Both arms received axillary dissection. BCT patients had radiation to the whole breast followed by a boost. At a median follow-up of 25.7 years, overall survival was 43.8% for the MRM group and 37.9% for BCT ($P = 0.38$). Although the cumulative incidence of a disease-free survival event was higher in BCT patients (29.0% MRM vs. 56.4% BCT, $P = 0.0017$), the additional treatment failures were primarily isolated ipsilateral breast tumor recurrences (IBTR's) requiring salvage mastectomy. 22.3% of BCT patients experienced an IBTR. Distant disease and second cancers were similar in both arms. After 25 years, long term survival between BCT and MRM continues to be similar in patients treated for early stage breast cancer. Patients receiving BCT may be at risk for additional treatment-related morbidity, which may occur as a late event. Further studies are required to delineate patients at higher risk for these events, and prolonged follow up should be encouraged after treatment for all women.

Introduction

At the turn of the 20th century, treatment of breast cancer was dominated by techniques of surgical radicalism, believing that complete extirpation of the breast and surrounding tissue was required to arrest centrifugal spread of tumor. The Halsted radical mastectomy, the gold standard of therapy during this time, was the end-result of the progressively larger margins used by surgeons of the era to efface all remnants of contiguous tissue possibly harboring disease [11]. Beginning with Bernard Fisher's landmark B-04 trial, therapeutic equivalence of increasingly less extensive surgery has been demonstrated in a prospective manner through a number of specific trials [9].

Following the results of B-04, six major phase III trials were initiated in North America and Europe to investigate breast conservation [3, 4, 8, 15, 17, 18]. With up to 20 years of published follow-up data for these trials, breast conserving therapy has been demonstrated to be an accepted alternative to mastectomy with similar survival outcomes. Despite considerable variations in inclusion criteria and treatment details in these trials, pooled analysis of this data has continued to reinforce individual trial findings of noninferiority [5].

We currently present the updated findings of the National Cancer Institute Breast Conservation Trial, which is one of the 6 major original early breast cancer trials [12, 13, 15]. This investigation was originally initiated in 1979, with accrual ending in 1987. Unique to this trial is the use of modern chemotherapy regimens including doxorubicin and cyclophosphamide, the use of CT-simulation for radiotherapy planning, and the length and detail of follow-up. More than half of the surviving patients originally enrolled on this protocol continue to be followed at the Clinical Center at the National Institutes of Health (NIH) to this day. The median follow-up of this trial is now 25.7 years, and among the six major breast conservation trials will be the longest reported follow up. This article updates

our previous reports of the trial, as we continue to demonstrate no significant differences in overall survival between the two treatment groups.

Methods

Patient characteristics

This was a single-institution, prospective, randomized clinical trial conducted by NCI at the Clinical Center of the NIH. A detailed description of the study design has previously been reported and this study was approved by the NIH Institutional Review Board [13]. Due to changes in the modern treatment of breast cancer, specific aspects of the study design will be re-emphasized here. Between July 1979 and December 1987, 247 women with pathologically confirmed invasive breast tumors 5 cm or less with clinically negative or positive axillary lymph nodes were enrolled on this trial. Patients were considered ineligible if they had evidence of metastatic disease or previous cancer, were a poor operative risk, or were found to have multi-centric disease. Patients were then stratified by age, clinical nodal status, and the presence of cardiac disease which would preclude them from treatment. Randomization was performed in a 1:1 ratio by the Statistical Data Management Group of the Biometric Research Group of the NCI and the trial was stopped when accrual goals were met. Patients were assigned to treatment either with total mastectomy plus axillary dissection (MRM) or excisional biopsy of the tumor and axillary dissection followed by radiotherapy (BCT).

Intervention

Patients in the MRM group underwent a Patey MRM and level I–III lymph node dissection, as previously described [7]. No postoperative chest wall irradiation was administered and patients were offered breast reconstruction.

Patients in the BCT group initially underwent an excisional biopsy, which was frequently performed at an outside institution (75% of patients). Although microscopically free surgical margins were not required at this time, re-excision was performed if it was felt gross tumor remained. All patients had an axillary dissection at NCI. Following surgery, patients received external beam radiation delivered to 4,500–5,040 cGy to the entire breast with 4–6 MeV photons in 180 cGy fractions 5 days per week. Patients with nodal disease, extracapsular spread, or axillary involvement were treated with a supraclavicular field to 4,500–5,040 cGy. In patients with positive nodes or medial quadrant primaries, tangent fields extended to include internal mammary nodes. CT simulations were performed for all treatment and beginning in 1981, lung inhomogeneity correction factors were applied. A 1,500–2,000 cGy boost to the tumor bed was given using an Iridium-192 implant (1979–1983) or an electron beam (1984–1987).

Chemotherapy with cyclophosphamide and doxorubicin was administered to all patients with positive nodes after surgery. Initially, doxorubicin was given intravenously to 30 mg/m^2 on Day 1. On days 3–6, cyclophosphamide was dose escalated orally starting at 150 mg/m^2 until hemato-logical toxicity was noted. Twelve cycles were given every 28 days. Interim analysis showed minimal toxicity and multiple amendments were made to the dosing

regimen [14]. In 1983, the cyclophosphamide dose was increased to 200 mg/m^2 and in 1985 was increased to 40 mg/m^2 over only 9 cycles of a shorter period of 21 days. Beginning in 1985 when estrogen testing became more routine, node-positive, postmenopausal patients were also given tamoxifen for 5 years.

Statistical methods

The primary end point was overall survival which was measured from date of enrollment until death from any cause or last known date of survival if alive. It was initially determined that 105 patients were required to be enrolled on each arm to have a 80% power for a 95% confidence limit. Secondary endpoints of disease-free survival and rates of local recurrence were measured from the date of enrollment until recurrence or the last follow-up visit without evidence of disease. Events in the calculation of disease-free survival include any local, regional, or distant recurrence. Contralateral, second cancers or deaths from any cause were not included and were censored at the time of the event. In previous reports of this trial, patients with an isolated ipsilateral breast recurrence (IBTR) successfully treated by mastectomy were considered to be disease-free. [12, 13, 15]. However, emerging evidence suggests these events may be important prognostic factors [2, 20]. The current authors felt it best to include these events as local recurrences and this notion has supported by other trials [17, 18]. Recurrences in the internal mammary, supraclavicular, or ipsilateral axillary nodes were classified as regional occurrences. All other locations were classified as distant recurrences. Distant events following contralateral breast cancers were censored at the time of the event due to the ambiguity of the origin of recurrence.

Overall survival and disease-free survival were compared using the log-rank test and Kaplan–Meier survival estimates were generated. Due to competing causes of death, Cox proportional cause-specific hazard was fit and used to compare the treatment difference in disease-free survival and other cause-specific hazards. Hazard ratio was calculated with MRM as the baseline hazard. Walds test was used to calculate the *P* value of the treatment effect. Cause-specific cumulative incidence estimated at 25 years was generated. Univariate and multivariate survival analysis was performed and Walds test was used to calculate the *P* value of each variable. Variables at the 0.05 level were included in the multivariate analysis. Effect of time dependence of IBTR on overall survival was estimated by two approaches; the first used the landmark analysis, with time set at 5 years and the second used Cox proportional hazard model by treating IBTR as a time-dependent covariate (Supplemental Methods) [1].

Results

Patient characteristics

Of 247 patients, 237 participated in the trial because 10 did not wish to be randomized. In total, 116 patients were treated with MRM and 121 patients received BCT (Fig. 1). Patient characteristics were similar on both arms of the trial. The mean age of the patients was 51.6 and 50.0 years on the MRM and BCT arms, respectively. Proportions of side of the breast affected, menopausal status, quadrant of disease, tumor size, and number of lymph nodes positive were also similar (Table 1).

Locoregional recurrence

The cumulative incidence of a local recurrence at 25.7 years in the BCT arm was 21.9% and 0.9% in MRM arm (HR = 29.9, $P < 0.001$, Table 2). In the mastectomy group, there was 1 chest wall recurrence, 2 isolated axillary recurrences, and 2 simultaneous local and regional recurrences. In the BCT arm, there were 27 IBTR's and 85.2% of those recurrences occurred within the same quadrant as the initial tumor. There was only one simultaneous local and regional recurrence in the BCT group. More than 1 out of every 5 patients (22.3%) in the BCT arm experienced an IBTR requiring salvage mastectomy. Median time to IBTR was 5.3 years, although 3 patients experienced late isolated local recurrences after 20 years of follow up. Median survival for patients experiencing an IBTR less than 5 years after diagnosis was 20.2 years, and was 24.1 years if it occurred after 5 years ($P = 0.71$). When an IBTR was treated as a time-dependent covariate in the Cox proportional hazards model, the hazard ratio of IBTR was 1.72 (95% CI: 0.91–3.25, $P = 0.094$). The incidence of IBTRs did not seem to correlate with age (Fig. 3).

Distant metastases and other cancers

Distant metastases occurring alone or simultaneously with a local or regional event occurred in 30 patients in the MRM arm and 35 patients in the BCT arm. There was no significant difference in risk of distant metastases (HR = 1.1 with a 95% CI of 0.67–1.79, $P = 0.71$). Median time to distant metastasis was 3.1 years after MRM and 4.0 years after BCT. The risk of contralateral breast cancer was not increased with the use of radiotherapy, with 11 events in the BCT arm and 15 events in the MRM arm (HR = 0.92 with a 95% CI of 0.62–1.36, $P = 0.66$). Median time to the development of contralateral cancers was 6.1 years in the MRM arm and 9.4 years in the BCT arm. The incidence of non-breast cancers was similar, with 13 events in the MRM arm and 12 events in the BCT arm (Table 2).

Overall survival and disease-free survival

At a median follow-up of 25.7 years, survival was 43.8% in the MRM group and 37.9% in the BCT group $P = 0.38$ (Fig. 2). Although the survival curves are superimposed up to 25 years, the MRM arm seems to have a slight advantage there after. There appeared to be a direct correlation between age at enrollment and hazard for death at 25 years (Fig. 3, Supplemental Table 1). Age greater than 50 years old, left sided tumors, tumors >2 cm, and >4 lymph nodes positive were significant predictors of decreased survival on multivariate analysis (Supplemental Table 2). Survival in patients with 1–3 lymph nodes positive was not found to be an independent predictor of survival. The risk of developing a DFS event was significantly different between the MRM and BCT arm ($P = 0.0017$). The cumulative incidence was 29.0% in the MRM group and 56.4% in the BCT group. Only the treatment arm of BCT and tumors >2 cm were significant on multivariate analysis as independent predictors of disease-free survival (Supplemental Table 3).

Discussion

After over 25 years of follow up, data from our trial continues to demonstrate no survival differences when comparing lumpectomy followed by whole breast radiation versus mastectomy. These results have been recapitulated by the 5 other major trials of this time

with extended follow up [3, 4, 8, 17, 18]. Despite differences in eligibility criteria and treatment technique between trials, three iterations of meta-analyses of these trials from the Early Breast Cancer Trialist Group Collaboration (EBCTG) have confirmed noninferiority of breast conservation therapy compared with mastectomy [5, 19].

This single-institution trial differs in methodology from its contemporaries in a number of ways. Although smaller in number than others, it reports the longest follow up and has as theme of the most contemporary treatment characteristics. This was one of the first trials to use CT-based radiotherapy planning to reduce normal tissue toxicity and one of the earliest uses of adjuvant anthracycline chemotherapy in setting of radiotherapy for early breast cancer [14]. However, certain limitations should be noted. Pathological margins were not assessed after tumor excisions in the breast conservation group, allowing for the possibility of microscopic disease. This is especially noteworthy given the less restrictive size criteria of 5 cm or less, which was only shared by the Danish and EORTC trials [4, 17]. In addition, this trial included a particularly extensive level I-III axillary dissection (median 23.0 nodes dissected).

Despite these differences in study design, overall survival and distant metastases in this trial appear to be consistent with other studies. In contrast, however, is the high rate of ipsilateral breast tumor recurrences (IBTR) experienced by patients in the BCT group. The NCI trial has reported the highest cumulative incidence of IBTRs with 23.2% at 25 years, as compared with 14.3% for NASBP B-06 at 20 years, 8.8% for the Milan trial at 20 years, and 9% for the IGR trial at 15 years [3, 8, 18]. Although 23.2% is a high rate of IBTRs, in this study, 11% of patients had contralateral cancers which suggest that if the ipsilateral breast develops new cancers at the same rate, this would account for half of the IBTRs. However, contributing factors to this high rate include the previously described inclusion of larger tumors and inadequate evaluation of margins and residual disease. Trials reporting lower incidence included smaller tumor sizes and more stringent margin evaluation. Furthermore, the high number of these in breast events may also be related to length of follow-up, as 3 of the IBTR events noted in this trial occurred in patients who were free of disease for over 20 years.

In recent years, the significance of IBTRs have come into question as larger pooled analyses have suggested IBTRs may be a significant risk factor for mortality [2, 20]. Related to, and confounding this issue is the difficulty in distinguishing these tumors as true recurrences of initial disease or de novo development of second cancers in patients already at high risk for disease. Molecular analysis regarding these subtypes has indicated they have distinct natural histories, suggesting the heterogeneous nature of these recurrences [16]. At the time of our trial, the distinction of type of recurrence could only be made by pure anatomic localization, making the classification of these tumors unreliable. A central question regarding these in-breast recurrences is their significance as modifiable risk factors, or simply prognostic markers reflecting a proclivity for the development of additional cancer. If they are indeed biologically significant risk factors exclusive to those undergoing BCT, our trial was underpowered to detect them as such. Despite 27 patients in the BCT group experiencing these events, we were unable to detect any survival differences between the two treatments. This is an expected finding, as the most recent EBCTG meta-analysis has estimated that it

would take the prevention of four such recurrences to avoid one mortality, indicating the need for larger sample sizes to detect a survival difference due to these events [5].

With extended periods of follow up, it was observed that the risk of competing causes of death becomes a significant factor. At 25 years, approximately one quarter of patients expired without clinical evidence of disease. In these patients, treatment morbidity may have indirectly influenced survival outcomes. The most recent EBCTG meta-analysis has suggested a 1.3% increase in non-breast cancer death in patients receiving radiotherapy after surgery [5]. Although there was an additional 5 non-breast cancer deaths in the BCT arm, this trial was not adequately powered to detect late differences in non-breast mortality. However, multivariate analysis of our cohort did find left-sided disease to be a significant predictor for mortality. Previous reports have suggested left-sided cancers may be a risk factor for cardiac morbidity [6]. To investigate the role of potential cardiotoxicity from treatment, extensive cardiac studies of 60 of the surviving patients in this trial are currently being conducted at the NCI (unpublished data).

As data continues to mature on the long term survival of patients with early stage breast cancer, it is apparent that this issue of treatment morbidity comes into focus. Survival outcomes have improved to the extent that minimizing toxicity of locoregional treatment in selected patients has become a priority. Trends in surgical de-escalation have continued, with a recent report by Giuliano and colleagues demonstrating non-inferiority of sentinel lymph node biopsy when compared to full axillary dissections [10]. Data from this trial seems to support these findings, as no significant survival benefit was noticed when compared to other trials, despite differences in the extent of axillary dissection (Danish trial: median 8.2 nodes dissected, NCI trial: median 23.0 nodes) [4].

This 25 year follow-up of the NCI trial confirms similar long-term survival outcomes between breast conservation therapy and mastectomy in women with early stage breast cancer. Despite an increased number of in-breast recurrences, these events did not seem to translate to an increased risk of distant failure or mortality. However, it should be noted that patients receiving breast conservation may be at risk for additional treatment-related morbidity, of which may occur as a late event. Further studies are required to delineate patients at higher risk for these events, and prolonged follow up should be encouraged in women choosing this therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations

BCT   Breast conserving therapy

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MRM	Modified radical mastectomy
IBTR	Ipsilateral breast tumor recurrence
NIH	National Institutes of Health
NCI	National Cancer Institute
EBCTG	Early Breast Cancer Trialists Group

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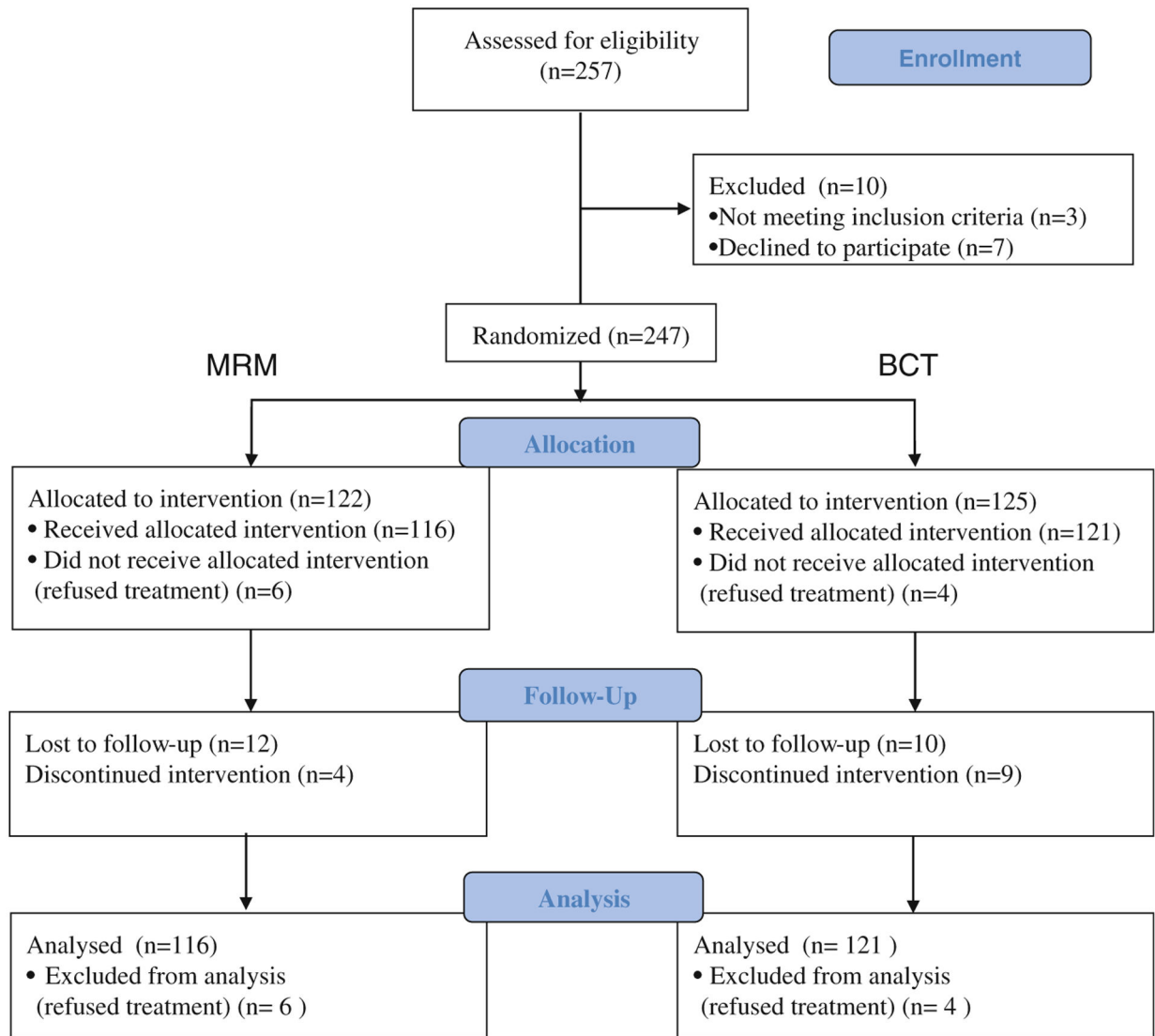
Fig. 1.
Study flow. *MRM* indicates modified radical mastectomy and *BCT* indicates breast
conservation therapy
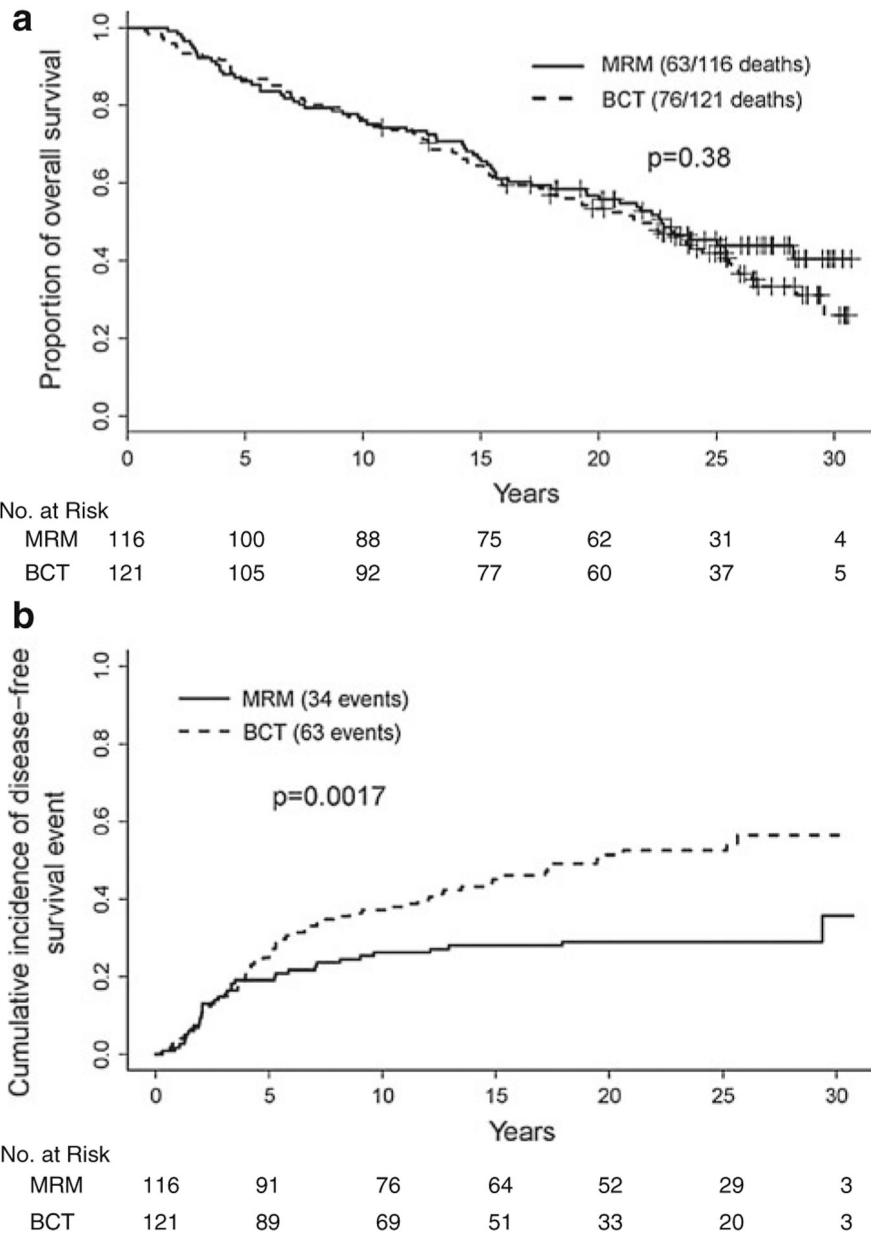
Fig. 2.
Kaplan–Meier estimates of overall survival and cumulative incidence of disease-free survival between the MRM group compared with the BCT group. (*MRM* indicates modified radical mastectomy and *BCT* indicates breast conservation therapy)
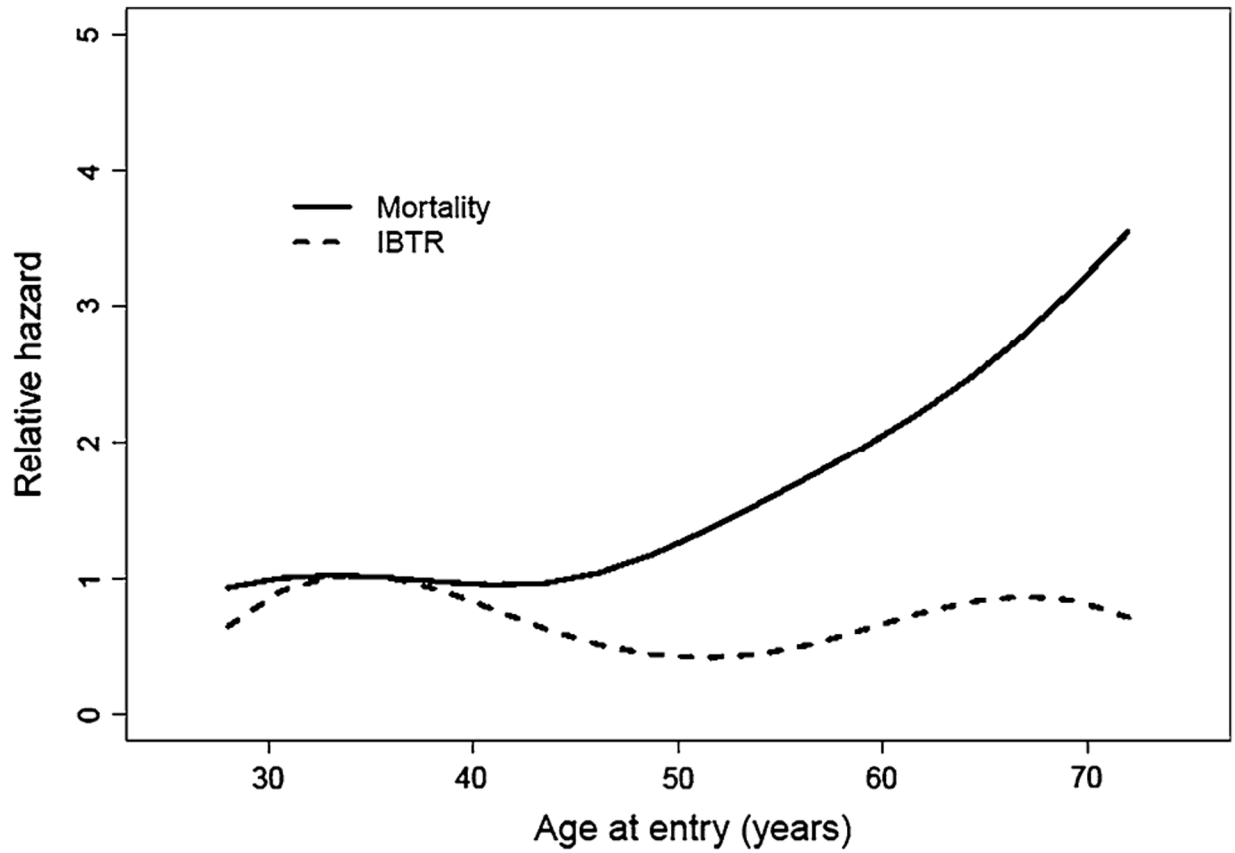
Fig. 3.
Risk of mortality and ipsilateral breast cancer by age for the BCT treatment group. Age was grouped into 10 years intervals, and Cox proportional hazards model was used to estimate the relative risk of death and ipsilateral breast tumor recurrence (IBTR) in each age group for patients in the BCT treatment group. The reference age group was (30, 40). The smoothed version of these relative hazards was performed by cubine spline interpolation

Table 1

Patient characteristics

	Mastectomy (*n* = 116), %	BCT (*n* = 121), %
Age (median)		
50	46	47
>50	54	53
Mass side		
Left	52	58
Right	48	42
Race		
Non-white	5	7
White	95	93
Menopausal status		
Pre	49	50
Post	51	50
Quadrant of disease		
Outer and central	76	74
Inner	24	26
Positive LN's		
0	58	61
1–3	28	28
4–9	8	4
>10	6	7
Tumor size (cm)		
0–2.0	48	43
2.1–4.0	43	50
4.1–5.0	9	7
Estrogen receptor		
Negative	11	15
Positive	46	43
Unknown	43	42

Table 2

Event table

First event	Mastectomy		BCT		Hazard ratio BCT/mastectomy (95% CI)	P value
	Events, #	Cumulative incidence at 26 years, % (SE)	Events, #	Cumulative incidence at 26 years, % (SE)		
All breast cancer	50	43.4 (4.9)	70	58.5 (4.8)	1.50 (1.04, 2.16)	0.028
IBTR	N/A	0.9 (0.9)	27	21.9 (3.9)	N/A	N/A
Breast cancer at logcalregional site	5	3.5 (1.7)	28	23.6 (4.0)	6.61 (2.55, 17.14)	<0.001
Breast cancer at distant site	30	26.4 (4.2)	35	30.0 (4.3)	1.10 (0.67, 1.79)	0.71
Contralateral breast cancer	15	13.6 (3.5)	11	9.1 (2.8)	0.92 (0.62, 1.36)	0.66
Non-breast cancer	13	13.3 (3.6)	12	10.6 (3.0)	1.08 (0.72, 1.62)	0.71