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RESEARCH

Management of ipsilateral breast tumor recurrence after prior breast conservation therapy

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Abstract

Purpose Mastectomy is traditionally recommended for local recurrence after breast conservation therapy (BCT), the combination of lumpectomy followed by whole-breast radiotherapy. Recent studies suggest that repeat BCT (lumpectomy and re-irradiation) may be feasible for select patients. We sought to evaluate the clinical characteristics, management strategies, and outcomes of patients treated for ipsilateral breast tumor recurrence (IBTR) after initial BCT and assess the impact of a newly adopted multidisciplinary algorithm for repeat BCT (lumpectomy and re-irradiation).

Methods We identified patients with stage 0–III breast cancer treated with initial BCT who underwent surgery for IBTR between January 2016 and May 2023. Patient, tumor, and treatment characteristics were analyzed, and outcomes were compared before and after the adoption of the repeat BCT algorithm.

Results Among 546 patients treated for IBTR, 48% were eligible for repeat BCT. After criteria adoption, mastectomy rates decreased by 16%. The proportion of eligible patients undergoing lumpectomy alone (BCS) for IBTR increased by 9% while only a modest increase in lumpectomy and re-irradiation (repeat BCT) was observed (7%). Rates of BCS for IBTR were higher than repeat BCT among older patients. Clinical outcomes were comparable between patients treated with BCS, BCT, or mastectomy.

Conclusion Repeat BCT (lumpectomy and re-irradiation) is a viable option for select patients with IBTR, offering comparable outcomes to mastectomy. The adoption of standardized criteria for repeat BCT has increased its use, highlighting the importance of multidisciplinary approaches in treatment planning.

Keywords Breast cancer · Ipsilateral breast tumor recurrence · Repeat breast conservation · Re-irradiation

Introduction

Breast conservation therapy (BCT), the combination of breast-conserving surgery (BCS) followed by whole-breast radiotherapy, is the preferred local treatment strategy for early-stage breast cancer with modern 10-year rates of local recurrence ranging from 2 to 10% [1–3]. Although rates of ipsilateral breast tumor recurrence (IBTR) have decreased substantially with improved imaging, attention to margins, and use of targeted therapies, the traditional dogma and current National Comprehensive Cancer Network (NCCN) guideline recommendation are that mastectomy is the most appropriate surgical option for women who experience a local recurrence after BCT [4–8]. Recognizing that not all local recurrences portend the same impact on long-term outcome, investigators have been exploring the possibility of repeat BCT in select patients and several retrospective reviews and case series have reported feasibility of repeat breast preservation (i.e., BCT or BCS) without significant morbidity [9, 10]. Most series have demonstrated an association between patient age at the time of IBTR and outcome.

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One of the main concerns regarding repeat BCT (lumpectomy and re-irradiation) is the potential toxicity of re-irradiation. To address this, the NRG Oncology/Radiotherapy Oncology Group (RTOG) performed a prospective, phase II clinical trial to evaluate the safety and potential efficacy of repeat BCT in patients with local breast recurrence after prior BCT [11]. Trial eligibility criteria were rather liberal and included unifocal breast lesions that were ≤3 cm in size and a disease-free interval (DFI) of at least one year. At a median follow-up of 5.5 years, a total of 58 patients had excellent 5-year distant metastasis-free survival and estimated 5-year overall survival (OS), both of which were 94.8% (95% CI: 84.8%–98.3%) [12]. Importantly, treatment-related toxicities were acceptable with 64% of patients experiencing only grade 1 toxicity, 7% grade 2, and <2% of patients experiencing grade 3 toxicity.

Given the growing body of literature examining repeat BCT and the results of the NRG/RTOG 1041 trial, our multidisciplinary team of breast surgical oncologists and radiation oncologists worked together to establish eligibility criteria for an algorithm to consider repeat BCT for IBTR. Patients are considered eligible if they are 55 years of age or older, with an interval of at least 5 years from prior radiation, with newly diagnosed estrogen receptor (ER)-positive ductal carcinoma in situ (DCIS) or T1, clinically node-negative unifocal invasive disease. Here, we report clinical characteristics, local–regional management strategies, and outcomes among patients treated for IBTR after initial BCT prior to and after the adoption of our multidisciplinary management algorithm. We estimate the proportion of patients who would have qualified for repeat BCT based on our current algorithm and determine the extent to which IBTR management has changed in the time since consensus criteria adoption. In addition, as age at the time of IBTR has been associated with choice of surgical procedure [13], we explored whether application of CALGB 9343 eligibility criteria may be contributing to decisions in IBTR management.

Methods

We reviewed our Dana-Faber Brigham Cancer Center Breast Oncology Program prospectively maintained database to identify patients with a history of stage 0–III breast cancer treated with BCT at initial cancer diagnosis who underwent surgical treatment for an IBTR at our institution from January 2016 to May 2023. This project was approved by the Dana-Farber Cancer Institute Institutional Review Board.

Patient, tumor, and clinical characteristics examined included age at initial cancer diagnosis, age at recurrence, time interval from initial cancer to IBTR, hormone receptor and human epidermal growth factor receptor 2 (HER2) status, clinical and pathologic tumor size, management of initial cancer, and management of IBTR. Chart review was performed to capture all recurrence events (local, regional, and distant) that occurred after management of the IBTR. Clinical and tumor characteristics at initial presentation and at IBTR were compared across groups stratified by IBTR histology (DCIS vs invasive) and management strategy using chi-square testing.

We estimated the proportion of patients who would have been eligible for repeat BCT (lumpectomy and re-irradiation) using our current multidisciplinary consensus criteria before and after its adoption in April 2020: age ≥55 years, DFI ≥5 years, ER-positive, DCIS, or unifocal cT1 N0 breast cancer. Differences in IBTR management strategy before and after consensus criteria adoption were examined.

We also sought to determine if patterns observed in IBTR management could be explained by providers extrapolating the results of the CALGB 9343 trial, which showed that radiotherapy may be safely omitted in certain patients in the treatment of primary tumors, to IBTR treatment. Patients were defined as CALGB 9343 eligible if the following criteria were met at the time of IBTR occurrence: age 70 years or older, cT2 disease or smaller, cN0, ER-positive, and HER2-negative. Patient characteristics and IBTR management strategy were compared between groups according to eligibility.

Kaplan–Meier unadjusted survival curves were used to estimate 2-year local recurrence-free survival (LRFS), distant recurrence-free survival (DRFS), and OS by IBTR management strategy, with additional exploratory analysis by time to recurrence (early <5 years vs late >5 years) and by breast cancer subtype. LRFS was defined as freedom from local or regional recurrence. DRFS was defined as freedom from distant recurrence. OS was defined as freedom from death of any cause. Cox-proportional hazards survival modeling was used for adjusted survival analysis, with adjustment for age and hormone receptor status. All analyses were performed using SPSS v.29 (IBM Corp., Armonk, NY). Chi-square tests were used to compare categorical variables between groups, and two-sided Fisher's exact test was used in cases with an expected cell count fewer than 5. Continuous variables were compared using two-sided Student's t-tests with equal variances assumed. P values <0.05 were considered statistically significant.

Results

From January 2016 to May 2023, 546 patients underwent surgery for an IBTR after a prior history of BCT for either DCIS ($n=161$) or invasive cancer ($n=379$). Original tumor histology was unknown in six cases. Overall, 445 (82%) presented with an invasive IBTR and 101 (18%) presented with DCIS at IBTR. The median age at IBTR was 64.5 years

(range: 34–97 years), and the median time interval from initial BCT to IBTR was 11.7 years (0.3–43.3 years). Clinical characteristics of the cohort stratified by IBTR histology (DCIS versus invasive disease) are shown in Table 1. Invasive IBTRs were more common than non-invasive recurrence, both for those initially treated for DCIS and those initially treated for invasive cancer (70% for DCIS, 86% for invasive cancer, $p < 0.01$). The majority of both invasive and DCIS IBTR were ER-positive (77% and 80%, respectively). Among them, 27 (33%) with a DCIS IBTR and 280 (82%) with an invasive IBTR received endocrine therapy. Among those with invasive recurrences, 61 (14%) had HER2-positive disease, 42 (69%) of whom received anti-HER2 directed therapy. Although pathologic tumor size was not available for all invasive IBTRs, median invasive pathological tumor size at recurrence for those in whom the data were available ($n = 325$) was 1.1 cm (0.1–11.5 cm).

Candidates for repeat BCT management for IBTR

Application of our multidisciplinary algorithm for consideration of repeat BCT (lumpectomy and re-irradiation) in patients with IBTR identified 262 eligible patients (48%). Population characteristics for eligible and non-eligible patients are compared in Table 2. As expected, IBTR treatment differed significantly between eligible and non-eligible patients. Among eligible patients, 143 (55%) had their IBTR diagnosed before the consensus criteria adoption and 119 (45%) after (Table 3). IBTR treatment with total mastectomy with or without radiotherapy (TM ± RT) was performed in 173 (66%) patients who may have been candidates for repeat BCT, 68 of whom were treated after consensus criteria adoption. Repeat BCT was performed in 3 (2.1%) patients before and in 11 (9.2%) patients after criteria adoption. When stratified by initial cancer histology, there was no significant difference in treatment before and after criteria adoption among those with initial DCIS (Table 4). However, among those with initial invasive cancer, treatment did differ, with the number of patients undergoing TM ± RT decreasing by 15.5%. Numbers of patients undergoing repeat BCT remained relatively low, with only 9.7% of patients with initial DCIS and 9.3% of patients with initial invasive disease receiving repeat BCT after criteria adoption.

Application of CALGB 9343 eligibility criteria

Applying the CALGB 9343 eligibility criteria at the time of IBTR occurrence, we found that among our entire cohort, 112 patients (17%) met CALGB eligibility criteria at IBTR. Of these patients, 55 (47%) were treated with BCS alone. CALGB-eligible patients were more likely to undergo BCS rather than repeat BCT (lumpectomy and re-irradiation) for their IBTR (50% vs 7.3%) compared to non-eligible patients (11.1% vs 3.6%). IBTR management by CALGB eligibility for those undergoing initial lumpectomy with or without radiotherapy is summarized in Fig. 1.

Clinical outcomes by IBTR management strategy and disease characteristics

Kaplan–Meier survival curves for 2-year LRFS, DRFS, and OS by IBTR treatment strategy are presented in Fig. 2. Unadjusted 2-year LRFS was 98% for BCS, 100% for repeat BCT, and 99% for TM ± RT. Two-year DRFS was 99% for

Table 1 Population characteristics by IBTR histology

Variables	Total ($N = 546$)	DCIS IBTR ($n = 101$)	Invasive IBTR ($n = 445$)	p-value
Initial presentation				
Median patient age, years (range)	50 (26–91)	49 (32–79)	50 (26–91)	0.52
Histology, *n* (%)				**< 0.001**
DCIS	161	48 (29.8)	113 (70.2)	
Invasive	379	53 (14.0)	326 (86.0)	
Unknown	6	0	6 (100.0)	
Presentation at IBTR				
Median patient age, years (range)	65 (34–97)	63 (36–88)	65 (34–97)	**0.04**
Median DFI, years (range)	11.7 (0.3–43.3)	11.1 (0.8–37.9)	12.0 (0.3–43.3)	0.06
ER positivity, *n* (%)[a]	423	81 (80.2)	342 (76.9)	0.40
HER2 positivity, *n* (%)[a]	–	–	61 (13.7)	–
Median pT size, cm (range)[b]	–	–	1.1 (0.1–11.5)	–

Percent of row totals shown for categorical variables. *P* values comparing initial DCIS to invasive IBTR. Bold values are significant at $p < 0.05$

IBTR ipsilateral breast tumor recurrence, *DCIS* ductal carcinoma in situ, *DFI* disease-free interval, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2, *pT* pathological tumor

[a]Percent of column, [b]$N = 325$ patients

Table 2 Patient characteristics by Dana-Farber Brigham Cancer Center consensus for repeat BCT eligibility

Variables	Eligible ($n = 262$)	Not eligible ($n = 284$)	p-value
Initial presentation			
Median patient age, years (range)	51 (32–91)	49 (26–85)	0.06
Histology, *n* (%)			0.66
DCIS	82 (31.3)	79 (27.8)	
Invasive	177 (67.6)	202 (71.1)	
Unknown	3 (1.1)	3 (1.1)	
Presentation at IBTR			
Median patient age, years (range)	69 (55–97)	59 (34–91)	**< 0.001**
Median DFI, years (range)	16.3 (5.1–43.3)	5.7 (0.3–37.9)	**< 0.001**
Median pT size, cm (range)[a]	1.1 (0.2–10.0)	1.1 (0.1–11.5)	**0.03**
Histology, *n* (%)			0.38
DCIS	44 (16.8)	57 (20.1)	
Invasive	218 (83.2)	227 (79.9)	
Treatment, *n* (%)			**< 0.001**
BCS	75 (28.6)	23 (8.1)	
BCT	14 (5.3)	9 (3.2)	
TM alone	167 (63.7)	231 (81.3)	
TM + RT	6 (2.3)	21 (7.4)	

Percent of column totals shown for categorical variables. *P* values comparing patients eligible for repeat BCT vs those ineligible. Bold values are significant at $p < 0.05$

IBTR ipsilateral breast tumor recurrence, *DCIS* ductal carcinoma in situ, *DFI* disease-free interval, *pT* pathological tumor, *BCS* breast-conserving surgery, *BCT* breast conservation therapy, *TM* total mastectomy, *RT* radiotherapy

[a]$N = 325$ patients

Table 3 IBTR management among eligible patients before and after criteria adoption

Variables	Before April 2020 ($n = 143$)	After April 2020 ($n = 119$)	p-value
Treatment, *n* (%)			**0.01**
BCS	35 (24.5)	40 (33.6)	
BCT	3 (2.1)	11 (9.2)	
TM alone	102 (71.3)	65 (54.6)	
TM + RT	3 (2.1)	3 (2.5)	

Percent of column totals shown for categorical variables. *P* values comparing eligible patients before and after multidisciplinary criteria adoption in April 2020. Bold values are significant at $p < 0.05$

BCS breast-conserving surgery, *BCT* breast conservation therapy, *TM* total mastectomy, *RT* radiotherapy

BCS, 100% for repeat BCT, and 97% for TM ± RT. Two-year OS was 95% for BCS, 96% for repeat BCT, and 98% for TM ± RT. There was no difference in LRFS or DRFS between treatment groups; however, 2-year OS was greater among those treated with TM ± RT on unadjusted survival analysis (Table 5). However, this survival difference did not persist after adjusting for age and ER positivity. When we examined outcomes by subtype of invasive recurrence, there was a significant association between HR/HER2-negative recurrence and DRFS; this did not persist with other outcomes (Supplementary Fig. 1). When examined by early (< 5 years) vs late (> 5 years) recurrence, there was no difference in survival outcomes (Supplementary Fig. 2).

Discussion

In this study, we examined patient, tumor, and treatment characteristics of a cohort of patients who presented to our institution with an IBTR after initial BCT. The majority of IBTRs were invasive, ER positive, and had DFIs greater than 10 years. As anticipated, the majority (78%) of patients were treated with mastectomy with or without radiotherapy, though patients were less likely to be treated with mastectomy after the adoption of consensus criteria for repeat BCT (lumpectomy and re-irradiation). We also found older patients were more likely to undergo BCS without repeat radiotherapy for locoregional management of IBTR. After adjusting for age and hormone receptor status, we did not find any difference in LRFS, DRFS, or OS at two years by IBTR locoregional management strategy.

As data emerge on the safety and efficacy of re-irradiation in select patient cohorts such as those treated in the NRG/RTOG 1041 trial, we are confronted with the challenge of identifying real-world patients who are optimal candidates for conservative management of IBTR [11]. Prior studies

Table 4 IBTR management among eligible patients before and after criteria adoption by initial cancer histology

Variables	Initial DCIS ($n = 82$)			Initial invasive ($n = 177$)		
	Before adoption ($n = 51$)	After adoption ($n = 31$)	p-value	Before adoption ($n = 91$)	After adoption ($n = 86$)	p-value
IBTR management, n (%)			0.394			**0.01**
BCS	11 (21.6)	10 (32.3)		24 (26.4)	29 (33.7)	
BCT	2 (3.9)	3 (9.7)		1 (1.1)	8 (9.3)	
TM alone	36 (70.6)	18 (58.1)		65 (71.4)	46 (53.5)	
TM + RT	2 (3.9)	0		1 (1.1)	3 (3.5)	

P values comparing IBTR management before and after consensus criteria adoption. Bold values are significant at $p < 0.05$

IBTR ipsilateral breast tumor recurrence, *DCIS* ductal carcinoma in situ, *BCS* breast-conserving surgery, *BCT* breast conservation therapy, *TM* total mastectomy, *RT* radiotherapy

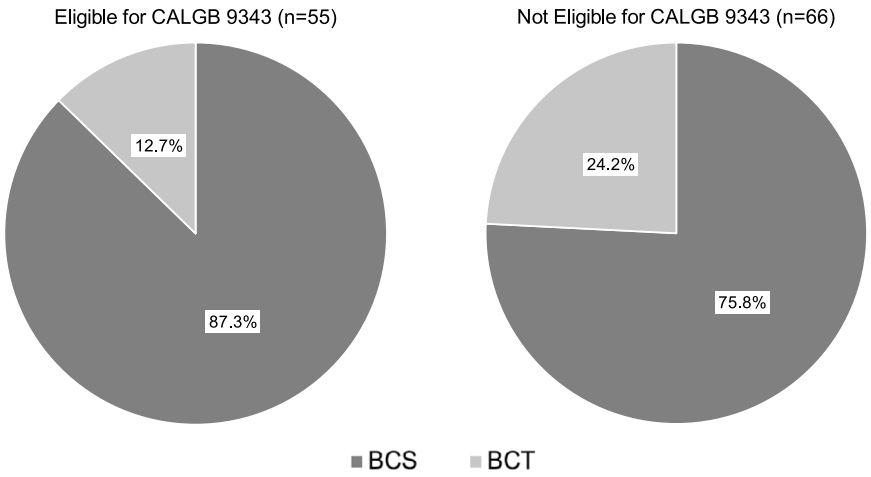

Fig. 1 IBTR management among patients undergoing lumpectomy, stratified by CALGB 9343 eligibility. *IBTR* ipsilateral breast tumor recurrence, *BCS* breast-conserving surgery, *BCT* breast conservation therapy

assessing feasibility of repeat BCT have found DFI from initial cancer to IBTR and tumor size to be important predictors of subsequent recurrence. In a previous report of a single institution experience, among 161 patients with invasive IBTR after BCT treated with repeat BCS, DFI of < 4 years, and tumor size of > 2 cm were both associated with an increased risk of a second IBTR [14]. Similarly, a retrospective series of 348 patients with IBTR after BCT reported that tumor size > 2 cm and DFI < 2 years were associated with developing a second IBTR after repeat BCT [15]. Hormone receptor status of the IBTR has also been evaluated as a factor associated with a second local recurrence. A study of 78 patients with IBTR after BCT treated with repeat BCS in Japan found DFI < 2 years and ER negativity to be associated with increased risk of second local recurrence [16]. Data from these and similar trials likely informed patient selection for more recent trials including the NRG/RTOG 1041. Patients eligible for the NRG/RTOG 1041 trial included those older than 18 years of age who presented with a unifocal in-breast recurrence less than 3 cm by MRI without evidence of skin involvement, who had a DFI of at least 1 year, and a negative metastatic work-up [12]. Similarly, our criteria for repeat BCT consider DFI, tumor size, and age, as well as ER status.

Several studies with longer follow-up have also suggested that survival outcomes are similar between BCT and mastectomy in the management of IBTR. A French retrospective series of 217 patients with IBTR treated with BCS and brachytherapy found repeat BCT to be feasible with similar survival outcomes at 4 years compared to mastectomy [17]. On multivariable analysis, they noted histologic grade and tumor size to be prognostic of outcomes. A study from Yale identified 146 patients with IBTR prior to 1999 surgically managed by either salvage mastectomy or salvage BCS and found ER status, number of chromosomes per cell, detection by mammogram, and tumor size to be prognostic of a localized relapse. There was no significant difference between rates of 10-year OS with mastectomy (65.7%) compared to BCS (58.0%) [18]. Another study supporting equivalent OS between repeat

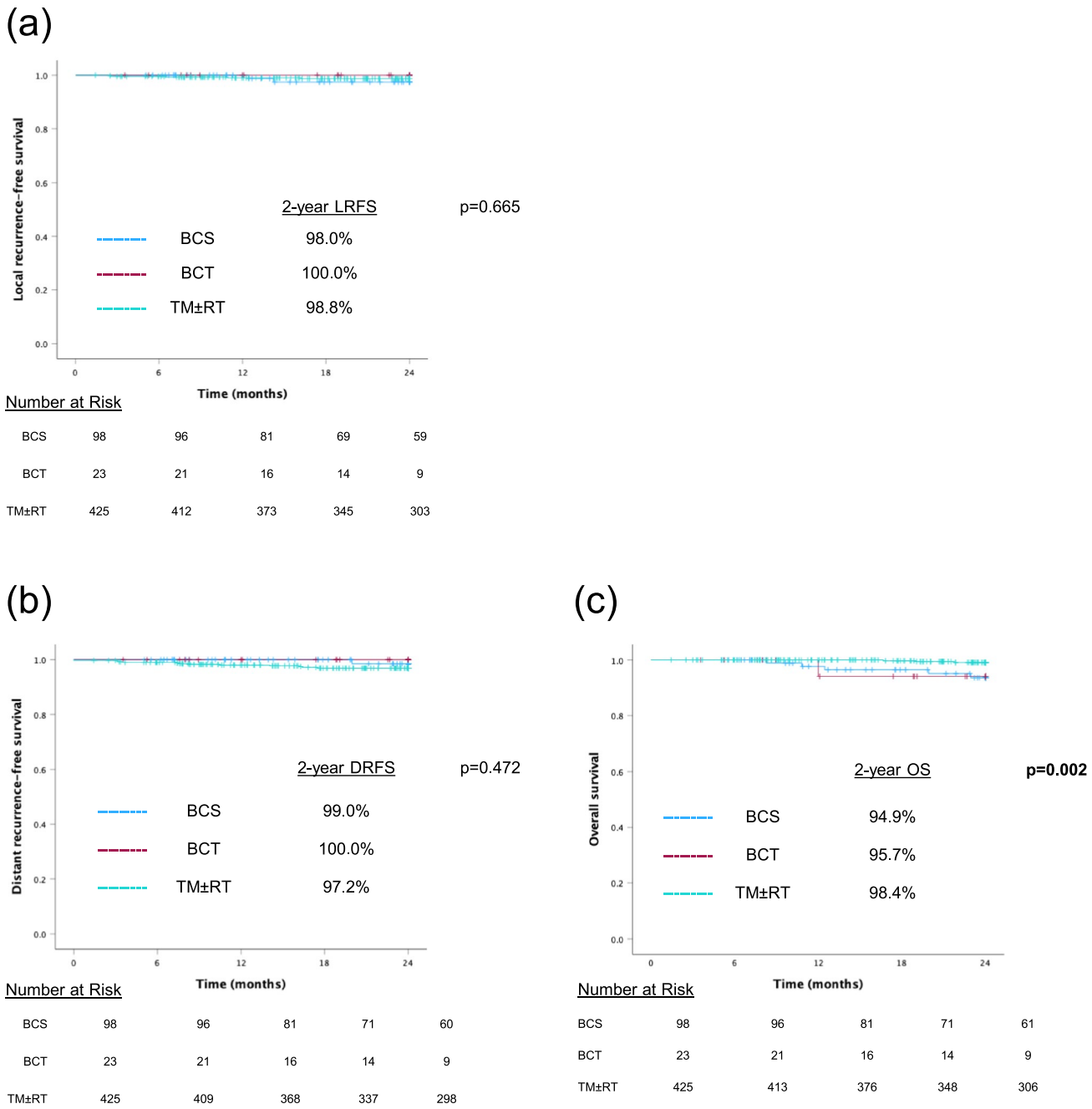

Fig. 2 Kaplan–Meier unadjusted survival curves. **a** LRFS in all patients (N= 546). **b** DRFS in invasive IBTR patients (N= 546). **c** OS in invasive IBTR patients (N= 546). *LRFS* local recurrence-free survival, *DRFS* distant recurrence-free survival, *IBTR* ipsilateral breast tumor recurrence, *OS* overall survival, *BCS* breast-conserving surgery, *BCT* breast conservation therapy, *TM* total mastectomy, *RT* radiotherapy

BCS and mastectomy from Korea retrospectively identified 335 patients with IBTR [19]. They compared survival outcomes of repeat lumpectomy with mastectomy after propensity matching for age at initial operation, T and N stage, ER status, HER2 status, IBTR tumor size, and use of adjuvant therapies and found no differences in 10-year OS (89.7% vs 83.5%) or breast cancer-specific survival (89.7% vs. 84.0%). More recently, the prospective multicenter single-arm NRG 1014 trial also demonstrated excellent OS and distant disease-free survival of 95% at 5 years in patients treated with repeat BCT for IBTR. Taken together, these data suggest that selected patients with IBTR can be treated with BCT without compromising long-term oncologic safety and efficacy [12].

Table 5 Unadjusted and adjusted survival outcomes by IBTR management strategy

	2-year LRFS		2-year DRFS		2-year OS	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Unadjusted						
BCT vs BCS	0.0	–	0.0	–	1.1	(0.1–9.4)
TM ± RT vs BCS	0.6	(0.1–2.8)	2.7	(0.3–20.5)	0.1	(0.0–0.5)
Adjusted[a]						
BCT vs BCS	0.0	–	0.0	–	0.6	(0.1–7.0)
TM ± RT vs BCS	1.1	(0.2–6.9)	1.3	(0.1–11.4)	0.2	(0.0–1.3)

IBTR ipsilateral breast tumor recurrence, *LRFS* local recurrence-free survival, *DRFS* distant recurrence-free survival, *OS* overall survival, *BCS* breast-conserving surgery, *BCT* breast conservation therapy, *TM* total mastectomy, *RT* radiotherapy

[a]Model adjusted for age and ER status of IBTR

Comparable outcomes for management of IBTR with either mastectomy or repeat BCS/BCT in select patients speaks to the opportunity for agreed upon criteria for patient selection. After careful consideration of the available data, our team agreed upon selection criteria which would have afforded 105 of the 256 patients who underwent mastectomy for IBTR before criteria adoption (41%) the option to consider repeat BCT. After criteria adoption, though the majority of eligible patients (57%) are still being treated with mastectomy, the number of patients undergoing BCS or BCT at IBTR increased substantially (from 27% before to 43% after). However, the rates of BCT for IBTR remain lower than BCS, with only a 7% increase in the number of eligible patients receiving repeat BCT.

One factor that may explain the choice in treatment at IBTR is age. A study of 322 patients treated for an IBTR at Memorial Sloan Kettering Cancer Center found that patients with IBTR managed with repeat BCS were on average 13 years older than those patients managed with mastectomy [20]. The impact of age on choice of local therapy is likely multifactorial, but one contributing factor may be application of the data from the prospective randomized CALGB 9343 trial to patients who experience an IBTR many years after initial BCT. In the CALGB trial, there was no difference in LRFS, DRFS, or OS among 636 patients aged 70 years and older with an early-stage ER-positive breast cancer randomized to lumpectomy alone or lumpectomy with radiotherapy [13]. Although patients with recurrence were excluded from this trial, it may be that clinicians are considering these findings and applying similar principles to IBTR patients meeting CALGB 9343 eligibility criteria. To determine if this might help explain the patterns, we observed in IBTR management, we looked at CALGB 9343 eligibility at the time of IBTR occurrence. Excluding patients who underwent mastectomy, we found that a greater proportion of CALGB-eligible patients underwent BCS for their IBTR rather than repeat BCT. This suggests that surgeons are comfortable extrapolating CALGB 9343 eligibility criteria from the primary tumor setting to patients with IBTR.

Limitations of this analysis include the retrospective nature of the study resulting in patient selection bias for repeat BCT/BCS vs mastectomy. This includes the inability to assess repeat BCT candidacy based on physical exam, which would potentially eliminate some patients due to concerns for poor cosmesis. In addition, with a median follow-up time of 34 months, this cohort will require continued evaluation to document accurate long-term local–regional recurrence rates. Although not a goal of this study, data on side effects and cosmesis following re-irradiation in our patient population would further allow fine tuning of patient selection for repeat BCT. As our multidisciplinary algorithm becomes more widely incorporated into our practice, future studies may address many of these limitations.

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Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by JMJ with the assistance of TAK and OK. The first draft of the manuscript was written by JMJ and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript

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Data availability The data that support the findings of this study are available from the corresponding author, TAK, upon reasonable request.

Declarations

Conflict of interest EAM reports compensated service on scientific advisory boards for AstraZeneca, BioNTech, Merck and Moderna; uncompensated service on steering committees for Bristol Myers Squibb and Roche/Genentech; speakers honoraria and travel support from Merck Sharp & Dohme; and institutional research support from Roche/Genentech (via SU2 C grant) and Gilead. EAM also reports research funding from Susan Komen for the Cure for which she serves as a Scientific Advisor, and uncompensated participation as a member of the American Society of Clinical Oncology Board of Directors. TAK reports speaker honoraria for Exact Sciences and compensated service on the FES Steering Committee, GE Healthcare, compensated service as faculty for PrecisCa cancer information service, and compensated service advisory board, Veracyte.

Ethical approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Dana-Farber Cancer Institute Institutional Review Board.

Consent to participate The study was approved by the Dana-Farber Cancer Institute's Institutional Review Board with a waiver of consent.

Consent for publication Not applicable.

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