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EPIDEMIOLOGY

Accelerated partial breast irradiation compared with whole breast radiation therapy: a breast cancer cohort study measuring change in radiation side-effects severity and quality of life

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Abstract
Purpose Radiotherapy (RT) after breast-conserving surgery for early-stage breast cancer patients has similar survival benefits with whole breast RT (WBRT) or accelerated partial breast irradiation (APBI). However, the impact of RT type and side-effects severity on change in quality of life (QOL) is unknown. We examined changes in RT side-effects severity and QOL by RT type.
Methods We analyzed data from a cohort of 285 newly diagnosed early-stage breast cancer patients with tumor size ≤3.0 cm and lymph node-negative disease. Patients (93 [32.6%] stage 0; 49 [17.2%] non-white; mean age = 59.3 years) completed four interviews (6 weeks, 6, 12, and 24 months) after definitive surgical treatment. We measured severity of RT side effects, fatigue and skin irritation, using a 5-point scale (1 "not at all" to 5 "all the time") and measured QOL using the Functional Assessment of Cancer Therapy-Breast (FACT-B) and RAND 36-item Health Survey Vitality subscale. Repeated-measures analysis of covariance of each outcome controlled for demographic, clinical/treatment, and psychosocial factors.
Results Patients initiated RT by 6 months (113 received APBI; 172 received WBRT) and completed RT by 12 months. Patients receiving WBRT (vs. APBI) reported greater increase in fatigue and skin irritation severity from 6-week to 6-month interviews (each $P < 0.001$). Improvement in neither total FACT-B nor Vitality differed significantly by RT type over 2-year follow-up.
Conclusions Findings suggest that early-stage breast cancer patients can benefit from less-severe, short-term side effects of APBI with no differential impact on QOL change within 2-year follow-up.

Keywords Breast cancer · Radiation therapy · Side effects · Quality of life · Accelerated treatments

Introduction

Standard of care for early-stage breast cancer is breast-conserving surgery (BCS) plus radiation (RT) for women under age 70 and, for those over age 70, BCS with or without RT [1–4]. Recent studies demonstrate that accelerated partial breast irradiation (APBI) provides, in shorter time, similar rates of local control and similar breast cancer-specific and overall survival outcomes as treatment with whole breast radiation therapy (WBRT) in early-stage breast cancer patients [5–10]. However, a number of systematic reviews reported a lack of evidence about short-term RT side effects and their impact on changes in quality of life (QOL) [11–14]. One review of randomized clinical trials comparing PBI/APBI and conventional or hypofractionated WBRT found that no studies reported on the relative effects of PBI/APBI and WBRT on QOL [15].

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Although RT may negatively impact patients' QOL [16, 17], favorable QOL outcomes have been reported in breast cancer patients receiving ABPI [18–20], but these studies did not directly compare QOL to patients who received WBRT. Other studies directly comparing fatigue [21], skin toxicity [22], and cosmetic outcomes [5, 23] in breast cancer patients treated with either WBRT or ABPI did not measure QOL as an outcome of interest. Several other studies explored QOL outcomes in breast cancer patients who received RT with either APBI or WBRT [24–32]. However, these studies were limited by small patient samples [25, 28–31], using a cross-sectional design [28, 29, 32], using stratified analyses without directly comparing QOL by RT type [25–27], or did not examine the impact of RT side effects on change in QOL [24]. Using data from an early-stage breast cancer cohort study, we examined changes in QOL by type of RT (WBRT or APBI), controlling for the severity RT-related side effects as well as demographic, clinical, treatment, and psychosocial correlates of QOL.

Methods

Participants

Between October 2003 and June 2007, early-stage breast cancer patients treated at the Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine and at Saint Louis University School of Medicine were prospectively recruited for a cohort study evaluating QOL changes and similarities/differences in aspects of QOL in 549 women with and 547 same-aged women without a breast cancer history [33–35]. Eligibility criteria included English fluency, age 40 and older (based on screening mammography recommendations [36, 37]), no prior breast-cancer history, no receipt of neoadjuvant chemotherapy, and no evidence of cognitive impairment on the Orientation-Memory-Concentration Test [38] administered to all women 65 years of age or older. Participants were recruited 2-3 weeks after a first primary stage 0-IIA breast-cancer diagnosis determined by surgical pathology (patients) or after a negative/benign screening mammogram (controls). This study was approved by the Institutional Review Board at each university.

Specially trained interviewers obtained informed consent from all study participants and conducted computer-assisted telephone interviews 6 weeks (Time1), 6 months (Time2), 1 year (Time3), and 2 years (Time4) following definitive surgical treatment (patients) or screening mammogram (controls), with routine follow-up quality-assurance checks for randomly selected 10% of participants. By interview, we administered newly developed and previously validated measures of QOL, and other variables hypothesized to be associated with QOL in breast cancer patients.

Measures

We conducted a secondary analysis of data from this cohort study, analyzing data for patients who reported receiving RT at either Time1 or Time2, as self-reported RT is a reliable alternative to the medical record [39–42]. Patients were included if they received BCS and met clinical criteria to receive either APBI or WBRT, including a diagnosis of node-negative disease and a primary tumor size $\leq$3.0 cm by surgical pathology [43, 44].

We collected patient demographics and measured QOL at each interview using the FACT-B [45] and the Vitality subscale of the RAND 36-Item Health Survey 1.0 [46]. The FACT-B is a multidimensional measure of QOL that asks patients to indicate how true each item was for them "during the past 7 days" using a 5-point scale ("not at all" to "very much"). Total scores range from 0 to 144 with higher scores reflecting better QOL. The RAND Vitality subscale measures patient's energy and fatigue with four items asking how they felt "during the past 4 weeks" using a 5-point scale ("none of the time" to "all the time"); standardized scores range from 0 to 100 with higher scores reflecting more Vitality.

To measure severity of two common RT side effects, fatigue and skin irritation [47–50], we asked patients who reported receipt of RT at Time1 and/or Time2 to indicate how much they were bothered by these side effects in the last month: "You have (or had) burns/dried skin/itchy skin from radiation," and "You are (or were) very tired after radiation." Patients responded to each item using a 5-point scale from "not at all" (1) to "all the time" (5); higher scores indicate greater severity of each RT side effect.

As potential covariates of RT side-effects severity and QOL, we used validated measures of patients' perceived availability of social support (19-item Medical Outcomes Study Social Support Survey [51]), comorbidity [52] (using the Charlson Comorbidity Index scoring algorithm [53]), and state anxiety (21-item *Beck Anxiety Inventory*® [54]). Higher scores indicate greater availability of social support, comorbidity, and state anxiety. History of depression at Time1 was measured by an affirmative response to either, "Has a doctor ever told you that you had depression?" or "Have you ever been treated for depression with medication or psychotherapy?" We used a previously validated, 8-item questionnaire [34, 35] to measure severity of surgical side effects; higher mean scores indicate more severe surgical side effects.

Patients' clinical data, including cancer stage (ductal carcinoma in situ [55], stage I/IIA), tumor size, lymph node positivity, estrogen receptor status (positive/negative), and type of definitive surgical treatment (BCS, mastectomy), were determined by surgical pathology. Receipt of RT (yes/no), type of RT received (APBI, WBRT), receipt of chemotherapy (yes/no), and endocrine therapy (yes/no) were obtained by interview and the medical record.

Data analysis

Using analysis of variance (ANOVA) and Pearson product-moment correlations, we identified covariates of each RT side-effects-severity measure (i.e., fatigue and skin irritation) and of each QOL measure (i.e., total FACT-B and RAND Vitality subscale). Chi square tests examined associations among categorical variables. Cohen's kappa [56] measured agreement between medical record data and patients' self-reported receipt of RT, chemotherapy, and endocrine therapy (yes, no) and type of RT (APBI, WBRT). Analysis of covariance (ANCOVA) tested differences in RT side-effects severity by RT type, controlling for covariates significantly associated with RT side-effects severity and/or QOL at Time1. We analyzed changes in each of fatigue and skin irritation severity from Time1 to Time2 in those patients who reported receiving RT at both time points as well as changes in each QOL measure (i.e., total FACT-B and RAND Vitality subscale) from Time1-Time4 using repeated-measures ANCOVAs (RM-ANCOVAs) grouping by RT type and adjusting for RT side-effects severity and other covariates. All analyses were performed using IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY).

Results

Of 772 patients invited to participate in the larger cohort study, 549 (71%) enrolled and completed the first interview between October 2003 and July 2007. Participants and non-participants did not differ significantly by pathologic cancer stage ($P = 0.837$), surgery type (BCS vs. mastectomy; $P = 0.095$), or marital status (married vs. non-married; $P = 0.072$). However, compared with non-participants, participants were younger (mean [SD], 58.3 [10.6] vs. 60.6 [12.6] years; $P = 0.011$) and were more likely to be White (79.2 vs. 63.8%; $P < 0.001$).

Of the 549 patients, we excluded 212 patients who would not have been eligible to receive APBI, including 193 patients who received a mastectomy, and 19 patients who received BCS who had a primary tumor size >3.0 cm or had positive nodes. We also excluded 22 patients who reported they did not receive RT, 12 patients who did not report the type of RT received, 8 patients who dropped out of the study after Time1, and 10 patients who initiated RT between Time2 and Time3, and therefore could not have answered the two RT side-effects-severity items asked during the first two interviews. Patient characteristics by RT type for the 285 patients in the study sample are shown in Table 1. Retention was high, with 275 patients (96%) in this sample completing all four interviews.

Telephone interviews were completed a mean 6.5 weeks (Time1) and 6.2 (Time2), 12.3 (Time3), and 24.5 (Time4) months following definitive surgical treatment. Since we collected more complete treatment data by interview than by medical record review, we examined agreement between the medical record and patient-reported treatment data. At Time1, 121 patients (43%) reported at least initiating RT; at Time2, all 285 patients reported at least initiating RT (Table 1), which was confirmed for all patients by medical record review. For the 258 patients whose type of RT was found in the medical record, we observed near-perfect agreement (kappa = 0.81–1.00) [56] between the medical record and patient-reported type of RT (kappa = 0.98). Of the 110 patients confirmed to have received APBI per the medical record, 94 patients received brachytherapy (34 [36.2%] interstitial, 37 [39.4%] intracavitary, and 23 [24.5%] not otherwise specified [NOS]), 12 patients received a regional dose of 3600 cGy, two received a regional dose of 3400 cGy, and two were treated with "external beam NOS." We observed near-perfect agreement between the medical record and patient-reported receipt of chemotherapy (kappa = 0.97) and endocrine therapy (kappa = 0.94), as we observed for RT.

Of 25 patients who had initiated chemotherapy at Time1, only one patient also had initiated RT at Time1. By Time2, 53 patients had initiated chemotherapy, and the proportions of patients who received APBI and WBRT did not differ significantly (20/113 [17.7%] vs. 33/172 [19.2%], respectively; $P = 0.752$). All patients had completed chemotherapy and RT by Time3.

Of 53 patients who had initiated endocrine therapy at Time1, 35 patients also had initiated RT. At Time2, 169 patients had initiated endocrine therapy, and the proportions who received APBI and WBRT did not differ significantly (69/113 [61.1%] vs. 100/172 [58.1%], respectively, $P = 0.848$). Similarly, the proportions of patients receiving endocrine therapy at Time3 (n = 198) and Time4 (n = 184) also did not differ significantly by RT type (results not shown).

Patients who received WBRT reported significantly greater severity of fatigue ($P = 0.001$) and skin irritation ($P < 0.001$) than patients who received APBI at Time2 only (Table 2). Younger age, greater severity of surgical side effects, greater state anxiety, and worse QOL on the FACT-B were significantly correlated with greater severity

Table 1 Characteristics of patients in the study sample at Time1 who had at least initiated radiation therapy by Time2 ($N = 285$)

	APBI ($n = 113$)	WBRT ($n = 172$)	P value[a]
Race			0.155
White, *n* (%)	98 (86.7)	138 (80.2)	
Non-White, *n* (%)	15 (13.3)	34 (19.8)	
Education			0.732
Less than grade 12, *n* (%)	9 (8.0)	11 (6.4)	
Grade 12, *n* (%)	30 (26.5)	41 (23.8)	
More than grade 12, *n* (%)	74 (65.5)	120 (69.8)	
Marital status			0.612
Married/Member of an unmarried couple, *n* (%)	63 (55.8)	106 (61.6)	
Divorced/separated, *n* (%)	21 (18.6)	29 (16.9)	
Widowed, *n* (%)	21 (18.6)	23 (13.4)	
Never married, *n* (%)	8 (7.1)	14 (8.1)	
Employment status			0.246
At least part-time, *n* (%)	54 (47.8)	96 (55.8)	
Retired, *n* (%)	41 (36.3)	45 (26.2)	
Homemaker, *n* (%)	10 (8.8)	13 (7.6)	
Unable to work/unemployed, *n* (%)	8 (7.1)	18 (10.5)	
Annual income			0.357
Less than $25,000, *n* (%)	34 (30.1)	39 (22.7)	
$25,000–$75,000, *n* (%)	43 (38.1)	63 (36.6)	
More than $75,000, *n* (%)	29 (25.7)	53 (30.8)	
Refused/don't know, *n* (%)	7 (6.2)	17 (9.9)	
History of depression			0.971
Yes, *n* (%)	39 (34.5)	59 (34.3)	
No, *n* (%)	74 (65.5)	113 (65.7)	
Pathologic stage			0.005
DCIS, *n* (%)	26 (23.0)	67 (39.0)	
Stage I/IIA, *n* (%)	87 (77.0)	105 (61.0)	
Tumor ER-positive status			0.005
Yes, *n* (%)	92 (81.4)	110 (64.0)	
No, *n* (%)	13 (11.5)	33 (19.2)	
Missing	8 (7.1)	29 (16.9)	
Self-reported endocrine therapy[b]			0.007
Yes, *n* (%)	31 (27.4)	22 (12.8)	
No, *n* (%)	81 (71.7)	147 (85.5)	
Don't Know	1 (0.9)	3 (1.7)	
Self-reported chemotherapy[c]			0.001
Yes, *n* (%)	2 (1.8%)	23 (13.4%)	
No, *n* (%)	111 (98.2%)	149 (86.6%)	
Self-reported receipt of RT			0.003
RT at least initiated by Time1, *n* (%)	60 (53.1)	61 (35.5)	
RT at least initiated between Time1 and Time2, *n* (%)	53 (46.9)	111 (64.5)	
Age, mean (SD)	61.0 (10.2)	58.2 (9.8)	0.019
Social support, mean (SD)	4.5 (0.7)	4.4 (0.6)	0.491
Surgical side effects, mean (SD)	1.4 (0.4)	1.4 (0.5)	0.681
Comorbidity, mean (SD)	0.6 (1.0)	0.5 (0.9)	0.522
State anxiety, mean (SD)	4.7 (5.9)	6.0 (6.1)	0.072
BMI,[d] mean (SD)	29.2 (7.4)	28.6 (6.7)	0.499

Table 1 continued

	APBI ($n = 113$)	WBRT ($n = 172$)	P value[a]
Tumor size, in cm,[e] mean (SD)	1.1 (0.60)	1.2 (0.67)	0.149
Range	(0.1-3.0)	(0.1-3.0)	

APBI accelerated partial breast irradiation, *WBRT* whole breast radiation therapy, *DCIS* ductal carcinoma in situ, *ER* estrogen receptor, *RT* radiation therapy, *SD* standard deviation, *BMI* body mass index

[a] Tests of significance were one-way analyses of variance for continuous variables and Chi square tests for categorical variables

[b] Responses based on patient-reported receipt of adjuvant endocrine therapy at Time1 among the patients who at least initiated RT by Time2

[c] Responses based on patient-reported receipt of adjuvant chemotherapy at Time1 among the patients who at least initiated RT by Time2

[d] Two participants refused to provide their weight, so we were unable calculate BMI at Time1

[e] Tumor size was not available in the medical record for two of 192 patients with invasive disease

of both fatigue and skin irritation side effects at Time2 (Table 3; each $P < 0.05$).

Patients who received WBRT reported worse QOL on the total FACT-B measure than patients who received APBI at Time1 only (Table 4), but we did not observe any QOL differences by RT type in Vitality (Table 5). In the RM-ANCOVA models testing change in RT side-effects severity and QOL by RT type, all variables significantly associated with RT side-effects severity and/or QOL shown in Tables 2, 3, 4 and 5 (age, education, employment status, marital status, social support, surgical side effects, state anxiety, history of depression, BMI) were included as covariates. We also included as covariates receipt of chemotherapy at Time2 and a binary variable for receipt of endocrine therapy at any interview (yes/no), as all patients included had at least initiated RT and chemotherapy by Time2 and the number of patients reporting use of endocrine therapy varied over the course of the study (Tables 4, 5 footnote). We included severity of RT-related fatigue and skin irritation side effects at Time2 as covariates in the models testing change in QOL by RT type, as these variables were associated with worse QOL at Time2 (Table 3). To avoid overfitting the data, we did not adjust for cancer stage, which was associated with both RT type (Table 1) and receipt of chemotherapy ($P < 0.001$), nor did we adjust for income, which was associated with patients' education and employment status (each $P < 0.001$) and reported by fewer participants (8.4% did not respond). We did not adjust for comorbidity as patients reported few comorbid conditions and comorbidity was positively associated with age and BMI (Table 3).

In separate RM-ANCOVA models for change in RT side-effects severity among women who responded to these items at both Time1 and Time2 (Figs. 1, 2), women who received WBRT reported increasingly more severe RT-related fatigue and skin irritation compared with women who received APBI (each $P < 0.001$). Side-effects severity at Time2 was significantly higher for patients who received WBRT compared with APBI for both fatigue ($P = 0.007$) and skin irritation ($P < 0.001$).

In the RM-ANCOVA models for change in QOL controlling for severity of RT-related fatigue and skin irritation side effects and all other covariates, we did not observe a significant improvement in either the RAND Vitality subscale (Fig. 3) or total FACT-B score (Fig. 4) over 2-year follow-up across all patients. The change in these QOL measures also did not differ significantly by RT type (i.e., the time-by-RT type interaction was not significant).

Discussion

This cohort study of early-stage breast cancer patients with similar tumor size (≤3.0 cm) and node-negative disease [44] contributes to the limited knowledge about changes in QOL and RT side-effects severity over time by type of RT received. We observed that patients treated with APBI reported less severe RT-related side effects (both fatigue and skin irritation) than patients treated with WBRT at the 6-month interview following definitive surgical treatment. Eligible patients may elect to receive APBI over WBRT because of the convenience and targeted nature of APBI [57] or the inherent advantage of APBI to complete treatment quickly. Some studies have reported that breast cancer patients who received APBI report satisfaction with treatment [58] and good cosmetic outcomes [5, 22, 59], while other studies reported unacceptable cosmetic outcomes following APBI [60, 61]. In a systematic review of published and unpublished trials, PBI/APBI was associated with lower likelihood of acute, but not late, skin toxicity compared with WBRT, although cosmetic outcome and local recurrence-free survival appeared to be worse with PBI/APBI in the studies reviewed [15].

Radiation-related fatigue [47, 62] and skin irritation [48] are commonly reported RT side effects [50]. The frequency of reporting these side effects increases throughout

Table 2 Unadjusted mean (SD) RT side-effects-severity scores for patients receiving RT at the first (Time1) and second interviews (Time2), for each demographic and clinical factor of interest

	Fatigue				Skin irritation			
	Time1 (n = 121)	P value	Time2 (n = 285)	P value	Time1 (n = 121)	P value	Time2 (n = 284)[a]	P value
Type of RT								
APBI	2.2 (1.3)	0.133	2.3 (1.3)	0.001	1.7 (1.1)	0.878	1.7 (1.1)	<0.001
WBRT	1.9 (1.0)		2.8 (1.3)		1.7 (0.9)		2.9 (1.2)	
Race		0.069		0.705		0.241		0.055
White	2.1 (1.2)		2.6 (1.4)		1.7 (1.0)		2.4 (1.3)	
Non-White	1.5 (1.0)		2.5 (1.2)		2.0 (1.1)		2.8 (1.3)	
Education		0.845		0.340		0.184		0.627
Less than grade 12	2.2 (1.5)		2.9 (1.4)		2.2 (1.1)		2.5 (1.4)	
Grade 12	2.0 (1.1)		2.7 (1.3)		1.5 (0.9)		2.3 (1.2)	
More than grade 12	2.0 (1.1)		2.5 (1.3)		1.7 (1.0)		2.5 (1.3)	
Marital status		0.283		0.350		0.404		0.198
Married/member of an unmarried couple	2.1 (1.2)		2.6 (1.3)		1.7 (1.0)		2.4 (1.3)	
Divorced/separated	2.3 (1.4)		2.7 (1.4)		2.0 (1.0)		2.7 (1.3)	
Widowed	1.6 (0.8)		2.3 (1.3)		1.6 (1.0)		2.1 (1.2)	
Never married	1.8 (1.1)		2.8 (1.2)		1.2 (0.4)		2.5 (1.3)	
Employment status		0.235		0.002		0.318		0.004
At least part-time	2.1 (1.2)		2.6 (1.3)		1.8 (1.0)		2.6 (1.3)	
Retired	1.8 (1.1)		2.3 (1.3)		1.6 (1.0)		2.1 (1.2)	
Homemaker	2.0 (0.8)		2.4 (1.2)		1.6 (0.9)		2.2 (1.2)	
Unable to work/unemployed	2.7 (1.6)		3.4 (1.4)		2.3 (1.5)		2.9 (1.2)	
Annual income		0.428		0.378		0.584		0.976
Less than $25,000	2.3 (1.3)		2.8 (1.4)		1.9 (1.1)		2.5 (1.3)	
$25,000–$75,000	2.1 (1.2)		2.5 (1.3)		1.7 (1.0)		2.4 (1.4)	
More than $75,000	1.9 (1.1)		2.6 (1.3)		1.6 (0.9)		2.4 (1.2)	
Refused/don't know	1.6 (1.0)		2.3 (1.0)		1.6 (0.8)		2.4 (1.1)	
History of depression		0.001		<0.001		0.170		0.038
Yes	2.5 (1.3)		3.0 (1.3)		1.9 (1.0)		2.7 (1.3)	
No	1.8 (1.0)		2.4 (1.3)		1.6 (1.0)		2.3 (1.3)	
Pathologic stage		0.914		0.274		0.616		0.006
DCIS	2.0 (1.2)		2.7 (1.3)		1.8 (1.0)		2.7 (1.2)	
Stage I/IIA	2.0 (1.2)		2.5 (1.4)		1.7 (1.0)		2.3 (1.3)	
Endocrine therapy[b]		0.232		0.810		0.337		0.253
Yes	2.3 (1.3)		2.6 (1.4)		1.9 (1.1)		2.3 (1.3)	
No	1.9 (1.1)		2.6 (1.3)		1.6 (0.9)		2.6 (1.3)	
Doesn't know	2.3 (1.2)		2.4 (1.4)		1.7 (1.2)		2.4 (1.2)	
Chemotherapy[c]		0.983		0.688		0.485		0.799
Yes	2.0		2.6 (1.3)		1.0		2.4 (1.3)	
No	2.0 (1.2)		2.6 (1.3)		1.7 (1.0)		2.5 (1.3)	

SD standard deviation, *RT* radiation therapy, *APBI* accelerated partial breast irradiation, *WBRT* whole breast radiation therapy, *DCIS* ductal carcinoma in situ

Tests of significance were one-way analysis of variance

[a] One participant did not answer the item about skin irritation during the Time2 interview

[b] Based on patient-reported receipt of adjuvant endocrine therapy at Time1 ($n = 53$) and Time2 ($n = 169$)

[c] Based on patient-reported receipt of chemotherapy at Time1 ($n = 25$) and Time2 ($n = 53$). Of the 25 patients who received chemotherapy at T1, only one patient had also initiated RT by T1, thus no SD is shown

Table 3 Pearson product-moment correlations among RT side-effects severity, quality of life, and the continuous covariates of interest at the second interview ($n = 285$)

	2	3	4	5	6	7	8	9	10
1. Fatigue severity	0.248[a]	−0.293[a]	−0.385[a]	−0.147[b]	0.235[a]	−0.129[b]	0.300[a]	0.026	0.027
2. Skin irritation severity[c]	1.000	−0.202[a]	−0.102	−0.269[a]	0.217[a]	−0.033	0.220[a]	0.084	−0.019
3. Total FACT-B[d]		1.000	0.682[a]	0.196[a]	−0.470[a]	0.478[a]	−0.649[a]	−0.085	−0.134[b]
4. RAND Vitality subscale			1.000	0.045	−0.321[a]	0.248[a]	−0.492[a]	−0.140[b]	−0.142[b]
5. Age				1.000	−0.217[a]	0.089	−0.242[a]	0.041	0.201[a]
6. Surgical side effects					1.000	−0.095	0.399[a]	0.129[b]	0.040
7. Social support						1.000	−0.236[a]	−0.020	−0.027
8. State anxiety							1.000	0.006	0.043
9. BMI[e]								1.000	0.230[a]
10. Comorbidity									1.000

RT radiation therapy, *BMI* body mass index, *FACT-B* functional assessment of cancer therapy-breast, *BMI* body mass index

[a] $P < 0.01$

[b] $P < 0.05$

[c] One participant did not respond to the skin irritation item at Time2; $n = 284$

[d] One participant did not respond to enough individual items to compute the Total FACT-B at Time2, $n = 284$

[e] Three women lacked data to compute body mass index at Time2; $n = 282$

treatment [47, 48], and fatigue in patients who received RT is reported to worsen over time compared with patients who did not receive RT [16]. Studies comparing women receiving tamoxifen with or without WBRT following BCS have reported similar QOL outcomes (physical functioning, general health, pain, and breast symptoms) at 12-month follow-up [63], and few adverse events of RT-related fatigue and skin erythema were reported at 5-year follow-up [64]. However, greater breast symptoms have been reported by older patients treated (vs. not treated) with RT at 5-year follow-up [65]. We found that patients treated with WBRT reported more severe fatigue and skin irritation than patients treated with APBI at 6-month follow-up, and among those patients who had initiated RT by the first interview, patients treated with WBRT reported a greater increase in the severity of fatigue and skin irritation at 6-month follow-up than patients treated with APBI (Figs. 1, 2). Patients in our sample who received WBRT might have had worse prognosis, as they were more likely to have received chemotherapy at Time1 and less likely to have had estrogen receptor-positive tumors, which also may offer better prognosis in some subsets of patients [66, 67]. Interestingly, using Surveillance Epidemiology and End Results program data, Liu et al. [68] found that patients with estrogen receptor-positive tumors were more likely to receive brachytherapy compared with WBRT.

We did not observe a significant improvement in QOL across all patients in this subsample over time nor did we observe that improvement in QOL differed by type of RT in either the Vitality or FACT-B models over the 2-year follow-up (Figs. 3, 4). Our findings expand upon the few studies that examined QOL outcomes after RT [24–32], each of which had notable limitations, e.g., having small samples [25, 28–31], a cross-sectional design [28, 29, 32], not directly comparing QOL outcomes by RT type [25–27], or not examining the impact of RT side-effects severity on change in QOL [24]. To the best of our knowledge, no previous studies have reported *change in the severity of RT-related side effects* in relation to both APBI and WBRT, and none have examined, as we have done here, *changes in QOL over time by type of RT, adjusting for the severity of RT-related side effects* as well as demographic, clinical, treatment, and psychosocial factors. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-39/Radiation Therapy Oncology Group (RTOG) 0413 Phase III randomized trial [69] is comparing survival and QOL outcomes in stage 0–II breast cancer patients treated with conventional WBRT versus partial breast RT. The results of this large, multicenter trial will be able to compare the impact of APBI and WBRT on RT-related side effects as well as on QOL and fill in some notable gaps in knowledge to help inform treatment decision-making.

At 6-month follow-up, we observed less severe RT-related fatigue and skin irritation side effects with APBI compared with WBRT, which may be expected given the abbreviated course of treatment and more focused RT exposure using APBI. However, since breast cancer patients treated with RT report persistent fatigue years after completing treatment [49, 70] and cancer-related fatigue is associated with worse QOL in long-term breast cancer

Table 4 Unadjusted mean (SD) quality of life scores as measured by the FACT-B total score for each interview (Time1–Time4), by each demographic and clinical factor of interest

	FACT-B total score							
	Time1 ($n = 285$)	P value	Time2 ($n = 284$)[a]	P value	Time3 ($n = 281$)	P value	Time4 ($n = 275$)	P value
Race		0.630		0.729		0.703		0.335
White	118.2 (17.1)		120.6 (17.5)		119.6 (15.5)		122.7 (16.2)	
Non-White	119.5 (18.7)		119.6 (17.9)		118.6 (16.1)		120.1 (18.8)	
Education		0.128		0.448		0.007		0.014
Less than grade 12	110.9 (18.4)		115.5 (19.4)		109.6 (14.5)		112.5 (16.0)	
Grade 12	119.4 (15.4)		120.7 (17.1)		118.4 (15.6)		121.3 (17.2)	
More than grade 12	118.9 (17.8)		120.8 (17.5)		120.8 (15.3)		123.6 (16.2)	
Marital status		0.003		0.012		0.006		0.004
Married/partnered	119.8 (15.4)		121.0 (16.5)		121.7 (13.1)		124.3 (15.3)	
Divorced/separated	110.4 (22.9)		114.0 (22.8)		113.2 (19.7)		114.8 (20.9)	
Widowed	122.1 (14.5)		125.7 (11.1)		119.3 (16.2)		123.9 (13.5)	
Never married	119.3 (17.9)		119.5 (19.0)		116.5 (17.2)		119.8 (17.4)	
Employment status		<0.001		<0.001		<0.001		<0.001
At least part-time	118.8 (15.7)		122.1 (14.8)		120.9 (13.7)		123.5 (14.6)	
Retired	123.6 (13.6)		123.2 (14.9)		121.8 (14.4)		126.5 (12.3)	
Homemaker	120.1 (15.2)		120.2 (21.5)		119.9 (15.1)		123.6 (18.2)	
Unable to work/ Unemployed	98.2 (24.3)		101.6 (24.7)		102.3 (20.1)		98.0 (21.5)	
Annual income		0.139		0.008		0.008		<0.001
Less than $25,000	114.4 (22.6)		114.4 (24.2)		114.4 (19.2)		114.6 (21.7)	
$25,000–$75,000	119.3 (14.4)		122.0 (15.3)		119.8 (14.9)		124.0 (14.1)	
More than $75,000	120.6 (14.9)		123.3 (12.1)		122.0 (12.8)		125.6 (12.9)	
Refused/don't know	119.5 (17.7)		121.6 (15.5)		123.8 (11.0)		125.7 (14.7)	
History of depression		<0.001		<0.001		0.001		<0.001
Yes	110.4 (18.9)		114.1 (21.6)		115.0 (17.6)		116.5 (19.8)	
No	122.7 (14.9)		123.7 (13.9)		121.7 (13.9)		125.2 (14.0)	
Pathologic stage		0.988		0.827		0.721		0.846
DCIS	118.4 (17.3)		120.7 (17.9)		119.9 (16.2)		122.0 (18.9)	
Stage I/IIA	118.5 (17.4)		120.2 (17.4)		119.2 (15.3)		122.4 (15.5)	
Type of RT		0.001		0.094		0.257		0.123
APBI[b]	122.6 (14.0)		122.5 (15.7)		120.7 (14.4)		124.2 (13.8)	
WBRT[c]	115.7 (18.8)		119.0 (18.6)		118.6 (16.2)		121.0 (18.2)	
Endocrine therapy[d]		0.445		0.063		0.200		0.600
Yes	115.7 (17.2)		122.1 (15.6)		120.5 (14.0)		122.8 (15.0)	
No	119.0 (17.4)		117.1 (20.1)		116.8 (18.8)		120.9 (19.8)	
Doesn't know	120.3 (18.2)		123.4 (17.9)		119.5 (10.6)		126.8 (15.3)	
Chemotherapy[e]		0.027		<0.001		0.083		0.235
Yes	111.1 (24.4)		112.8 (23.4)		116.1 (19.7)		119.7 (18.5)	
No	119.1 (16.4)		122.2 (15.4)		120.2 (14.4)		122.8 (16.2)	

DCIS ductal carcinoma in situ, *RT* radiation therapy, *APBI* accelerated partial breast irradiation, *WBRT* whole breast radiation therapy, *SD* standard deviation, *FACT-B* functional assessment of cancer therapy-breast

Tests of significance were one-way analysis of variance

[a] One participant did not respond to enough individual items to compute the Total FACT-B at Time2 ($n = 284$)

[b] 60 patients reported receiving APBI at Time1, 113 patients reported receiving APBI at Time2

[c] 61 patients reported receiving WBRT at Time1, 172 patients reported receiving WBRT at Time2

[d] Based on patient-reported receipt of adjuvant endocrine therapy at Time1 ($n = 53$), Time2 ($n = 169$), Time3 ($n = 198$), and Time4 ($n = 184$)

[e] Based on patient-reported receipt of chemotherapy at Time1 ($n = 25$) and Time2–Time4 ($n = 53$) as all patients had received chemotherapy by Time2

Table 5 Unadjusted mean (SD) quality of life scores as measured by the RAND vitality subscale for each interview (Time1–Time4), by each demographic and clinical factor of interest

	RAND vitality subscale							
	Time1 ($n = 285$)	P value	Time2 ($n = 285$)	P value	Time3 ($n = 281$)	P value	Time4 ($n = 275$)	P value
Race		0.356		0.852		0.979		0.567
White	55.3 (21.8)		59.9 (24.6)		62.3 (23.0)		62.1 (22.5)	
Non-White	58.5 (22.2)		59.2 (23.9)		62.2 (21.6)		60.0 (23.1)	
Education		0.007		0.002		0.001		0.009
Less than grade 12	41.5 (22.3)		42.5 (26.8)		45.0 (24.8)		47.4 (20.7)	
Grade 12	55.1 (19.8)		58.2 (22.3)		61.1 (21.9)		60.8 (23.4)	
More than Grade 12	57.6 (22.1)		62.1 (24.3)		64.5 (22.1)		63.6 (22.0)	
Marital status		0.205		0.653		0.670		0.205
Married/member of an unmarried couple	55.7 (21.7)		60.0 (24.1)		63.6 (21.6)		62.8 (22.3)	
Divorced/Separated	51.1 (25.2)		56.6 (27.4)		59.6 (24.7)		55.5 (25.3)	
Widowed	60.3 (19.2)		63.0 (23.0)		60.3 (26.4)		64.5 (20.5)	
Never married	58.6 (18.3)		58.9 (23.5)		62.6 (18.7)		62.0 (19.9)	
Employment status		<0.001		<0.001		<0.001		<0.001
At least part-time	56.0 (21.5)		61.4 (23.0)		64.7 (20.3)		63.6 (21.8)	
Retired	60.3 (20.9)		62.9 (24.2)		65.2 (22.4)		65.2 (18.4)	
Homemaker	58.0 (18.4)		60.0 (23.8)		62.2 (20.6)		64.1 (25.4)	
Unable to work/unemployed	38.3 (22.2)		39.6 (25.8)		38.0 (26.4)		34.3 (21.5)	
Annual income		0.411		0.055		0.039		0.007
Less than $25,000	52.6 (23.6)		53.2 (28.2)		56.6 (26.5)		53.7 (25.5)	
$25,000–$75,000	56.0 (21.3)		61.4 (23.3)		62.9 (22.1)		63.4 (21.5)	
More than $75,000	57.2 (20.6)		63.4 (20.5)		67.1 (19.3)		65.2 (19.0)	
Refused/Don't know	60.2 (23.0)		60.2 (26.5)		60.0 (21.6)		65.6 (25.2)	
History of depression		<0.001		<0.001		<0.001		<0.001
Yes	47.1 (20.7)		52.0 (24.3)		54.4 (24.1)		53.3 (22.7)	
No	60.4 (21.1)		63.9 (23.5)		66.3 (21.0)		65.9 (21.4)	
Pathologic stage		0.597		0.097		0.510		0.792
DCIS	56.8 (22.4)		63.2 (22.4)		63.6 (21.9)		61.2 (21.8)	
Stage I/IIA	55.4 (21.6)		58.1 (25.2)		61.6 (23.2)		62.0 (23.0)	
Type of RT		0.257		0.921		0.442		0.589
APBI[a]	57.7 (20.5)		60.0 (24.9)		63.6 (21.6)		62.6 (21.2)	
WBRT[b]	54.7 (22.7)		60.0 (24.2)		61.4 (23.5)		61.1 (23.5)	
Endocrine therapy[c]		0.451		0.025		0.856		0.661
Yes	53.0 (19.9)		62.8 (23.1)		62.8 (22.0)		62.4 (21.4)	
No	56.6 (22.4)		54.4 (24.4)		61.1 (24.9)		60.7 (25.1)	
Doesn't Know	48.8 (12.5)		61.5 (32.8)		60.0 (0.00)		53.8 (22.9)	
Chemotherapy[d]		0.559		0.003		0.603		0.705
Yes	53.4 (22.0)		50.8 (26.4)		63.8 (23.5)		62.8 (24.3)	
No	56.1 (21.9)		61.8 (23.5)		61.9 (22.6)		61.5 (22.3)	

DCIS ductal carcinoma in situ, *RT* radiation therapy, *APBI* accelerated partial breast irradiation, *WBRT* whole breast radiation therapy, *SD* standard deviation

Tests of significance were one-way analysis of variance

[a] 60 patients reported receiving APBI at Time1, 113 patients reported receiving APBI at Time2

[b] 61 patients reported receiving WBRT at Time1, 172 patients reported receiving WBRT at Time2

[c] Based on patient-reported receipt of adjuvant endocrine therapy at Time1 ($n = 53$), Time2 ($n = 169$), Time3 ($n = 198$), and Time4 ($n = 184$)

[d] Based on patient-reported receipt of chemotherapy at Time1 ($n = 25$) and Time2–Time4 ($n = 53$) as all patients had received chemotherapy by Time2

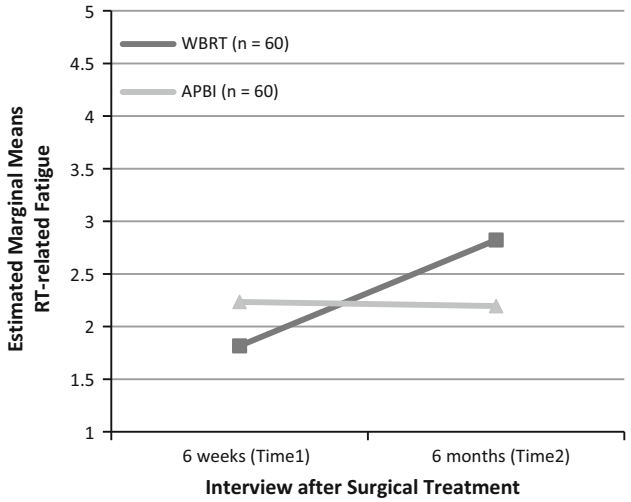

Fig. 1 Repeated-measures analysis of covariance of severity of fatigue at Time1 and Time2 by type of radiation therapy (RT)—whole breast radiation therapy (WBRT) or accelerated partial breast irradiation (APBI)—for those 120 patients who had initiated RT at Time1, adjusting for all covariates. Higher scores indicate greater severity of fatigue. Women who received WBRT reported a greater increase in fatigue at Time2 than women who received APBI ($P < 0.001$)

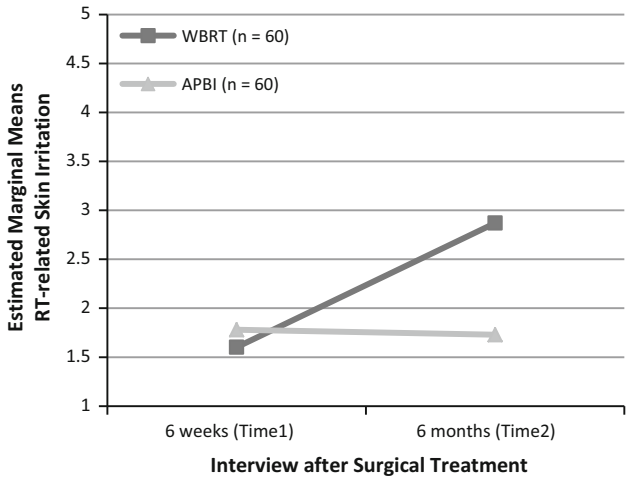

Fig. 2 Repeated-measures analysis of covariance of severity of skin irritation at Time1 and Time2 by type of radiation therapy (RT)—whole breast radiation therapy (WBRT) or accelerated partial breast irradiation (APBI)—for those 120 patients who had initiated RT at Time1, adjusting for all covariates. Higher scores indicate greater severity of skin irritation. Women who received WBRT reported a greater increase in skin irritation at Time2 ($P < 0.001$) than women who received APBI

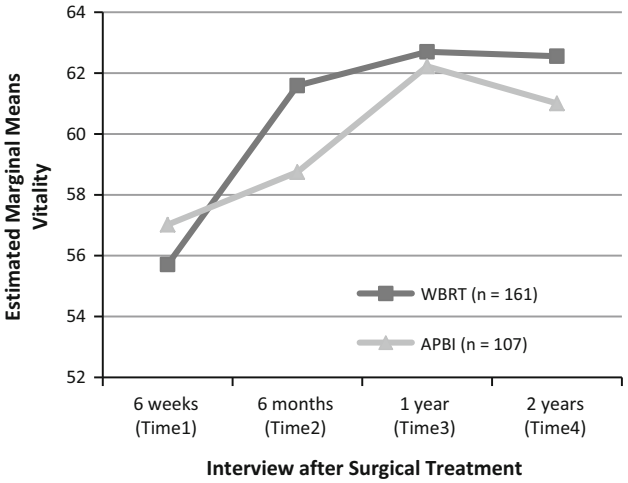

Fig. 3 Repeated-measures analysis of covariance of RAND 36-item health survey vitality subscale scores over time by type of radiation therapy (RT)—whole breast radiation therapy (WBRT) or accelerated partial breast irradiation (APBI)—adjusting for all covariates ($N = 268$). Higher scores indicate greater vitality. Change over time was not statistically significant regardless of type of RT

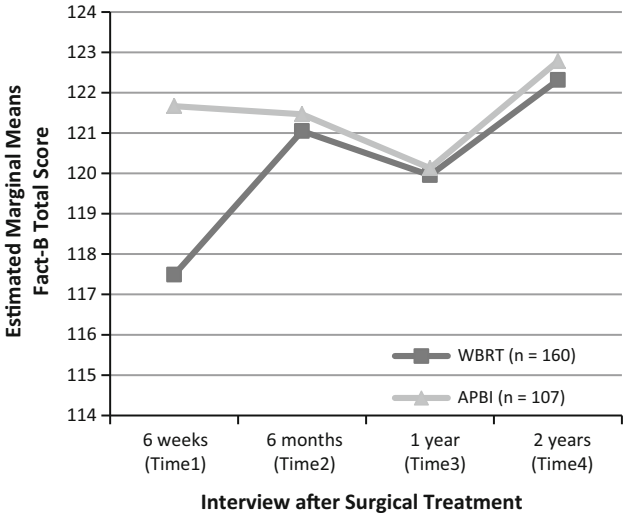

Fig. 4 Repeated-measures analysis of covariance of total FACT-B scores over time by type of radiation therapy (RT)—whole breast radiation therapy (WBRT) or accelerated partial breast irradiation (APBI)—adjusting for all covariates ($N = 267$). Higher scores indicate better quality of life. Change over time was not statistically significant regardless of type of RT

survivors [70], future research is warranted to determine if less severe RT-related side effects in the short term are associated with improved long-term QOL in breast cancer survivors. Jeffe et al. reported that the adverse effect of chemotherapy on total FACT-B scores was more prominent in early-stage breast cancer patients who received BCS than mastectomy, suggesting that this finding was potentially due to the cumulative effects of RT following BCS [71]. Findings reported here suggest further that the negative cumulative effect of RT on change in both Vitality and the FACT-B total scores over two-year follow-up occurs regardless of type of RT received after definitive surgical treatment. As APBI was associated with less

severe RT-related side effects than WBRT in the short term within six months of surgery, and more severe RT-related side effects were associated with poorer QOL outcomes (Table 3), these findings may be especially important for early-stage breast cancer patients who also may require adjuvant chemotherapy following BCS, as RT options associated with less severe side effects (at least in the short term) may be preferred.

This study has some strengths and limitations. While we benefited from a relatively large, prospective cohort of early-stage breast cancer patients meeting much of the criteria set forth by the American Society for Radiation Oncology (ASTRO) for "suitable" and "cautionary" patient groups considered for treatment with APBI [44], we did not conduct a randomized controlled trial, which could have eliminated potential sources of bias resulting from unmeasured confounders and limited our ability to make causal inferences. Such a trial, the large, multi-site NSABP B-39/RTOG 0413 study [69], began recruiting in 2005, 2 years after we began recruiting for our cohort study and their results comparing the effects of WBRT and APBI on QOL have not yet been reported [69]. We could not account for the timing of initiation or duration of RT or the type of APBI received, which could have had an impact on RT side-effects severity and QOL changes over time, as this information was not available for all patients in the medical record. We could not confirm self-reported RT type for 27 patients or type of APBI reported by three patients, although near-perfect agreement was observed between the medical record and self-reported RT type by 258 patients. Additionally, our cohort study was not powered based on the aims of the secondary analysis reported here. An appropriately designed study specifically to examine the type, timing, and duration of RT on QOL outcomes is still needed. We also did not know whether all patients who met the ASTRO criteria for "suitable" and "cautionary" use of APBI [44] had been offered a choice between WBRT and APBI and, if they were offered a choice, which patients elected to receive WBRT over APBI. Although hypofractionated WBRT is now recommended treatment in breast cancer patients meeting specific criteria [72, 73], we could not compare between patients receiving conventional and hypofractionated WBRT, as our study began enrollment in 2003 before this treatment recommendation was made. As with all self-reported data, social desirability bias has been reported in both telephone [74] and face-to-face interviews [75]. However, other research supports using telephone surveys, even where sensitive health information is being collected [76]. As we recruited women 40 years of age or older from a National Cancer Institute-designated comprehensive cancer center and another academic medical center in St. Louis, MO, our results may not be generalizable to younger breast cancer patients, who often report worse QOL than older patients [77–79], or to patients receiving treatment in rural or community settings. Although the racial/ethnic composition of our sample was representative of the St. Louis metropolitan area, few non-white participants were Hispanic or Asian, further limiting generalizability.

In conclusion, early-stage breast cancer patients can benefit from less-severe, short-term side effects of APBI with no differential impact on QOL improvements in the first two years after diagnosis. Rigorously designed and implemented longitudinal studies examining late-effects of treatment and long-term QOL outcomes in early-stage breast cancer survivors are warranted given the expected longevity of this group of survivors [80].

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest, financial or otherwise.

Ethical approval The IRBs at both Washington University and Saint Louis University approved this study. All procedures performed were in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments and the institutional review boards (IRBs) at both Washington University and Saint Louis University.

Informed consent Informed consent was obtained from all individual participants included in the study.

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