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Original article

Comparison of chronic toxicities between brachytherapy-based accelerated partial breast irradiation and whole breast irradiation using intensity modulated radiotherapy

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ABSTRACT

Purpose: Brachytherapy-based APBI (bAPBI) shortens treatment duration and limits dose to normal tissue. While studies have demonstrated similar local control when comparing bAPBI and whole breast irradiation using intensity modulated radiotherapy (WBI-IMRT), comparison of late side effects is limited. Here, we report chronic toxicity profiles associated with these two treatment modalities.
Methods: 1034 patients with early stage breast cancer were treated at a single institution; 489 received standard-fractionation WBI-IMRT between 2000 and 2013 and 545 received bAPBI (interstitial 40%, applicator-based 60%) between 1993 and 2013. Chronic toxicity was evaluated ≥6 months utilizing CTCAE version 3.0; cosmesis was evaluated using the Harvard scale.
Results: Median follow-up was 4.6 years (range 0.1–13.4) for WBI-IMRT versus 6.7 years (range 0.1–20.1) for bAPBI ($p < 0.001$). Compared to WBI-IMRT, bAPBI was associated with higher rates of ≥grade 2 seroma formation (14.4% vs 2.9%, $p < 0.001$), telangiectasia (12.3% vs 2.1%, $p = 0.002$) and symptomatic fat necrosis (10.2% vs 3.6%, $p < 0.001$). Lower rates of hyperpigmentation were observed (5.8% vs 14.5%; $p = 0.001$). Infection rates were similar (3.3% vs 1.3%, $p = 0.07$). There was no difference between rates of fair (6.1% vs. 4.1%, $p = 0.30$) or poor (0.2% vs. 0.5%, $p =$ NS) cosmesis. Mastectomy rates for local recurrence (3.1% for WBI-IMRT and 1.2% for bAPBI, $p = 0.06$), or for other reasons (0.8% and 0.6%, $p = 0.60$) were similar between groups.
Conclusion: With 5-year follow-up, WBI-IMRT and bAPBI are associated with similar, acceptable rates of toxicity. These data further support the utilization of bAPBI as a modality to deliver adjuvant radiation in a safe and efficacious manner.

Introduction

Multiple randomized controlled trials comparing mastectomy to breast conserving therapy (BCT), consisting of lumpectomy followed by whole breast irradiation (WBI), have consistently demonstrated equivalent clinical outcomes for definitive management of early stage breast cancer [1–4]. As such, a focus on treatments that maintain quality of life without jeopardizing cancer control or survival rates has become of increasing interest. Studies have shown that up to 20% of patients fail to receive adjuvant radiotherapy due to a variety of factors, including travel distance to a radiation facility and protracted treatment schedules, which are traditionally 3–6.5 weeks in duration [5,6]. Accelerated partial breast irradiation (APBI) represents a treatment modality that shortens adjuvant radiotherapy to five days or less [7]. This modality may translate into improved quality of life by reducing treatment duration, increasing the accessibility of BCT, and potentially reducing toxicities by treating smaller volumes of normal breast tissue, heart, and regional lymphatics.

Commonly utilized APBI techniques include three-dimensional conformal external beam (3D-CRT) and brachytherapy-based (bAPBI) radiotherapy. While prospective studies and matched-

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pair analyses comparing APBI to WBI have demonstrated excellent long-term clinical outcomes [8,9], documentation of late toxicities remains relatively sparse. It is known, however, that toxicity profiles can vary significantly between APBI techniques. An interim analysis of 3 years of follow-up from the RAPID trial, which randomized patients to 3D-CRT or WBI, demonstrated inferior cosmetic outcomes (29% fair to poor vs 17%; $p < 0.001$) with increased rates of grade 1 (53% vs 43%; $p < 0.001$), and 2 (12% vs 3%; $p < 0.001$) chronic toxicity in the APBI group compared to WBI [10]. On the other hand, Polgar et al. reported more favorable cosmesis with bAPBI (18.8% fair to poor vs 34.4%; $p = 0.009$) compared to photon-based WBI with an average of 5 years of follow-up [11].

The administration of WBI has evolved over the past decade, incorporating 3dimensional-conformal techniques and intensity modulation. WBI-IMRT has been shown in prospective and randomized trials to decrease both acute and chronic toxicity when compared to more conventional WBI techniques, such as standardized 2D planning with wedge-based external beam radiotherapy [12–14].

To date, there are no data comparing bAPBI to WBI-IMRT in the context of toxicity and cosmetic outcomes with prolonged follow-up. Therefore, the purpose of this study is to compare chronic toxicity rates for patients treated with these two modalities.

Materials/methods

Patient population

A total of 1034 patients with early stage breast cancer, stage 0 to IIB, were treated with adjuvant breast irradiation at a single institution from 1993 to 2013 as part of their breast conserving therapy. Four hundred eighty-nine patients received WBI-IMRT from 2000 to 2013, and 545 received bAPBI from 1993 to 2013. Patients who received WBI prior to 2000 were treated with opposed tangents with or without wedges and were not included in this analysis. This study was approved by the WBH Institutional Review Board (HIC no. 2012-220).

Details of radiotherapy

Patients treated with WBI-IMRT first underwent a 3D CT scan in the supine position for planning purposes with Alpha Cradle immobilization (Smithers Medical Products, Canton, OH). Active Breathing Control was used for left-sided tumors at the discretion of the treating physician [15]. A median of 45 Gy was delivered to the whole breast (range 40.05–50.4 Gy) with a median 16 Gy supplemental boost to the surgical cavity (range 0–22 Gy, 98% receiving boost). 9.4% of patients received radiotherapy either to the level III/supraclavicular nodes ($N = 39$; 8.0%) or full axilla ($N = 7$; 1.4%). Radiation plans between 2000 and 2002 were created with the use of forward planning, utilizing a “field in field” technique delivered with multiple static multi-leaf collimator segments (MLC) with optimized dose homogeneity (Pinnacle, ADAC laboratories, Milpitas, CA), the details of which have been published previously [16]. After 2002, planning was performed with inverse-planned multi-segment IMRT, with objectives to limit the volume of the breast receiving 105% of the prescription dose to 15% ($V105 < 15\%$), the $V110 < 10\%$, and the $V115 < 5\%$.

Brachytherapy-based APBI consisted of multi-planar interstitial needle placement, single-and multi-lumen balloons, and strut-based implants Patients who received 3D-CRT ($N = 217$) were excluded from this analysis, as recently published randomized data has shown inferior rates of chronic toxicity and cosmesis with this technique compared to WBI [10]. Patients treated with interstitial needles received either low-dose-rate (LDR; $N = 119$) brachytherapy consisting of 50 Gy (0.52/Gy/h over a 96 h period) or high-dose-rate (HDR; $N = 99$) brachytherapy to a total of 32–34 Gy given twice daily (BID) in 8–10 fractions. Single-lumen MammoSite (Hologic, Inc., Bedford, MA; $N = 207$), multi-lumen MammoSite and Contura (SenoRx, Inc., Aliso Viejo, CA; $N = 101$) balloons, and SAVI strut-based (Cianna Medical, Aliso Viejo, CA; $N = 19$) applicators were used to deliver HDR brachytherapy with a dose of 34 Gy given BID in 10 fractions.

Cosmesis and toxicity assessment

Chronic toxicity was defined as an event occurring $\geq$6 months after treatment completion. Toxicity was assessed by the treating radiation oncologist at regularly scheduled follow-up visits. Scoring was performed utilizing the National Cancer Institute's Common Terminology Criteria for Adverse Events version 3.0 (CTCAE www.eortc.be/services/doc/ctc/ctcaev3.pdf) on a scale of 0–4 based on clinician assessment. Events included breast pain, hyperpigmentation, hypopigmentation, breast edema, induration/fibrosis, volume reduction, and telangiectasia. Of note, there are no CTCAE v3.0 “grade 3” designations for hypopigmentation, edema, fat necrosis, or seroma formation. Fat necrosis was graded as a “1” if asymptomatic, found only on mammogram, and as a “2” if symptomatic. Seroma formation was graded in a similar fashion. Cosmesis was evaluated on a four-category scale, including excellent, good, fair and poor, using the Harvard criteria [17].

Statistical methods

Categorical variables were analyzed using the Pearson Chi-Square test and continuous variables using the independent samples T-test. The Kaplan–Meier method was utilized to calculate ipsilateral breast tumor recurrence (IBTR). Time to IBTR was calculated from the date of radiotherapy completion to the date of the event. Analyses were performed using SPSS version 20 (SYSTAT Software, Chicago, IL). P values of $\leq$0.05 were considered statistically significant.

Results

Patient characteristics, including clinical, pathologic, and treatment-related factors, are presented in Table 1. WBI-IMRT patients were significantly younger (median 61 vs 65 years old, $p < 0.001$), with larger tumors volumes (median size 13.8 vs 10.9 mm; $p < 0.001$) and were more likely to be node positive (15% vs 7.3%; $p < 0.001$) and with higher-grade disease (20% vs 18%, $p = 0.03$). WBI-IMRT patients were also more likely to receive adjuvant hormonal therapy (70% vs 59%; $p < 0.001$) and chemotherapy (70% vs 15%; $p < 0.001$). Median follow up time was 6.7 years (range 0.1–20.1) and 3.9 years (range 0.1–13.4) for bAPBI and WBI-IMRT, respectively ($p < 0.001$); median follow-up for interstitial APBI was 13.0 years as compared with 5.1 years for applicator based APBI.

Rates of Grade 2 or greater maximum chronic toxicity by technique are presented in Table 2. WBI-IMRT was associated with higher rates of hyperpigmentation (14.5% vs 5.8%; $p = 0.001$), whereas bAPBI had higher rates of telangiectasia (12.3% vs 2.1%; $p < 0.001$), symptomatic fat necrosis (10.2% vs 3.6%; $p < 0.001$), and seroma formation (14.4% vs 2.9%; $p < 0.001$). There were no significant differences noted regarding rates of hypopigmentation, edema, pain, induration/fibrosis, or volume reduction (all $p > 0.05$). Infection rates were similar (1.3% vs 3.3%, $p = 0.07$) between groups. Table 3 presents rates of grade 3 or greater toxicity by technique. No differences in rates of hyperpigmentation, breast pain, induration/fibrosis, volume reduction,