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CLINICAL INVESTIGATION **Breast**

PREDICTORS OF LONG-TERM TOXICITY USING THREE-DIMENSIONAL CONFORMAL EXTERNAL BEAM RADIOTHERAPY TO DELIVER ACCELERATED PARTIAL BREAST IRRADIATION

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Purpose: We analyzed variables associated with long-term toxicity using three-dimensional conformal external beam radiation therapy (3D-CRT) to deliver accelerated partial breast irradiation.

Methods and Materials: One hundred patients treated with 3D-CRT accelerated partial breast irradiation were evaluated using Common Terminology Criteria for Adverse Events version 4.0 scale. Cosmesis was scored using Harvard criteria. Multiple dosimetric and volumetric parameters were analyzed for their association with worst and last (W/L) toxicity outcomes.

Results: Sixty-two patients had a minimum of 36 months of toxicity follow-up (median follow-up, 4.8 years). The W/L incidence of poor-fair cosmesis, any telangiectasia, and grade ≥2 induration, volume reduction, and pain were 16.4%/11.5%, 24.2%/14.5%, 16.1%/9.7%, 17.7%/12.9%, and 11.3%/3.2%, respectively. Only the incidence of any telangiectasia was found to be predicted by any dosimetric parameter, with the absolute breast volume receiving 5% to 50% of the prescription dose (192.5 cGy–1925 cGy) being significant. No associations with maximum dose, volumes of lumpectomy cavity, breast, modified planning target volume, and PTV, dose homogeneity index, number of fields, and photon energy used were identified with any of the aforementioned toxicities. Non-upper outer quadrant location was associated with grade ≥2 volume reduction (p = 0.02 W/p = 0.04 L). A small cavity-to-skin distance was associated with a grade ≥2 induration (p = 0.03 W/p = 0.01 L), a borderline significant association with grade ≥2 volume reduction (p = 0.06 W/p = 0.06 L) and poor-fair cosmesis (p = 0.08 W/p = 0.09 L), with threshold distances ranging from 5 to 8 mm.

Conclusions: No dose–volume relationships associated with long-term toxicity were identified in this large patient cohort with extended follow-up. Cosmetic results were good-to-excellent in 88% of patients at 5 years.

Accelerated partial breast irradiation, External beam radiation therapy, Breast cancer, Cosmesis, Toxicity.

INTRODUCTION

Three-dimensional conformal external beam radiotherapy (3D-CRT) is being explored as one of several different techniques used to deliver accelerated partial breast irradiation (APBI). Although most early studies using this APBI technique have demonstrated good results (1–3), two recently published trials have reported significant short-term toxicities (4, 5). Hepel *et al.* (5) reported data for 64 patients treated at Tufts University, using guidelines similar to those found in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-39/ Radiation Therapy Oncology Group (RTOG) protocol 0413 phase III trial (5, 6). With a median follow-up of 15 months, 10% of patients experienced moderate-to-severe late toxicity, and 18.4% of patients had poor-fair cosmesis. Subcutaneous fibrosis was the most prevalent toxicity seen, with 25% of patients experiencing grades 2 to 4 fibrosis. Univariate logistic regression analysis demonstrated that the development of fibrosis was correlated with (*1*) the maximum dose (Dmax) within the breast, (*2*) the ratio of the 3D-CRT target volume (PTV_EVAL) to the breast volume, and (*3*) the size of low and intermediate dose volumes measured as a percentage of the prescription dose (V5%–V50%), as a proportion of the overall volume of the breast.

In a prospective study from the University of Michigan, Jagsi *et al.* (4) reported on 34 patients treated with 38.5 Gy in 10 fractions using inverse-planned, intensity-modulated radiotherapy with deep-breath hold (4). According to those authors, the dose–volume guidelines and constraints used

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were similar to those outlined in the NSABP B-39 / RTOG 0413 phase III trial. With a median follow-up of 2.5 years, 7 patients developed unacceptable cosmetic toxicity, prompting the premature closure of that trial.

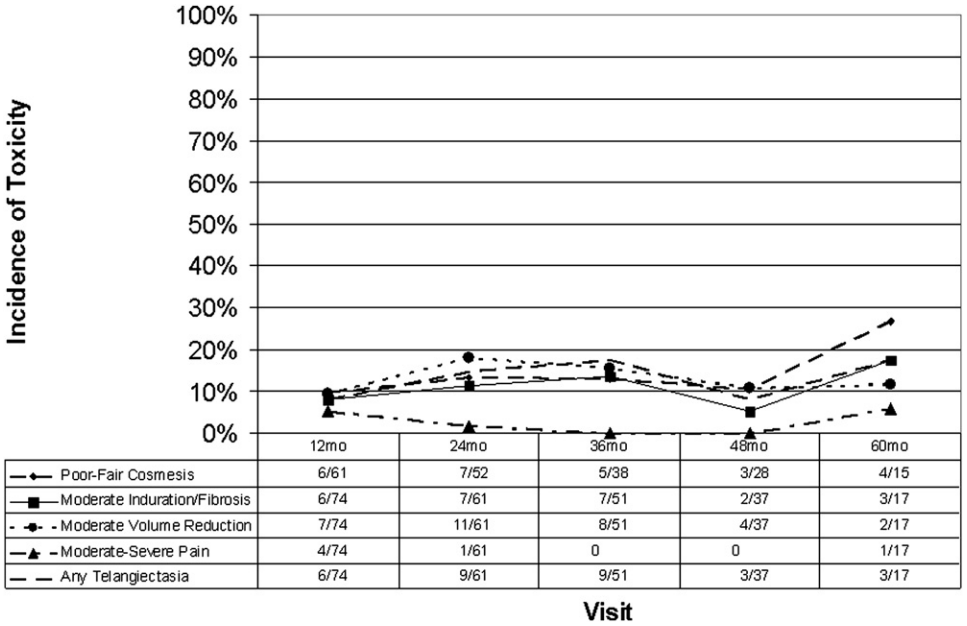
To assess the relevance of these recent reports to future participants in the NSABP B-39/RTOG 0413 phase III trial, the NSABP Data Safety Monitoring Committee issued a detailed report on toxicity experienced by all patients enrolled in that study by treatment arm (7). That report found no significant concerns related to toxicity for patients enrolled in the trial, in which there is careful reporting of adverse events. Furthermore, with a mean follow-up of 32 months, minimal differences in serious adverse events have been seen in patients treated with whole-breast irradiation versus those treated with one of the three APBI techniques, with grade 3 toxicities found in <1% of patients. Notably, approximately 70% of women randomized to receive APBI in the NSABP B-39/RTOG 0413 trial have received their treatment using 3D-CRT. Therefore, with over 3,200 patients enrolled in that large, prospective randomized phase III trial, there has been no confirmation of the Tufts University (5) or University of Michigan (4) experience with toxicity. A recent letter to the editor of this journal highlighted the low rates of grade ≥2 and ≥3 toxicities among patients treated with APBI enrolled on the NSABP B-39/RTOG-0413 trial, with <10% of patients reporting grade ≥2 fibrosis/cosmesis and <2% of patients with grade 3 or 4 (8).

Given the above-described debate, we sought to reexamine our own institution's data. Our intention was to examine a large cohort of patients treated with 3D-CRT to deliver APBI, now with longer follow-up. We supplemented our original data by incorporating toxicity assessments by both radiation oncologists and breast surgeons in order to verify our institution's relatively low rates of toxicity. Additionally, we analyzed a wider set of dosimetric, volumetric, and geometric parameters that might predict toxicity. Even with acceptably low rates of toxicity, we believed that a large enough number of women had received APBI via 3D-CRT at our institution, such that if a dosimetric correlation with toxicity existed, it should emerge.

METHODS AND MATERIALS

A total of 100 consecutive patients treated with APBI via 3D-CRT treated at the William Beaumont Hospital made up the study population, with follow-up ranging from 0.04 to 8.88 years (median, 5.06 years). Treatment planning was performed according to our previously published technique (9). All patients underwent computed tomography (CT)-based 3D planning. The lumpectomy cavity was defined by the seroma, postoperative changes, and surgical clips, when available. The lumpectomy cavity was expanded uniformly by 10 to 15 mm to define the clinical target volume (CTV); this expanded volume was contracted by 5 mm from the skin surface and by the extent of posterior breast tissue (excluding the chest wall and pectoralis muscles). The planning target volume (PTV) was defined by using a uniform 10-mm expansion of the CTV. For evaluation purposes, a modified PTV, PTV_EVAL, was created that consisted of the PTV excluding all volume outside of the ipsilateral breast and the first 5 mm of tissue under the skin. The whole-breast volume (WBV) was defined as all tissue volume within the boundaries of standard whole-breast tangential fields, as defined by medial and lateral catheters, excluding tissues deep to the chest wall. The prescribed dose was 3,400 cGy or 3,850 cGy in 10 fractions.

At each visit to a physician in the department of radiation oncology within our hospital, the patient was reassessed for cosmesis and toxicity. When available, physician's notes from follow-up visits to the breast surgeon were also included for cosmesis and toxicity assessment. The following toxicities were recorded: cosmesis,



	12mo	24mo	36mo	48mo	60mo
Poor-Fair Cosmesis	6/61	7/52	5/38	3/28	4/15
Moderate Induration/Fibrosis	6/74	7/61	7/51	2/37	3/17
Moderate Volume Reduction	7/74	11/61	8/51	4/37	2/17
Moderate-Severe Pain	4/74	1/61	0	0	1/17
Any Telangiectasia	6/74	9/61	9/51	3/37	3/17

Fig. 1. Toxicities over time. Among patients with a minimum of 36 months toxicity follow-up, the toxicity grades recorded at 12-month intervals, as recorded within 30 months prior to the ordinal month up to the next ordinal visit, are shown.