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CLINICAL INVESTIGATION **Breast**

ACCELERATED PARTIAL-BREAST IRRADIATION USING PROTON BEAMS: INITIAL CLINICAL EXPERIENCE

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Purpose: We present our initial clinical experience with proton, three-dimensional, conformal, external beam, partial-breast irradiation (3D-CPBI).

Methods and Materials: Twenty patients with Stage I breast cancer were treated with proton 3D-CPBI in a Phase I/II clinical trial. Patients were followed at 3 to 4 weeks, 6 to 8 weeks, 6 months, and every 6 months thereafter for recurrent disease, cosmetic outcome, toxicity, and patient satisfaction.

Results: With a median follow-up of 12 months (range, 8–22 months), no recurrent disease has been detected. Global breast cosmesis was judged by physicians to be good or excellent in 89% and 100% of cases at 6 months and 12 months, respectively. Patients rated global breast cosmesis as good or excellent in 100% of cases at both 6 and 12 months. Proton 3D-CPBI produced significant acute skin toxicity with moderate to severe skin color changes in 79% of patients at 3 to 4 weeks and moderate to severe moist desquamation in 22% of patients at 6 to 8 weeks. Telangiectasia was noted in 3 patients. Three patients reported rib tenderness in the treated area, and one rib fracture was documented. At last follow-up, 95% of patients reported total satisfaction with proton 3D-CPBI.

Conclusions: Based on our study results, proton 3D-CPBI offers good-to-excellent cosmetic outcomes in 89% to 100% of patients at 6-month and 12-month follow-up and nearly universal patient satisfaction. However, proton 3D-CPBI, as used in this study, does result in significant acute skin toxicity and may potentially be associated with late skin (telangiectasia) and rib toxicity. Because of the dosimetric advantages of proton 3D-CPBI, technique modifications are being explored to improve acute skin tolerance. © 2006 Elsevier Inc.

Breast cancer, Cosmesis, Partial-breast irradiation, Protons, Toxicity.

INTRODUCTION

Partial-breast irradiation (PBI) is being intensively investigated as an alternative to standard whole-breast irradiation (WBI) for the adjuvant treatment of patients with early-stage breast cancer after partial mastectomy (1–11). Several approaches to PBI have been reported including intracavitary brachytherapy (5), interstitial brachytherapy (6, 7), intraoperative radiation therapy (8, 9), permanent palladium seed implantation (10) and three-dimensional, conformal, external beam radiation therapy (11). External beam approaches to PBI offer several advantages over invasive techniques. Three-dimensional, conformal, external beam, partial-breast irradiation (3D-CPBI) is noninvasive and uses technology used routinely by both academic and community hospital-based radiation oncologists. External beam–based PBI is initiated after final pathologic evaluation of margins, lymph nodes, and other features that have an impact on recurrence risk. In addition, 3D-CPBI offers superior dose homogeneity compared with brachytherapy-based techniques. However, these advantages come at the cost of inferior target conformality and, consequently, reduced sparing of normal tissue (12).

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In an effort to retain the advantages of 3D-CPBI but to improve normal tissue sparing through enhanced target conformality, we investigated the use of protons for 3D-CPBI in the setting of a Phase I/II clinical trial (13). The use of protons was shown to improve planning target volume (PTV) conformality, to reduce substantially the volume of irradiated nontarget breast, and to reduce modestly the doses to the ipsilateral lung and heart (13). We report our initial clinical experience and evaluate the cosmesis, acute toxicities, and patient satisfaction with proton 3D-CPBI.

METHODS AND MATERIALS

Study population, simulation, treatment planning, and treatment

Twenty women prospectively enrolled on an institutional review board approved Phase I/II clinical trial of 3D-CPBI were treated with proton radiotherapy at the Francis H. Burr Proton Therapy Center at Massachusetts General Hospital between March 2004 and June 2005. This clinical trial permitted any external beam modality. The use of proton-based 3D-CPBI was determined by proton beam availability; no patient preselection criteria were used.

Patient eligibility, simulation, treatment planning and treatment has been described elsewhere (13). Briefly, all patients had unifocal, T1 tumors with tumor-free margin width of $\geq$2 mm and pathologically negative axillary nodes. Patients with histologic evidence of lymphovascular invasion, an extensive intraductal component, infiltrating lobular carcinoma, or infiltrating papillary carcinoma were excluded.

Chemotherapy was administered at the discretion of the treating medical oncologist. Radiation and chemotherapy were not concurrently delivered. Hormonal therapy and its timing were also given at the discretion of the treating medical oncologist.

All patients underwent computed tomography-guided breast simulation in the supine position on a breast board (Carbon Fiber Breast Board, model ARB114, Arplay Medical, Izeure, France). No additional breast immobilization was performed. The PTV was generated by expanding the radiographically defined lumpectomy cavity by 1.5 to 2.0 cm. The expanded volume was edited so that it came no closer than 5 mm to the skin surface and no deeper than the anterior chest wall/pectoralis muscles.

Orthogonal and beam's eye view radiographs were obtained before each fraction. The images were compared with treatment planning digitally reconstructed radiographs to recapitulate positioning at the time of simulation. Surgical clips (present in all patients) and bony anatomy were used to confirm proper patient positioning. Rotational positioning corrections were based on bony anatomy, and translational positioning corrections were based on surgical clips. Positioning corrections were made if any seed displacement was $\geq$3 mm. When patient repositioning was $<$5 mm, only a repeat beam's eye view radiograph was obtained. When any move was $\geq$5 mm, orthogonal and beam's eye view radiographs were repeated to confirm proper patient positioning.

The prescribed dose was 32 Cobalt Gray Equivalent (CGE) accounting for the higher relative biologic effectiveness (1.1) of protons compared with photons (14). Radiation was delivered in 4 CGE fractions, twice daily, over 4 days. The interfraction interval was at least 6 h. One to three fields were used to provide PTV coverage and less than 15% dose inhomogeneity. For patients treated with two to three fields, one field was treated per fraction.

Follow-up and cosmetic evaluation

Patients were evaluated at 3 to 4 weeks, 6 to 8 weeks, 6 months, and then every 6 months after completion of radiotherapy. Surveillance for disease recurrence included clinical examination at all time points and mammography at least on an annual basis. At each follow-up, patients were asked to judge the cosmetic outcome of the treated breast as follows: "excellent," designating little or no change; "good," minimal but noticeable change; "fair," significant change; "poor," severe change. Physicians were asked to judge the cosmetic outcome as follows: "excellent," indicating little or no observable change, perfect symmetry, no visible distortion or skin changes; "good," minimal but identifiable change, slight skin distortion, retraction or edema, any visible telangiectasia, mild hyperpigmentation; "fair," significant results of treatment noted, moderate distortion of the nipple or breast symmetry, moderate hyperpigmentation, prominent skin retraction/edema or telangiectasia; "poor," severe normal tissue sequelae, marked distortion, edema, fibrosis, or severe hyperpigmentation (15).

At each time point, patients were also asked to describe several potential toxicities on a four-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). These included breast pain at the site of radiation treatment, swelling of the breast, changes in breast color, thickening or lumpiness of the breast (fibrosis), or dimpling of the breast skin (retraction) and skin reactions that look red and possibly forming blisters or ulcers. In parallel, physicians graded breast pain, edema, skin color changes, fibrosis or retraction, and moist desquamation on an identical scale. Physicians were also asked to monitor for fat necrosis. Both physician and patient standardized evaluation forms requested information regarding any other unanticipated toxicity.

Finally, patients were asked to describe their satisfaction with proton 3D-CPBI as follows: totally satisfied; not totally satisfied but would choose partial-breast irradiation in 1 week again; or not totally satisfied and would choose the standard 6 weeks of external beam radiation.

RESULTS

Median follow-up is 12 months (range, 8–22 months). Baseline patient and tumor characteristics are shown in Table 1. The median interval between definitive surgery and 3D-CPBI was 55 days (range, 32–91 days for 19 patients who did not receive adjuvant chemotherapy). Among the 16 patients treated with hormonal therapy, 10 received tamoxifen and 6 received an aromatase inhibitor. The patient treated with cytotoxic therapy received 4 cycles of doxorubicin and cyclophosphamide followed by 4 cycles of paclitaxel on a dose-dense schedule. She began 3D-CPBI 11 days after completion of chemotherapy (174 days after definitive surgery). All 20 patients are without evidence of recurrent disease at last follow-up.

Physician and patient cosmetic assessments at each time point are shown in Table 2. Both patients and physicians noted a worsening of breast cosmesis within the first 6 months. Physicians rated cosmetic outcome as fair to poor in 16% and 37% of patients at 3 to 4 weeks and 6 to 8 weeks, respectively. Similarly, patients judged cosmesis as fair to poor in 20% and 21% of cases at the same time points. By 6 months, cosmesis had substantially improved.

Table 1. Patient and tumor characteristics (n = 20)

Characteristic	Median (range) or n (%)
Age	62 years (46–75 years)
Tumor size	0.8 cm (0.2–1.8 cm)
Tumor grade	
1	11 (55%)
2	7 (35%)
3	2 (10%)
Tumor histology	
Invasive ductal	18 (90%)
Invasive tubular	2 (10%)
Nodes sampled	2 (1–7)
ER status	
Positive	16 (80%)
Negative	4 (20%)
PR status	
Positive	16 (80%)
Negative	3 (15%)
Unknown	1 (5%)
HER2 status	
Positive	1 (5%)
Negative	17 (85%)
Unknown	2 (10%)
Hormonal therapy	16 (80%)
Cytotoxic chemotherapy	1 (5%)

Abbreviations: ER = estrogen receptor; PR = progesterone receptor.

Global breast cosmesis was judged by physicians to be good or excellent in 89% and 100% of cases at 6 months and 12 months, respectively. Patients rated global breast cosmesis as good or excellent in 100% of cases at both 6 and 12 months despite baseline (postsurgery, preradiotherapy) cosmesis of good or excellent in only 85% of cases. At last follow-up, patients and physicians rated cosmesis as good or excellent in 100% and 85% of cases, respectively. Representative examples of excellent, good and fair cosmetic outcomes at last follow-up are shown in Fig. 1. A representative example of the evolution of a typical patient's cosmetic results is shown in Fig. 2.

The prospectively gathered toxicities of breast pain, edema, skin color changes, fibrosis/retraction, and moist desquamation are shown in Table 3. Proton 3D-CPBI produced significant acute skin toxicity. Physicians noted moderate to severe skin color changes in 79% of patients at 3 to 4 weeks and moderate to severe moist desquamation in 22% of patients at 6 to 8 weeks. As expected, physicians did not observe desquamation at 6 months or beyond. Skin color changes improved beyond 6 to 8 weeks; however, at 6 months, patients and physicians still noted at least mild skin color changes in 65% and 72% of cases, respectively. By 12 months, skin color changes rated as mild or worse were less common than at earlier timepoints but were still reported by physicians and patients in 54% and 46% of cases, respectively.

Breast pain and edema were not prominent features of proton 3D-CPBI. Neither of these toxicities was noted to be moderate to severe in more than 15% of patients at any time point.

Significant discordance was observed between physician and patient assessments of fibrosis/retraction (Table 3). This was most notable at the earliest time points and may reflect physician efforts to dissociate postsurgical changes from radiation changes. At later time points, physician and patient assessments were more concordant and moderate to severe fibrosis/retraction was not seen in more than a single patient at follow-up of 6 months or more. Moderate, clinically suspected fat necrosis was observed in 1 patient at 12 months; however, fat necrosis was not mammographically appreciated.

Toxicities in addition to those listed in Table 3 have been observed. Telangiectasia has been appreciated in 3 patients.

Table 2. Overall cosmetic outcome

	Physician assessment (n (%))				Patient assessment (n (%))			
Time point	Excellent	Good	Fair	Poor	Excellent	Good	Fair	Poor
Baseline (n = 20)	16 (80)	4 (20)	0	0	9 (45)	8 (40)	3 (15)	0
3–4 Weeks (n = 20)*	7 (37)	9 (47)	3 (16)	0	7 (35)	9 (45)	4 (20)	0
6–8 Weeks (n = 20)†	8 (42)	4 (21)	6 (32)	1 (5)	5 (26)	10 (53)	3 (16)	1 (5)
6 Months (n = 20)‡	9 (50)	7 (39)	2 (11)	0	7 (41)	10 (59)	0	0
12 Months (n = 14)§	7 (54)	6 (46)	0	0	8 (62)	5 (38)	0	0
18 Months (n = 3)	1 (33)	0	2 (67)	0	2 (67)	1 (33)	0	0
24 Months (n = 1)	1 (100)	0	0	0	0	1 (100)	0	0

* Physician evaluation not obtained for 1 patient; cosmesis was rated as excellent by this patient.

† Physician and patient evaluation not obtained for 1 patient; for both the preceding and subsequent time points, physician rated cosmesis as good and patient rated cosmesis as excellent.

‡ Physician and patient evaluation not obtained for 2 patients and patient evaluation not obtained for an additional patient. For the 2 patients without an evaluation, physician rated cosmesis as excellent and patients rated cosmesis as good and excellent at the preceding time point. Only 1 of these 2 patients has been seen for 12-month follow-up, and cosmesis was rated as excellent by the physician and good by the patient. For the patient with a physician evaluation but no self-evaluation, physician rated cosmesis as good.

§ Physician and patient evaluation not obtained for 1 patient. Physician rated cosmesis as fair at preceding and subsequent time points. Patient rated cosmesis as good and excellent at the preceding and subsequent time points, respectively (see Methods and Materials for definition of cosmesis grades).

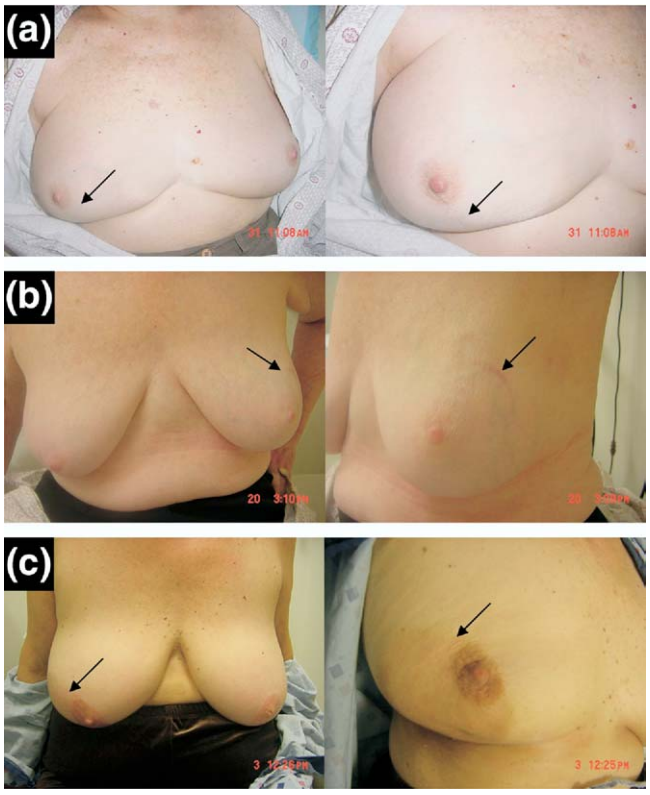

Fig. 1. Representative cosmetic outcomes at last follow-up (physician assessment). (a) Excellent cosmesis at 2 years. (b) Good cosmesis at 1 year. (c) Fair cosmesis at 18 months. Arrows highlight the treated area.

In 1 patient, an approximately 1-cm^2 telangiectasia first appeared at 6-month follow-up and has persisted. In the remaining 2 patients, the telangiectasia measured 2-cm^2 to 4-cm^2 and first appeared at 12-month and 24-month follow-up. For the patient with a 2- to 4-cm^2 telangiectasia first evident at 24 months, breast cosmesis was rated as excellent by the physician and good by the patient. The telangiectasia was noted in the inframammary fold and was not evident on global cosmetic assessment. Her 24-month follow-up examination is the example of an excellent cosmetic outcome, as shown in Fig. 1a.

Rib pain at the site of irradiation was reported by 3 patients. In 1 patient, the rib pain was first noted at 6 to 8 weeks follow-up and resolved by the 6-month follow-up. Review of this patient's radiation treatment plan demonstrated that the ribs did not lie within the high dose volume. In contrast, the 2 remaining patients had portions of underlying ribs within the high dose volume (32 CGE). In 1 of these patients, rib pain was first noted at 1 year and no further follow-up is available. In the second, the pain was first reported at 6-month follow-up and had been acutely exacerbated by violent coughing during a prolonged episode of bronchitis. Computed tomography revealed a rib fracture. The patient's rib pain resolved completely by 18-month follow-up.

Patient reported satisfaction with proton 3D-CPBI is shown in Table 4. At last follow-up, 95% of patients reported total satisfaction with proton 3D-CPBI. At no time did a patient endorse a preference for standard whole-breast irradiation.

DISCUSSION

Encouraging clinical results have led to intensified interest in PBI for the adjuvant treatment of fully excised, early-stage breast cancer (16–19). The bulk of these results derive from trials evaluating interstitial brachytherapy. As an alternative to brachytherapy, 3D-CPBI offers several

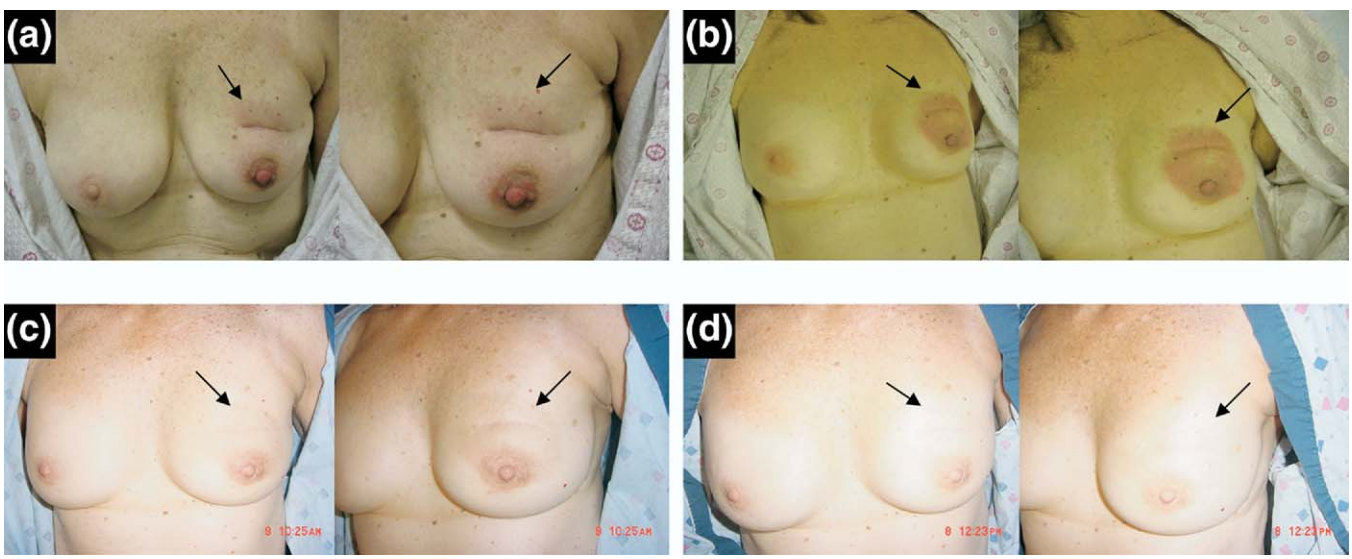

Fig. 2. Representative cosmetic time course for a single patient after proton 3D-CPBI (physician assessment). (a) Excellent cosmesis at 3 to 4 weeks. (b) Fair cosmesis at 6 to 8 weeks. (c) Good cosmesis at 6 months. (d) Excellent cosmesis at 12 months. Arrows highlight the treated area.

Table 3. Toxicities/complications

Parameter	Physician assessment (*n* (%))				Patient assessment (*n* (%))			
	None	Mild	Mod	Severe	None	Mild	Mod	Severe
Breast pain								
3–4 Weeks (*n* = 19/20)	10 (53)	7 (37)	2 (11)	0	9 (45)	8 (40)	2 (10)	1 (5)
6–8 Weeks (*n* = 19/19)	14 (74)	4 (21)	1 (5)	0	14 (74)	4 (21)	1 (5)	0
6 Months (*n* = 18/17)	14 (78)	4 (22)	0	0	12 (71)	5 (29)	0	0
12 Months (*n* = 13/13)	9 (69)	3 (23)	1 (8)	0	9 (69)	2 (15)	2 (15)	0
18 Months (*n* = 3/3)	3 (100)	0	0	0	3 (100)	0	0	0
24 Months (*n* = 1/1)	1 (100)	0	0	0	1 (100)	0	0	0
Breast edema								
3–4 Weeks (*n* = 19/20)	13 (68)	5 (26)	1 (5)	0	15 (75)	3 (15)	2 (10)	0
6–8 Weeks (*n* = 19/19)	15 (79)	4 (21)	0	0	15 (79)	3 (16)	1 (5)	0
6 Months (*n* = 18/17)	18 (100)	0	0	0	17 (100)	0	0	0
12 Months (*n* = 13/13)	12 (92)	1 (8)	0	0	12 (92)	1 (8)	0	0
18 Months (*n* = 3/3)	3 (100)	0	0	0	3 (100)	0	0	0
24 Months (*n* = 1/1)	1 (100)	0	0	0	1 (100)	0	0	0
Skin color changes								
3–4 Weeks (*n* = 19/20)	2 (11)	2 (11)	11 (58)	4 (21)	4 (20)	8 (40)	8 (40)	0
6–8 Weeks (*n* = 19/19)	5 (26)	4 (21)	3 (16)	7 (37)	4 (21)	7 (37)	7 (37)	1 (5)
6 Months (*n* = 18/17)	5 (28)	8 (44)	5 (28)	0	6 (35)	10 (59)	1 (6)	0
12 Months (*n* = 13/13)	6 (46)	4 (31)	3 (23)	0	7 (54)	6 (46)	0	0
18 Months (*n* = 3/3)	1 (33)	0	2 (67)	0	1 (33)	1 (33)	0	1 (33)
24 Months (*n* = 1/1)	1 (100)	0	0	0	1 (100)	0	0	0
Fibrosis/retraction								
3–4 Weeks (*n* = 19/20)	15 (79)	3 (16)	1 (5)	0	10 (50)	5 (25)	5 (25)	0
6–8 Weeks (*n* = 19/19)	16 (84)	3 (16)	0	0	11 (58)	6 (31)	2 (11)	0
6 Months (*n* = 18/17)	14 (78)	3 (17)	1 (6)	0	12 (71)	4 (24)	1 (6)	0
12 Months (*n* = 13/13)	11 (85)	2 (15)	0	0	12 (92)	0	1 (8)	0
18 Months (*n* = 3/3)	3 (100)	0	0	0	2 (67)	0	1 (33)	0
24 Months (*n* = 1/1)	0	1 (100)	0	0	1 (100)	0	0	0
Moist desquamation								
3–4 Weeks (*n* = 19/20)	15 (79)	2 (11)	2 (11)	0	11 (55)	4 (20)	3 (15)	2 (10)
6–8 Weeks (*n* = 19/19)	15 (79)	0	2 (11)	2 (11)	13 (68)	2 (11)	3 (16)	1 (5)
6 Months (*n* = 18/17)	18 (100)	0	0	0	15 (88)	2 (12)	0	0
12 Months (*n* = 13/13)	13 (100)	0	0	0	12 (92)	1 (8)	0	0
18 Months (*n* = 3/3)	3 (100)	0	0	0	3 (100)	0	0	0
24 Months (*n* = 1/1)	1 (100)	0	0	0	1 (100)	0	0	0

Abbreviation: Mod = moderate.

For each time point, *n* = x/y represents the number of evaluable responses from physicians (x) and patients (y) (for patient number, please see Table 2). Patients were asked to describe the severity of breast pain, breast swelling, skin color changes, thickening or lumpiness of the breast, or dimpling of the breast skin (fibrosis/retraction), and skin reactions that look red and possibly forming blisters and/or ulcers (moist desquamation).

distinct advantages including improved dose homogeneity and the elimination of additional breast trauma required by brachytherapy PBI. However, these advantages come at the expense of inferior target conformality and, consequently, larger volumes of irradiated nontarget tissue (12). In an effort to retain the advantages of 3D-CPBI while improving dose conformality, we investigated the use of protons in this setting (13). We report our initial clinical experience with proton 3D-CPBI after a median follow-up of 12 months.

Two institutions have reported clinical outcomes with photon-based, 3D-CPBI (20, 21). In a series of 31 patients treated with photon 3D-CPBI, Vicini *et al.* reported no local recurrences after a median follow-up of 10 months (20, 22). Similarly, Formenti *et al.* reported no local recurrences in a series of 47 patients treated with prone position, photon 3D-CPBI after a median follow-up of 18 months (21). Outcome data are not yet available for two additional photon 3D-CPBI series (22, 23). As seen with the early photon 3D-CPBI results, no recurrences were detected in the 20 patients treated with proton 3D-CPBI. In light of the short follow-up, small patient numbers, and favorable prognoses of enrolled patients, conclusions about the equivalence of 3D-CPBI to WBI are clearly premature. Nonetheless, preliminary results demonstrating no recurrences in any published 3D-CPBI series are reassuring.

Cosmetic outcomes of proton 3D-CPBI at 6 months and later are comparable to cosmetic outcomes reported for photon 3D-CPBI. Proton 3D-CPBI patients universally reported good to excellent cosmetic outcomes at 6-month, 12-month, and last follow-up despite fair cosmesis being reported by 15% of patients before radiotherapy. Physician evaluation was somewhat less favorable but good to excellent cosmetic outcomes were reported in at least 85% of

Table 4. Patient satisfaction

Time point	Totally satisfied, *n* (%)	Not totally satisfied; would choose PBI again, *n* (%)	Not totally satisfied; would choose WBI, *n* (%)
3–4 Weeks ($n = 20$)	19 (95)	1 (5)	0
6–8 Weeks ($n = 20$)*	15 (83)	3 (17)	0
6 Months ($n = 20$)†	15 (88)	2 (12)	0
12 Months ($n = 14$)‡	12 (92)	1 (8)	0
18 Months ($n = 3$)	3 (100)	0	0
24 Months ($n = 1$)	1 (100)	0	0

Abbreviations: PBI = partial-breast irradiation; WBI = whole-breast irradiation.

* Patient evaluation not obtained for 2 patients; for both the preceding and subsequent time points, patients reported total satisfaction.

† Patient evaluation not obtained for 3 patients. All 3 patients reported total satisfaction at the preceding time point. One patient has not been seen at 12-month follow-up; however, the remaining 2 patients reported total satisfaction at that time point.

‡ Patient evaluation not obtained for 1 patient. Patient reported "Not totally satisfied; would choose PBI again" at the preceding time point but reported total satisfaction at the subsequent time point.

cases at 6-month, 12-month, and last follow-up. In comparison, Formenti *et al.* reported 32 (94%) good to excellent cosmetic outcomes among 34 patients with at least 6-month follow-up (21). Similarly, Vicini *et al.* reported 100% good to excellent cosmetic outcomes in 18 patients with at least 6 months follow-up after photon 3D-CPBI (20).

Acute skin toxicity appears to be more severe with the proton 3D-CPBI technique used in our study than for patients treated with photon 3D-CPBI. Skin color changes peaked at 3 to 4 weeks when physicians noted moderate to severe changes in nearly 80% of patients. Moist desquamation peaked slightly later at the 6- to 8-week follow-up with moderate to severe desquamation noted in 22% of patients. In the William Beaumont Hospital experience with photon 3D-CPBI, Grade 0, 1, and 2 skin toxicities were observed in 29%, 61%, and 10% of patients 4 to 8 weeks after radiotherapy, respectively; no Grade 3 toxicity was seen (20). In Radiation Therapy Oncology Group (RTOG) protocol 0319, a Phase I/II trial to evaluate the feasibility of performing photon 3D-CPBI in a multicenter trial, acute (6-week) Grade 0, 1, 2, and 3 skin toxicity was observed in 40%, 42%, 15% and 2% of patients, respectively (22). Finally, Formenti and colleagues reported acute Grade 1 erythema in 56.7% of patients and Grade 2 erythema in 13.5% of patients treated with photon 3D-CPBI. In this series, only 5.4% of patients experienced any acute desquamation (21).

The increased acute skin toxicity associated with protons is readily explained by proton dosimetry and the technique used. Proton radiotherapy is delivered using spread-out Bragg peaks. This results in a higher entrance (i.e., skin) dose compared with high-energy photon fields (24). In many cases, particularly with relatively superficial target volumes, the skin dose approaches the dose maximum. In this series, even when multiple field plans were used, a single field was treated per fraction. Thus, fraction sizes to any treated skin approached the full 4 CGE delivered to the PTV. The clinical impact of this reduced skin-sparing and large fraction size was most notably evidenced in patients treated with a single proton field. Although only 2 of the 3 patients treated with a single field were evaluated at 6 to 8 weeks, both had suboptimal cosmetic results at that time point. One patient had a poor cosmetic outcome accompanied by severe moist desquamation and the other evaluated patient had a fair cosmetic outcome with moderate moist desquamation. For 2 of these 3 patients, physician-rated cosmesis at last follow-up was also suboptimal with outcomes rated as excellent for 1 patient (12 months) but only fair for the remaining 2 patients (18 months).

These observations led to a change in practice and no patients were subsequently treated with a one-field technique. In the future, only multiple field techniques will be used. Furthermore, when two proton fields are used, fields will not be allowed to overlap on the skin. Finally, efforts will be made to treat each field with every fraction. With these modifications, skin toxicity is expected to decline. Intensity-modulated proton therapy may also provide a means to reduce skin dose and, potentially, to reduce skin toxicity.

Despite significant resolution of acute skin toxicities by 6 months, concerns persist. Acute skin reactions have been shown to increase the risk of subsequent late skin toxicity (25–27). Acute skin reactions are strongly associated with subsequent telangiectasia and hyperpigmentation. Consequently, it is noteworthy that telangiectasia was observed in 3 patients among the 20 treated with this proton 3D-CPBI technique despite the relatively short follow-up. Furthermore, skin color changes have persisted in approximately 50% of patients for at least 12 months. After interstitial brachytherapy PBI, late skin color changes appear to increase in incidence for 2 years but then stabilize (28). In contrast, the incidence of Grade 1 telangiectasia increased from 5% at 6 months or less to 21% at 2 years and 42% at 5 or more years (28). Further follow-up of patients treated with proton 3D-CPBI is required to determine whether a comparable course for late skin toxicity is observed; how-

ever, an increase in the number of patients with telangiectasia is anticipated.

Bone damage, including rib fractures, is a well-documented complication of breast radiation therapy (29). Radiation-induced bone damage has been shown to be dependent on both total dose and fraction size (30). In an evaluation of radiation-induced rib fractures after postmastectomy chest wall irradiation, Overgaard reported that radiation regimens consisting of 12 fractions to a mean total dose of 46 to 51 Gy resulted in spontaneous rib fractures in 19% to 48% of patients, a 3- to 8-fold increase compared with that in a regimen consisting of 22 fractions to a mean total dose of 51 Gy (30). The risk of rib fracture after modern WBI is less than 2% (31). In our series, 3 patients treated with protons experienced postirradiation rib tenderness. In one instance, the rib pain was mild and transient and appeared very shortly after radiation therapy (6–8 weeks). Examination of isodose distributions in this patient also suggested the ribs were not within the volume receiving the prescribed dose. In contrast, the 2 remaining patients clearly had portions of anterior ribs within the volumes receiving the prescribed dose. In 1 patient, rib pain first appeared at 1 year and was localized to the site of irradiation. Additional follow-up for this patient is not yet available. In the remaining patient who experienced rib tenderness, pain was first reported 6 months after proton radiotherapy. The pain was exacerbated by violent coughing associated with a protracted bronchitis, and chest computed tomography revealed a rib fracture in the lateral 6th rib. Pain has since subsided. Initially, rib tenderness was not specifically evaluated during routine follow-up of 3D-CPBI patients. Consequently, the incidence of rib tenderness may be underestimated. However, based on these findings, rib tenderness is now systematically addressed at follow-up for all patients who received 3D-CPBI. Patient-reported rib pain may be unrelated to true bone toxicity (e.g., chest-wall myositis) or even unrelated to treatment (e.g., cough). However, these observations suggest that as investigations of 3D-CPBI proceed, critical attention will need to be paid to both rib dosimetry and toxicity. In addition, prone patient positioning may permit reductions in rib radiation doses and merits investigation particularly in patients in whom rib-sparing, supine 3D-CPBI plans cannot be generated.

Despite relatively high rates of acute skin toxicity, patients treated with proton 3D-CPBI expressed nearly universal satisfaction with this treatment regimen. Patient satisfaction did appear to track with skin reactions. The few instances of less than total satisfaction with proton 3D-CPBI clustered at early time points when skin reactions were most severe. Nonetheless, patient approval of this treatment regimen was the rule, with more than 90% of all responses indicating total satisfaction. In part, the overwhelming satisfaction with proton 3D-CPBI reflects growing patient interest in more convenient approaches to adjuvant radiotherapy for early-stage breast cancer. These findings emphasize the urgent need for solid evidence to support the equivalence of PBI to standard WBI that will only be available after completion of Phase III trials, such as the National Surgical Adjuvant Breast and Bowel Project Protocol B39 (RTOG 0413). In the absence of such data, strong patient preferences, rather than irrefutable evidence, may drive patterns of adjuvant breast cancer care.

A recent cost analysis suggested that proton 3D-CPBI was less expensive than both intracavitary and interstitial brachytherapy PBI while being 25% more expensive than standard WBI (13). In addition, the availability of proton radiation is anticipated to increase with 4 new facilities expected to begin treatment in 2006 worldwide including centers at M. D. Anderson Cancer Center and the University of Florida (13, 24). Consequently, the role for this technology in breast cancer treatment requires careful examination. The series reported here represents the first step in defining the utility of proton radiotherapy in 3D-CPBI and provides a foundation for further clinical investigation.

CONCLUSION

Proton 3D-CPBI offers dosimetric advantages over photon 3D-CPBI and provides comparable cosmetic outcomes in the short term. Patient satisfaction with proton 3D-CPBI is exceptionally high. However, as initially used, proton 3D-CPBI results in more acute skin toxicity than does photon 3D-CPBI, and preliminary results suggest this may translate into higher rates of late skin toxicity, particularly telangiectasia. Modifications in treatment technique may improve the acute skin tolerance of proton 3D-CPBI and are the subject of ongoing clinical investigations.

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