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Clinical Investigation

Partial Breast Radiation Therapy With Proton Beam: 5-Year Results With Cosmetic Outcomes

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Summary

Patients with early stage, nonlobular breast carcinoma were treated with partial breast irradiation using proton beam therapy in this phase 2 trial to determine efficacy, toxicity, and cosmetic results. One hundred subjects received 40 Gy in 10 fractions and had a median follow-up of 5 years. The in-breast recurrence-free survival rate was 97%, with low-grade skin toxicity. The cosmetic results assessed by patients and physicians were good to excellent in 90% of subjects and were well maintained through 5 years.

Purpose: We updated our previous report of a phase 2 trial using proton beam radiation therapy to deliver partial breast irradiation (PBI) in patients with early stage breast cancer.

Methods and Materials: Eligible subjects had invasive nonlobular carcinoma with a maximal dimension of 3 cm. Patients underwent partial mastectomy with negative margins; axillary lymph nodes were negative on sampling. Subjects received postoperative proton beam radiation therapy to the surgical bed. The dose delivered was 40 Gy in 10 fractions, once daily over 2 weeks. Multiple fields were treated daily, and skin-sparing techniques were used. Following treatment, patients were evaluated with clinical assessments and annual mammograms to monitor toxicity, tumor recurrence, and cosmesis.

Results: One hundred subjects were enrolled and treated. All patients completed the assigned treatment and were available for post-treatment analysis. The median follow-up was 60 months. Patients had a mean age of 63 years; 90% had ductal histology; the average tumor size was 1.3 cm. Actuarial data at 5 years included ipsilateral breast tumor recurrence-free survival of 97% (95% confidence interval: 100%-93%); disease-free survival of 94%; and overall survival of 95%. There were no cases of grade 3 or higher acute skin reactions, and late skin reactions included 7 cases of grade 1 telangiectasia. Patient- and physician-reported cosmesis was good to excellent in 90% of responses, was not changed from baseline measurements, and was well maintained throughout the entire 5-year follow-up period.

Conclusions: Proton beam radiation therapy for PBI produced excellent ipsilateral breast recurrence-free survival with minimal toxicity. The treatment proved to be adaptable to all breast sizes and lumpectomy cavity configurations. Cosmetic results

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appear to be excellent and unchanged from baseline out to 5 years following treatment. Cosmetic results may be improved over those reported with photon-based techniques due to reduced breast tissue exposure with proton beam, skin-sparing techniques, and the dose fractionation schedule used in this trial.

Introduction

Postoperative radiation therapy following a partial mastectomy is a well-established treatment for early stage breast cancer and has been shown to reduce breast tumor recurrence and improve survival (1, 2). For patients with small tumors, partial breast irradiation (PBI) may be as effective as whole-breast treatment, allowing shorter treatment courses and the potential for reduced side effects (3). These treatments are currently being compared in national randomized trials.

Multiple techniques are available to deliver PBI, including interstitial brachytherapy, intracavity radiation therapy, intraoperative radiation therapy, and external beam radiation therapy. There is currently no consensus as to which of these techniques is most efficacious. The goal of any PBI technique is to irradiate disease in the tumor bed and immediately surrounding tissues, while minimizing and/or eliminating exposure of nearby normal tissues such as heart, lung, and normal breast tissue. Treating smaller target volumes also allows the possibility of fractionation schedules that can substantially reduce the overall time of treatment. For external beam treatments, multiple published trials have compared proton beam radiation therapy to other PBI techniques in terms of dosimetric treatment planning (4–6). Those trials demonstrate improved sparing of normal tissues with the use of proton beam, suggesting it could be an excellent modality to achieve the above-stated goals. We initiated a phase 2 trial in an effort to demonstrate the efficacy and define the toxicity of the use of proton beam therapy for PBI, with the primary endpoint being freedom from breast tumor recurrence. In this report, we present an update to our previous reported results.

Methods and Materials

A phase 2 clinical trial was developed and received approval from the institutional review board at Loma Linda University Medical Center and was registered as national clinical trial NCT00614172. Eligible subjects had pathologically proven invasive carcinoma of the breast, following a partial mastectomy. Patients with invasive lobular carcinoma were excluded. All subjects were required to undergo sampling of the axillary lymph nodes via axillary lymph node biopsy or sentinel lymph node biopsy. All sampled nodes were required to be pathologically negative. Pathologic margins of the specimen were required to be negative by a minimum of 2 mm. Surgical clips were placed within the surgical cavity to allow identification of the surgical site and serve as fiducial markers for alignment of radiation fields. Exclusion criteria included patients with primary tumors greater than 3 cm in size and the presence of extensive ductal carcinoma in situ. Patients were treated once they had completely healed from their surgical procedure and prior to initiation of any systemic therapy.

All patients underwent a procedure in which a customized, rigid immobilization device was used to support the ipsilateral breast with the patient in a prone position while holding the contralateral breast away from the treatment area. This technique was chosen to minimize day-to-day setup variations, to ensure that the skin surface of the breast was immobilized in a reproducible way, and to eliminate respiration-induced breast motion. The technique has been described in detail in a previous publication (7). A computed tomography (CT) scan of the patient's chest was obtained with the patient in the treatment position to allow for computer-aided treatment planning. The lumpectomy cavity was identified and contoured using postsurgical seroma and surgical clips placed at the time of partial mastectomy. A 1-cm margin was created around the lumpectomy cavity which was edited from the skin of the breast and chest wall as needed. This volume served as the clinical target volume (CTV). An additional margin of 2 mm was added for daily setup variations. A multibeam proton plan was developed which generally required the use of 2 to 4 separate proton beam angles. If necessary, each individual beam aperture was edited to keep the composite 90% isodose line within the surface of the skin (Fig. 1). The prescribed dose was 40 Gy delivered in 10 fractions over 2 weeks. Daily treatments used image-guided therapy with in-room kilovoltage orthogonal imaging to place each treatment field. The surgical clips were used as fiducial markers for beam placement. Multiple fields were treated each day for all patients. All patients were followed for acute skin reactions, then at every 6 months with clinical examinations, and annually with mammograms and chest x-rays. Annual cosmetic assessments from the patient and the treating physician were obtained by using the Harvard scale method (8). Patients were evaluated by a medical oncologist to assess the need for adjuvant systemic therapy, although the study design did not require systemic therapy to be given.

Results

One-hundred subjects were enrolled and treated in this trial with a median follow-up of 60 months. All patients completed their assigned treatments without interruptions. Patient characteristics are seen in Table 1. Most patients

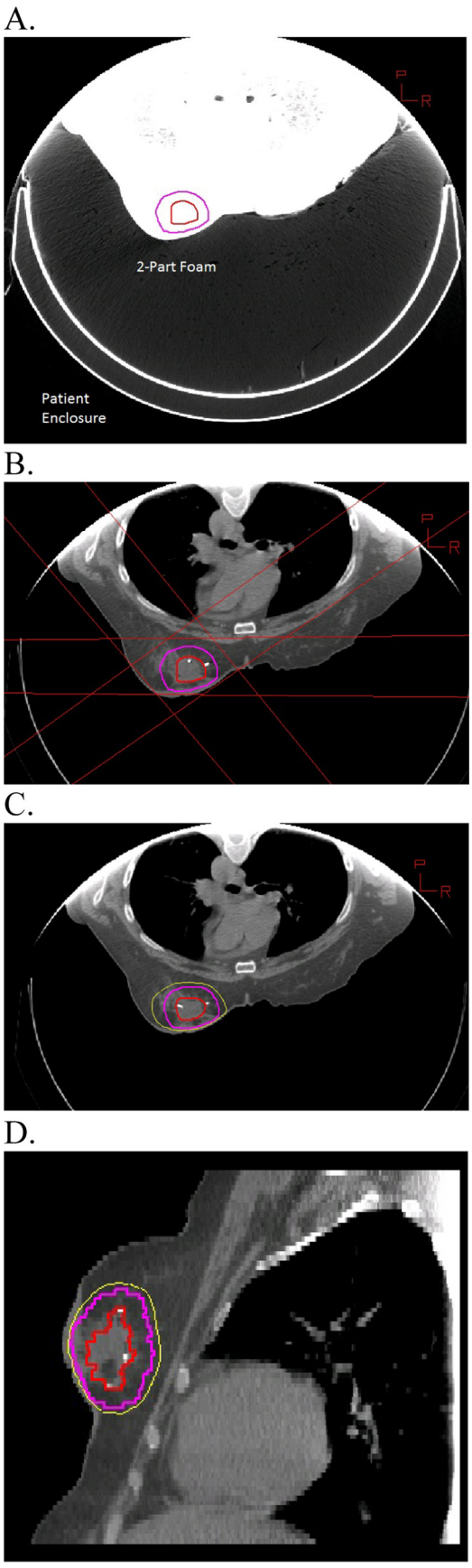

Fig. 1. The process of immobilization and skin-sparing treatment planning. (A) Prone immobilization with custom-made device to provide rigid support to the treated breast. (B) Left lateral view of LAO and RAO beams with beam edges modified to reduce skin dose. (C and D) Axial and sagittal images show the 90% isodose line within the skin surface. The lumpectomy cavity and CTV are outlined in red and pink respectively. CTV = clinical target volume; LAO = left anterior oblique; RAO = right anterior oblique.

had ductal histology, with a relatively even distribution between the right and left breasts. Mean tumor size was 1.3 cm, with most being estrogen receptor (ER) and progesterone receptor (PR) positive. Chemotherapy was given to 13% of the subjects following proton therapy, and 78% received hormone therapy. Survival endpoints were calculated using the Kaplan-Meier method. The 5-year breast tumor recurrence-free survival rate was 97% (95% confidence interval: 93%-100%) as shown in Figure 2. There were no local failures with recurrence at the original tumor site. The 5-year disease-free survival and overall survival rates were 94% and 95%, respectively.

Acute toxicity was monitored during therapy and during the 3 months following treatment completion. Toxicity to the skin during this time period included mild to moderate radiation dermatitis in 62% (graded as 1 or 2). There were no cases of grade 3 or higher skin toxicity, nor were other acute toxicities encountered. Late skin reactions included primarily development of grade 1 telangiectasias in 7% of the population. There was one case of clinical fat necrosis at 1 year after treatment that required drainage. There were no reported cases of rib fractures, clinical pneumonitis, or cardiac events during this follow-up period.

Patients and their treating physicians were surveyed each year during the follow-up period to assess the cosmetic results of the treated breast. A scale using excellent, good, fair, or poor was used to assess the cosmetic outcome. The percentages indicating a good or excellent cosmetic result at baseline and annually following treatment are shown in Figure 3. A good to excellent result of 90% was well maintained through 5 years of follow-up, with none of the assessments being statistically different from the baseline evaluation.

Discussion

PBI is being used with increasing frequency as an alternative to whole-breast radiation therapy (9). The rationale for the technique is based primarily on the ability to reduce the exposure of healthy tissues such as the lung, chest wall, and heart to irradiation. It is assumed that this would lead to a reduced frequency of complications in these structures. External beam radiation therapy has proven to be a commonly used method to deliver this treatment as it does not require an additional invasive procedure, unlike brachytherapy procedures. Although multiple methods of PBI delivery currently exist, there are no direct

Table 1 Patient characteristics

Subjects	Medical follow-up (60 months)
Age (yrs)	
Average	63
Range	41-83
Carcinoma histology type	
Ductal	90
Mucinous	5
Tubular	4
Medullary	1
Involved breast	
Right	48
Left	52
Tumor size (cm)	
Average	1.3
Range	0.3-2.8
Stage	
T1a	8
T1b	44
T1c	34
T2	14
Estrogen receptor status	
ER+	88
PR+	70

Abbreviation: ER = estrogen receptor.

comparisons of any of these techniques, leaving the decision in the hands of the patients and physicians.

External beam radiation therapy techniques to date primarily include photon-based methods using three-dimensional treatment planning. The physical properties inherent in proton therapy, however, have advantages over all photon techniques due to the Bragg peak effect. Multiple treatment planning comparisons have demonstrated that all normal tissue regions including heart, lung, chest wall, and normal breast tissue can be better protected with the use of proton beams. The clinical results presented in this report represent the largest, most mature data to date

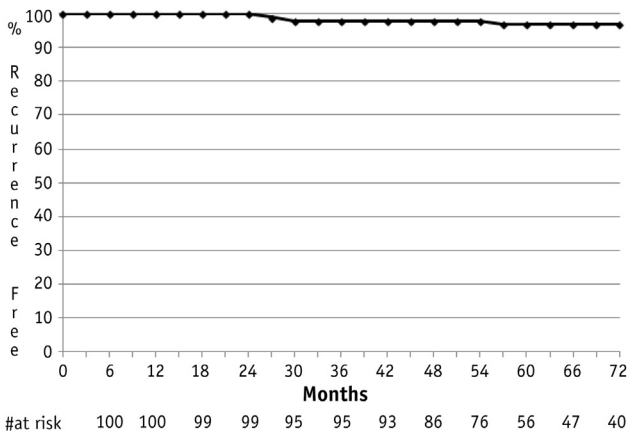

Fig. 2. Ipsilateral breast tumor-free survival.

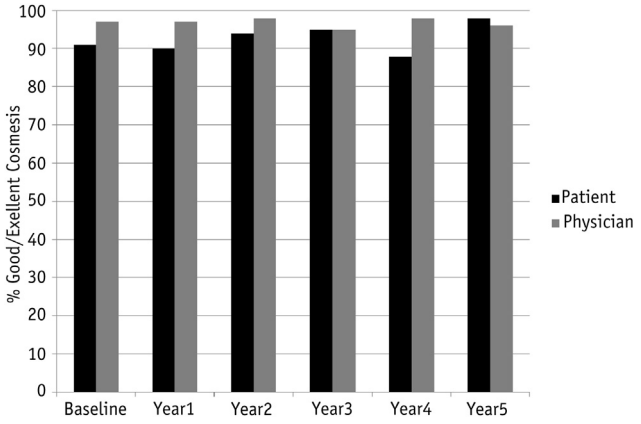

Fig. 3. Baseline and annual cosmetic survey results from patients and physicians.

describing results with the use of proton beams in patients eligible for PBI. All disease control endpoints and overall survival were excellent and are comparable to those produced with other PBI treatment methods. The object of PBI, however, is not to improve survival and tumor recurrence outcomes. The purpose of the technique is to minimize side effects and toxicities. Acute skin toxicity is a major concern when using proton therapy for PBI, as demonstrated in a previous report by Kozak et al (10), which reported an unacceptably high skin toxicity rate. In our trial, a unique immobilization system was developed in an effort to provide a reproducible position as well as one that allows the skin surface of the breast to be rigidly immobilized. This allows customized shaping of each individual proton beam in a way that can keep the 90% isodose line below the surface of the skin. This technique, along with the use of multiple treatment fields, was used for each case treated in this report, in contrast to the treatment method described by Kozak et al (10), which specified no skin-sparing techniques and used one treatment field per day. The technique appears to produce clinical results that protect the skin from serious acute toxicities as well as having a low rate (7%) of telangiectasia developing 5 years out from treatment, compared to 17% reported with photons in the Randomized Trial of Accelerated Partial Breast Irradiation (RAPID) trial (11). We would encourage any center interested in using proton beams for PBI to carefully consider using multiple beam arrangements and immobilization systems that allow reproducible positioning of the skin surface to provide reliable measurements of skin dose reduction. This technique of fixed breast immobilization, fiducial markers, and image guidance also allows treatment to be delivered with reduced margins, which can further decrease dose to nontarget breast tissue.

The cosmetic result in the treated breast is also an important endpoint for any breast cancer treatment. Breast-conserving therapy, as opposed to mastectomy, is done primarily for organ preservation and to provide a good cosmetic result. There have been reports associating poor

cosmetic outcomes with external beam techniques using photon therapy for PBI (12, 13). These have been shown to be correlated with the volume of normal breast tissue encompassed by the moderate and high-dose isodose curves. There have also been questions as to the durability of the cosmetic result with years of follow-up demonstrating a reduced satisfaction with the cosmetic result as time passes, as described in the RAPID trial (11). In our trial, we have demonstrated that the cosmetic results over a 5-year period following treatment are not significantly changed from those reported at baseline. If the cosmetic results achieved with proton beams are truly superior to those produced with photon techniques, we would offer two possible explanations. First, it has been demonstrated that proton beam irradiates less breast tissue than photon techniques do, which has been correlated with improved cosmetic outcomes (13). Second, the dose and fractionation schedule are likely to be important in late fibrotic complications, which can lead to poor cosmetic outcomes. Most reports describing photon PBI used an accelerated hyperfractionated schedule (14). Typically, doses in the range of 35 to 40 Gy were delivered in a 1-week treatment course using multiple fractions per day. Radiobiological rationale would suggest that such schedules may be beneficial from a tumor control standpoint, for unresectable tumors that have a rapid growth rate. This, however, is not the case with breast carcinoma following gross total resection. Such dosing has been used primarily to reproduce PBI schedules, given with interstitial brachytherapy, where catheters need to be removed within a week to minimize risk of infection. It is possible that these aggressive treatment schedules could lead to increased late toxicity such as fibrosis. When our trial was initiated, it was felt that twice-daily treatments were unnecessary for this clinical indication. Thus, we used a daily treatment schedule that would deliver the equivalent of a postoperative dose over a 2-week course, which may allow a greater extent of normal tissue repair and less fibrosis. In our experience, this treatment schedule proved to be convenient both to the patient and treatment facility.

Conclusions

Based on the results seen in our trial, we conclude that proton PBI can provide excellent results in terms of disease control, toxicity profile, and cosmetic results that may be used in patients who qualify for PBI. We have initiated a second phase 2 trial in an effort to explore expanding the indications for this treatment method and will continue to follow patients we have treated for long-term outcomes.

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