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Proton therapy in breast cancer

Proton beam radiotherapy as part of comprehensive regional nodal irradiation for locally advanced breast cancer

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ABSTRACT

Purpose: This study evaluates acute toxicity outcomes in breast cancer patients treated with adjuvant proton beam therapy (PBT).
Methods: From 2011 to 2016, 91 patients (93 cancers) were treated with adjuvant PBT targeting the intact breast/chest wall and comprehensive regional nodes including the axilla, supraclavicular fossa, and internal mammary lymph nodes. Toxicity was recorded weekly during treatment, one month following treatment, and then every 6 months according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Charts were retrospectively reviewed to verify toxicities, patient parameters, disease and treatment characteristics, and disease-related outcomes.
Results: Median follow-up was 15.5 months. Median PBT dose was 50.4 Gray relative biological effectiveness (GyRBE), with subsequent boost as clinically indicated ($N = 61$, median 10 GyRBE). Chemotherapy, when administered, was given adjuvantly ($N = 42$) or neoadjuvantly ($N = 46$). Grades 1, 2, and 3 dermatitis occurred in 23%, 72%, and 5%, respectively. Eight percent required treatment breaks owing to dermatitis. Median time to resolution of dermatitis was 32 days. Grades 1, 2, and 3 esophagitis developed in 31%, 33%, and 0%, respectively.
Conclusions: PBT displays acceptable toxicity in the setting of comprehensive regional nodal irradiation.

In recent years, there has been an increased focus on cardiac doses in breast radiotherapy (RT), and potential morbidity and mortality from radiation-induced cardiotoxicity [1,2]. Because of this, breast cancer radiotherapy techniques have evolved to further minimize cardiac dose, and potentially the associated long-term sequelae. Proton beam therapy (PBT) offers decreased dose to the heart and other organs at risk (OARs) as demonstrated by multiple published dosimetric analyses [3–9].

The concern regarding cardiotoxicity is amplified by recent data supporting the use of comprehensive regional nodal irradiation (CRNI), defined as elective treatment to axillary levels I-III, supraclavicular (SCV), and internal mammary lymph nodes (IMNs) [10–13]. Specifically, owing to the close anatomic proximity of the IMNs to the heart, performing CRNI can increase cardiac dose and thus the risk of long-term radiation-induced cardiotoxicity. Therefore, using PBT in the setting of CRNI may be advantageous by means of cardiac dose reduction. This notion has been corroborated dosimetrically, as several proton studies including IMN targets have reported lower mean heart doses [3,14–17].

However, clinical data examining the toxicity of this new technology are lacking thus far, and to date consist of three studies examining 12 [18], 18 [19], and 30 [20] patients. This report aims to expand on these data by evaluating toxicities in a single-institutional cohort of 93 breast cancer cases treated in 91 patients. For the first time, we also describe use of the emerging technique of pencil beam scanning (PBS) for breast cancer.

Materials and methods

Patients

Patients who received PBT at a single institution (2011–2016) for a breast cancer diagnosis ($N = 122$) were initially identified by searching specific breast cancer ICD-9 and 10 codes within the electronic medical record. Patients were included if they received primary adjuvant PBT to either the intact breast or chest wall plus the comprehensive regional lymphatics including axillary levels I-III, SCV, and IMNs. The presence of higher-risk disease in young

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patients warranting CRNI was an indication for PBT per the treating physician, to potentially spare radiation dose to the heart, contralateral breast, and other organs-at-risk to reduce the risk of long-term toxicity. Patients were excluded based on the following criteria: re-irradiation ($N = 21$), aggressive palliation in an inoperable patient ($N = 1$), partial breast irradiation ($N = 2$), isolated axillary recurrences ($N = 4$), or treatment to sites of distant metastatic disease ($N = 2$). One further patient who electively stopped treatment after 5 fractions was also excluded. In total, 91 patients met criteria for analysis. Patient records were reviewed in accordance with our institutional Advancements Through Outcomes Measures (ATOM) protocol and the Health Insurance Portability and Accountability Act (HIPAA).

Initial workup of all patients included diagnostic mammogram, breast and axillary ultrasound, and histological diagnosis. Breast MRI and metastatic workup with PET-CT and/or CT plus bone scan were obtained if deemed appropriate by the physicians evaluating the patient at initial diagnosis. Staging was determined by the American Joint Committee on Cancer TNM staging system (7th edition, 2010). Patients underwent mastectomy or breast conserving surgery with axillary management at the discretion of the treating surgeon. Chemotherapy regimens were determined by the treating medical oncologist. Whenever possible, multidisciplinary input guided patient treatment.

Radiotherapy

Custom immobilization was achieved using an alpha cradle, and CT simulation was then performed in the treatment planning position ($n = 20$ akimbo, $n = 71$ arms raised). Contouring was performed in Velocity (Varian Medical Systems, Palo Alto, CA) and treatment planning was performed using Xio software (Stockholm, Sweden) for patients treated with uniform scanning proton therapy, and in RayStation (RaySearch Corporation, Stockholm, Sweden) for patients treated with pencil beam scanning. Contouring of the tumor bed and the intact whole breast/chest wall clinical target volume (CTV) was performed based on Radiation Therapy Oncology Group consensus guidelines [21], with several modifications. These included extension of the breast/chest wall contours to the superficial aspect of the ribs/intercostals. Nodal contours covered contiguous draining lymphatic pathways including posterior to the clavicle. As part of CRNI, axillary levels I-III (depending on whether dissection versus sentinel node biopsy was performed), supraclavicular (SCV), and internal mammary nodes (IMNs) were treated. For patients with clinically positive IMNs located inferior to the volumes suggested by the RTOG atlas, the caudal extent of the volume was one intercostal level below the positive node. Planning target volume (PTV) in the post-mastectomy setting was defined as the nodal and chest wall CTV + 5 mm minus skin. In the setting of breast conservation, PTV was defined as a 7 mm expansion on intact breast and a 5 mm expansion on the nodal CTV.

In part because dosimetric nuances of PBT in the setting of CRNI are not well-defined, there is no consensus on dose constraints. In this study, cardiac dose constraints were V20 $\leq$21% of the prescribed dose; the heart V5 was $\leq$50% and $\leq$40% for left- and right-sided cases, respectively. Lung constraints included ipsilateral V20 $\leq$33% and V5 $\leq$42%, and contralateral V5 $\leq$10%. The maximum doses to 0.03 cm^3 of the esophagus and ipsilateral humeral head were set at <40 and <45 Gy RBE, respectively. Skin constraints varied over time, in part owing to the lack of well-defined constraints in the literature. Prior to September 2014, the PTV V110 hot spot goal was $\leq$10%. In September 2014, the PTV V110 goal was reduced to $\leq$3.5% when an internal review of dosimetry correlated PTV V110 $\leq$3.4% to acute grade 2 or higher skin toxicity [22]. The dose to 1 cm^3 (skin-PTV) was to be <115%. Evaluation CTV dose coverage included a D95% of 100% of the prescription dose, along with D99% of 95%.

PBT consisted of a three-dimensional uniform scanning (US) technique, followed by transition to a PBS technique in 2016 when this technology became available at our institution. This change was largely spurred from potential dosimetric advantages, such as decreased dose to skin surface and improvement in homogeneity. Secondary benefits included further dose reduction to cardiopulmonary organs, along with shorter planning and delivery time. For the US technique, patients were most commonly treated with a 4-beam arrangement consisting of superior and inferior anterior oblique fields plus superior and inferior anterosuperior oblique fields with offset matchlines. Treating all 4 fields per day versus alternating matchlines every other day was left to the treating radiation oncologist per plan evaluation. All US fields required custom apertures and compensators for lateral and distal beam shaping, respectively. PBS plans were treated using a single field.

Median dose to initial fields was 50.4 Gy relative biological effectiveness (RBE) (range, 44.8–50.4). Patients treated with breast conservation received a lumpectomy bed boost with a median dose of 10.0 Gy RBE (range, 8.0–16.0). Patients receiving postmastectomy PBT received a scar boost at the discretion of the treating physician; median dose 10.0 Gy RBE (range, 8.0–19.8).

Toxicity

Toxicity was recorded according to CTCAE version 4.0 weekly during treatment, 1 month following treatment and then every 6 months. Particular attention was paid to dermatitis, pain, skin infection, esophagitis and fatigue. In each follow-up visit, the time to resolution of the toxicity was evaluated. Late toxicity assessment also included pneumonitis and rib fracture.

Follow-up

Follow-up, defined from the end date of PBT, included clinical examination every 6 months following PBT. Mammography was performed annually for patients with breast conservation; imaging was ordered at the consensus recommendation of the surgeon, medical oncologist and radiation oncologist for postmastectomy patients. Patient charts were retrospectively reviewed to verify toxicities and to assess disease control. Follow-up chest computed tomography and/or systemic imaging was not routinely performed unless symptomatic or clinical examination prompted such. Locoregional failures were defined as imaging evidence of tumor in the ipsilateral breast or chest wall and/or ipsilateral regional lymphatics. All other failures were categorized as distant.

Results

Patient population

Table 1 displays complete clinicopathologic characteristics of the patient population. Ninety-three instances of breast cancer were treated in 91 patients ($N = 56$ left side, $N = 33$ right side, $N = 2$ bilateral). Median tumor size was 3.1 (range, 0.9–15.5) cm, and median age was 54 (range, 25–78) years. Table 2 illustrates treatment parameters. Twenty-nine percent ($N = 27$) received treatment to the intact breast in the setting of breast conservation, and 71% ($N = 66$) of patients were treated to the chest wall in the postmastectomy setting. Thirty-one of 87 postmastectomy patients (47%) underwent immediate reconstruction prior to PBT (total 33 instances). Margins were negative in 79 cases (85%); those with initially positive margins underwent re-excision. All but three patients underwent chemotherapy, with a nearly uniform split between adjuvant ($n = 42$, 46%) and neoadjuvant ($n = 46$, 51%)