Purpose

Dosimetric planning studies have described potential benefits for the use of proton radiation therapy (RT) for locally advanced breast cancer. We report acute toxicities and feasibility of proton delivery for 12 women treated with postmastectomy proton radiation with or without reconstruction.

Methods and Materials

Twelve patients were enrolled in an institutional review board-approved prospective clinical trial. The patients were assessed for skin toxicity, fatigue, and radiation pneumonitis during treatment and at 4 and 8 weeks after the completion of therapy. All patients consented to have photographs taken for documentation of skin toxicity.

Results

Eleven of 12 patients had left-sided breast cancer. One patient was treated for right-sided breast cancer with bilateral implants. Five women had permanent implants at the time of RT, and 7 did not have immediate reconstruction. All patients completed proton RT to a dose of 50.4 Gy (relative biological effectiveness [RBE]) to the chest wall and 45 to 50.4 Gy (RBE) to the regional lymphatics. No photon or electron component was used. The maximum skin toxicity during radiation was grade 2, according to the Common Terminology Criteria for Adverse Events (CTCAE). The maximum CTCAE fatigue was grade 3. There have been no cases of RT pneumonitis to date.

Conclusions

Proton RT for postmastectomy RT is feasible and well tolerated. This treatment may be warranted for selected patients with unfavorable cardiac anatomy, immediate reconstruction, or both that otherwise limits optimal RT delivery using standard methods.
Proton radiation is a form of particle radiation that allows for sparing of tissues distal to the target volume. Comparative planning studies for breast cancer patients suggest potential benefits for protons over standard radiation by improving target volume coverage and cardiopulmonary sparing. The entrance dose is higher for proton radiation, leading to some concern regarding skin tolerance. We report early outcomes in 12 women treated with postmastectomy proton radiation therapy on a prospective clinical trial.

Summary

Introduction

It is well established that postmastectomy radiation therapy (PMRT) improves disease-free survival and overall survival for locally advanced breast cancer (1). The goal of PMRT is to eradicate microscopic disease present in the chest wall and draining lymphatics. The challenge of delivering PMRT, especially for patients with left-sided disease, is to achieve a homogeneous therapeutic dose to target volumes while sparing healthy uninvolved tissues such as the heart and lungs. Standard external beam RT (EBRT) to the chest wall and regional lymphatics carries risks of cardiopulmonary toxicities, including radiation pneumonitis, pericardial disease, congestive heart failure, and coronary atherosclerosis (2, 3, 4). Although modern techniques minimize high-dose RT to avoidance structures, some patients with advanced disease, unfavorable anatomy, or both still present a challenge for RT planning, and compromise in target coverage or sparing of cardiopulmonary structures is often necessary. Early RT trials notably reported an increase in morbidity and mortality resulting from cardiac disease, predominantly in patients treated for left-sided breast cancer (5, 6). Lung toxicity, namely radiation pneumonitis, is reported in up to 5% of patients treated with breast or chest wall EBRT, with this risk increasing to as high as 14.6% with the use of concurrent chemotherapy (7, 8). Given the longevity expected in this patient population, these toxicities could potentially negate the benefits obtained from PMRT in some patients.

Breast reconstruction is now considered an integral component of treatment for invasive breast cancer. The decision to proceed with immediate or delayed reconstruction, however, often depends on the use of adjuvant RT. The benefits of immediate breast reconstruction are well known, including the need for only 1 surgical procedure, reduced costs, and psychosocial benefits for the patient. Owing to interference with RT delivery, however, patients are often recommended to delay reconstruction (9). Furthermore, bilateral mastectomy rates have continued to increase over the past 2 decades, in part because of the use of contralateral prophylactic mastectomy (10, 11). This scenario is particularly challenging for conventional PMRT planning because of the limitations in beam angles and often the inability to use electrons (9).

The physical properties of protons allow for the delivery of RT to the chest wall and draining lymphatics with radiobiological effectiveness similar to that of photon radiation therapy and nearly complete avoidance of cardiopulmonary structures. Additionally, given that proton fields are delivered en face, there is less effect of respiratory motion compared with photons (12). Previous comparative treatment planning studies show that proton therapy improves target coverage and dose homogeneity, decreases the dose to cardiac and pulmonary structures, and provides the lowest integral dose to surrounding tissues when compared with standard photons or intensity modulated RT (13). Protons also allow for RT in patients with immediate reconstruction without compromise of treatment plan or need for additional procedure to remove or reduce the size of the implant.
The dose delivered to the skin with 3-dimensional (3D) conformal protons is a full prescription dose, which is slightly higher than most PMRT techniques (ie, photons with 3-5 mm of bolus and electrons) and noticeably higher than whole-breast RT (ie, 6-MV photons) (13). For this reason, it is important to assess acute skin toxicity of proton treatment. We chose the postmastectomy population because of the desired increased skin dose and a perceived greater likelihood of encountering anatomy that would be technically challenging to treat with standard RT. Given that this is a population of patients for whom no clinical experience has been reported to date for the use of protons, to our knowledge, it is also important to monitor these patients for additional outcomes, and this is best done in the setting of a clinical trial.

We report the first clinical experience, to our knowledge, for the use of proton RT to treat breast cancer after mastectomy for patients in a prospective phase 1/2 trial. We describe the occurrence of skin toxicity, acute radiation pneumonitis, and fatigue during and within 8 weeks after the completion of RT.

Methods and Materials

Clinical trial

The primary objectives of this study were to determine the feasibility of using proton radiation for the treatment of invasive breast cancer after mastectomy based on the occurrence of grade 3 or higher radiation pneumonitis or any grade 4 toxicity within 3 months after the completion of radiation treatment.

Patient population

Twelve women with histologically confirmed invasive cancer confined to the breast and regional lymphatics were referred to the Massachusetts General Hospital for definitive chest wall radiation with or without regional lymphatic radiation using proton radiation in a prospective institutional review board-approved trial (clinicaltrials.gov # NCT01340495). All patients completed definitive mastectomy with or without adjuvant chemotherapy, hormone therapy, or both and were eligible for the study if they were considered to have unfavorable cardiac anatomy defined by an estimated dose ≥5% of heart receiving 20 Gy, the left anterior descending artery (LAD) receiving ≥20 Gy, or both, with conventional planning. Women with left-sided or right-sided breast cancer having immediate reconstruction with permanent implant(s) were also eligible if they were subsequently determined to have a suboptimal plan with conventional technique without removal or manipulation of breast implants. Patients with expanders or those who underwent breast conservation were not eligible. All patients with nodal involvement underwent computed tomography (CT) of the chest and abdomen and a bone scan to rule out metastatic disease. Each patient was evaluated for potential internal mammary node (IMN) metastasis based on CT or magnetic resonance imaging (MRI).

Radiation therapy technique

For RT planning, all patients underwent a CT scan with intravenous contrast medium for delineation of the LAD and left ventricle (2 patients did not receive intravenous contrast medium). The patients were immobilized with a custom Civco breast board in the supine position. Organs at risk were contoured according to Radiation Therapy Oncology Group guidelines with the exception of the chest wall volume, which did not include the ribs and deep portion of the intercostal muscles, by a board-certified radiation oncologist at the Massachusetts General Hospital (14). The chest wall did not include the ribs because the ribs are not considered to be at risk of harboring microscopic disease, and the inclusion of bone at the chest wall lung interface would have led to an increased volume of lung receiving proton radiation. The left
ventricle and region of the LAD were contoured as well (15). All patients were treated with passively scattered proton spread-out Bragg peak (SOBP) fields to 50.4 Gy (relative biological effectiveness [RBE]) to the chest wall and 45 to 50.4 Gy (RBE) to the regional lymphatics at risk (supraclavicular; level 1, 2, and 3 axilla; and IMN), using the RBE value of 1.1 (16). Nodal targets were dependent on stage of disease and extent of axillary node dissection. No patient received any component of photon or electron treatment. All fields were en face (anterior slight oblique fields). Most patients required matched fields because of the size limitation of the scattering nozzle (25-cm limit). The supraclavicular and chest wall fields were matched with a gap of 2 to 4 mm on the skin surface at the level of the head of the clavicle similar to photon techniques. Feathering over 1 cm in 2 steps was used to minimize hot and cold spots.

Each SOBP field is individually designed to include an aperture whose margins suffice to achieve prescription dose to the lateral target volume margins and a range-compensator to conform the distal prescription dose margin to the distal target volume. Our SOBP fields are dosimetrically robust by virtue of their high-frequency repetition rate of 10/s and by virtue of their calibrated depth-dose distribution defined by the distal range and modulation width. Dose robustness with respect to the target volume is addressed by our physics and clinical protocol as follows. The aperture margin is increased by 3 mm to account for setup uncertainty, where setup is based on daily x-ray verification of the isocenter with respect to the bony (rib) anatomy. The range compensator is similarly smeared by a radius of 3 mm. Breathing motion effects are minimal because the treatment field is (almost) parallel to the chest motion, and the changes in source to source distance (SSD) do not change the dose distribution. Finally, we account for range uncertainty by increasing the distal SOBP range by 3.5% + 1 mm. This results, in our protocol, in a worst-case dose estimate for distal structures, lung in these patients, and nominal prescription dose to the target volume.

Dosimetric data

Average dose-volume histograms (DVH) were generated to show combined DVH data for the 12 patients treated. For a representative case, we compared partially wide tangent fields and a mixed photon/electron technique with the 3D-conformal proton beam radiation plan. Comparative plans were performed with the attempt to achieve similar coverage of target volumes to that achieved with protons while maximally sparing cardiac and pulmonary structures.

Assessment of toxicity

All patients were seen before receiving RT, weekly during RT, and subsequently at 4 and 8 weeks after the completion of treatment. Acute toxicities of skin, fatigue, and radiation pneumonitis were graded by the Common Terminology Criteria for Adverse Events, version 4 (CTCAE v4). The patients consented to have a photograph taken to document skin toxicity each week during treatment and at the 4-week and 8-week follow-up visits. Stain echocardiograms were obtained before treatment and at the 4-week and 8-week follow-up visits.

Results

Study population

The patient characteristics are summarized in Table 1 (tbl1). Eleven of 12 patients enrolled had left-sided locally advanced breast cancer, and 1 patient had bilateral implants, which limited beam angles for a right-sided cancer. The median patient age was 42 years (range, 31-68 years). Five patients received neoadjuvant chemotherapy, and 7 received adjuvant chemotherapy (most commonly doxorubicin/cyclophosphamide
followed by paclitaxel). Three patients with HER2-positive tumors received adjuvant treatment with trastuzumab in addition to conventional chemotherapy. All chemotherapy was completed before radiation. Herceptin was continued and delivered concurrently with radiation for Her-2-positive patients. Five women underwent immediate reconstruction with unilateral or bilateral implants, and 1 underwent delayed reconstruction with a unilateral implant after the completion of RT. Ten patients were given hormone therapy (tamoxifen or letrozole) concurrently with radiation treatment or afterward. Three of 12 patients were suspected to have IMN involvement based on CT or MRI imaging; all had a complete response to chemotherapy before receiving radiation.

Table 1
Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n = 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, median (range)</td>
<td>42 (31-68)</td>
</tr>
<tr>
<td>Left-sided cancer</td>
<td>11</td>
</tr>
<tr>
<td>T1</td>
<td>2</td>
</tr>
<tr>
<td>T2</td>
<td>7</td>
</tr>
<tr>
<td>T3</td>
<td>3</td>
</tr>
<tr>
<td>N+</td>
<td>11</td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td>5</td>
</tr>
<tr>
<td>Luminal A/B</td>
<td>6</td>
</tr>
<tr>
<td>Triple negative</td>
<td>3</td>
</tr>
<tr>
<td>HER2/neu +</td>
<td>3</td>
</tr>
<tr>
<td>Immediate reconstruction</td>
<td>5</td>
</tr>
<tr>
<td>Bilateral</td>
<td>4</td>
</tr>
<tr>
<td>Unilateral</td>
<td>1</td>
</tr>
<tr>
<td>Delayed reconstruction</td>
<td>1</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy</td>
<td>5</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td>7</td>
</tr>
<tr>
<td>Hormonal therapy</td>
<td>10</td>
</tr>
<tr>
<td>IMN involvement</td>
<td>3</td>
</tr>
<tr>
<td>Duration of RT, days, median (range)</td>
<td>42 (37-45)</td>
</tr>
</tbody>
</table>

*Abbreviations: IMN = internal mammary node; RT = radiation therapy.*

Target volume dose
All patients received chest wall irradiation. Eleven received supraclavicular, level 3, and IMN RT. The inclusion of the level 1 and 2 axilla was dependent on axillary dissection and disease burden. Only 2 patients received radiation to the full axilla. For the 3 patients with suspected IMN involvement by CT or MRI, all had imaging repeated after chemotherapy that showed no evidence of disease at the time of RT. The IMN chain was treated to a dose of 50.4 Gy (RBE). The protocol allows for an optional chest wall boost to be delivered at the discretion of the treating radiation oncologist; however, no patient in this reported series received a chest wall boost. Figure 1 (fig1) shows the average DVH for target volumes and demonstrates the homogeneous and complete coverage that is achieved with proton RT. All patients had target volumes combined to form a structure “combined clinical target volume.” The average dose to 95% of the combined clinical target volume was 46.3 Gy (RBE) for the 12 patients in this series.

Fig. 1
Dose-volume histograms for chest wall, internal mammary nodes, level 3 axilla, and supraclavicular region averaged for patients treated with protons in this trial. IMN = internal mammary artery; SCR = supraclavicular.

Cardiopulmonary irradiation dose

Figure 2 (fig2) shows the average DVH for avoidance structures where these doses include the effect of the range uncertainty as explained earlier. In the left-sided RT group (11 patients), the average mean dose to heart was 0.44 Gy (range, 0.1-1.2 Gy), and the average mean volume of heart receiving 20 Gy ($V_{20}$) was 0.01% (range, 0%-2.4%). The average mean dose to the left ventricle (LV) was 0.09 Gy (range, 0-0.37 Gy), and the average mean $V_{20}$ of the LV was 0.0004% (range, 0%-0.2%). In all 12 patients, the average mean dose to lung was 6 Gy (range, 2.4-10.1 Gy), and the average mean $V_{20}$ of lung was 12.7% (range, 4.4%-22.1%).

Fig. 2
Dose-volume histograms for cardiac structures and ipsilateral lung averaged for patients treated with protons in this trial.
Acute toxicity

Patient toxicities, as scaled by the CTCAE v4 during RT and at the 4-week and 8-week follow-up visits, are summarized in Table 2 (tbl2). During RT, 9 patients had a maximum skin toxicity of grade 2, and 3 patients had a maximum skin toxicity of grade 1. At 4 weeks, no patients were determined to have a grade 2 skin toxicity; all patients had grade 1 erythema or hyperpigmentation. By 8 weeks after the completion of RT, most patients were noted to have hyperpigmentation. Figure 3 (fig3) depicts the skin reactions in patients at the end of RT and during follow-up. The maximum rated fatigue during radiation treatment was grade 3, which was reported by only 1 patient. At 4 weeks after the completion of RT, only 1 patient experienced grade 1 fatigue, and all others were asymptomatic. At 8 weeks follow-up, no patients experienced significant fatigue according to the CTCAE scale. During RT and at the 4-week and 8-week follow-up visits, there was no clinical or radiographic evidence of radiation pneumonitis. Analysis of cardiac toxicity is not reported in this preliminary analysis, but there were no cases of pericarditis or other cardiac toxicities. With a median follow-up time of 6 months (range, 3.5-11.2 months), there have been no reported cases of radiation pneumonitis. Analysis of cardiac toxicity is not included in this preliminary analysis.

Table 2
Acute toxicities

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Maximum during RT</th>
<th>4 weeks after RT</th>
<th>8 weeks after RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>0</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Grade 1</td>
<td>3</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Grade 2</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>6</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Grade 2</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviation: RT = radiation therapy.
Skin reactions at the end of proton radiation and after proton radiation for (a) a patient who underwent mastectomy without reconstruction, (b) a patient who underwent bilateral nipple-sparing mastectomy with permanent implants, and (c) a patient who underwent mastectomy without reconstruction followed by an expander/exchange reconstruction after radiation (last photo taken after surgery at 8-month follow-up visit). Figure depicts permanent implant.

Discussion

Protons provide full and homogeneous dose delivery to target volumes with complete sparing of distal organs (17). For breast cancer, this property provides nearly complete sparing of cardiac structures and markedly improved sparing of pulmonary structures, as demonstrated by dosimetric planning studies and the collective dosimetry for the 12 patients treated in this study (Figs. 4 and 5). Although it is too early to determine cardiopulmonary toxicities in our study, we predict that these will be lower than those seen with standard EBRT. In addition, optimal organ avoidance is achieved in the setting of full coverage of the IMN, a challenging structure to deliver full dose to with standard RT. Although the benefit of including the IMN is controversial, several studies showing survival benefit have included these nodes in the target volume (1 18). Additionally, soft tissue and muscle outside the target volumes can be spared from unnecessary radiation (Fig. 5). The median age of patients on this trial was 42 years; only 1 woman was older than 50. The overall reduced volume of tissue exposed to radiation may decrease the risk of secondary malignancy, which is of special concern in young women treated for breast cancer.
Fig. 4
Comparison plans for protons versus photons for the chest wall at the level of the heart, left ventricle, and left anterior descending artery aroused suspicion on imaging studies and a unilateral internal mammary artery. Partially wide tangent fields. Both electron/photon planning and partially wide tangent fields are suboptimal because of anatomy. Standard planning may have required removal of the implant. Proton radiation demonstrates excellent target volume coverage with sparing of cardiopulmonary structures without need for implant removal.

Fig. 5
Comparison plans for (a) protons versus (b) photons for the supraclavicular/axillary apex region demonstrating the avoidance of unnecessary radiation to soft tissues posterior to these structures and improved coverage of these nodal volumes. The use of photons to completely cover the lymphatics targeted with a dose of 45 Gy leads to a considerable hot spot in the anterior supraclavicular region.
Despite the increasing use of protons for many pediatric and adult malignancies, clinical experience with using protons for breast cancer to date is limited. To our knowledge, this is the first clinical trial delivering protons for patients with locally advanced breast cancer. We included both patients without reconstruction and patients with unilateral or bilateral implant reconstruction. We did not include women with expanders because of the dose uncertainty that would be introduced by the metallic port. We did not include autologous reconstruction or patients who had undergone breast-conserving therapy because of the difference in skin/surface dose compared with standard EBRT plans, along with the potential for dosimetric uncertainty caused by tissue changes as a result of breast and soft tissue edema (13). We did not face any barriers in treatment planning for the 12 patients treated in our study, and we found that adequate treatment plans could be generated for patients with limitations in arm extension.

We have favored a dose of 45 Gy (RBE) to the supraclavicular region and lymphatics because this area is generally treated with 6-MV photons, and skin reaction is considered more within the expected range with a dose of 45 Gy (RBE). However, all patients, regardless of dose, tolerated the treatment well. For patients with a high risk of nodal disease, 50.4 Gy (RBE) may be preferable. All patients received a dose of 50.4 Gy (RBE) to the chest wall without a boost, and this dose was well tolerated by all 12 patients in our trial. We did not see any cases of rib fracture, indicating that, as predicted, the dose is not biologically higher at the end of range in the ribs. Although the protons at the distal edge of the SOBP have increasing linear energy transfer, the number of protons is decreasing drastically. The combined effect is that the biological dose distribution has the same shape of the physical dose distribution depthwise, but is 1 mm deeper.

Proton treatment was well tolerated with respect to radiation dermatitis, fatigue, and pulmonary toxicity. Subjectively, skin reactions were mostly superficial and often with moderate to severe erythema and moderate to large areas of dry superficial desquamation. Minimal moist desquamation was seen at the end of RT or soon afterward. Cosmesis at 4 and 8 weeks was favorable, as much as most patients had only mild erythema or hyperpigmentation at these follow-up time points. One patient treated after mastectomy without reconstruction successfully underwent an expander reconstruction with exchange for permanent implant 6 months after the completion of proton radiation (Fig. 3 (fig3)).

Despite substantial costs, there is an increasing availability of proton RT in both the academic and the private sectors. Continuous improvement and competitive engineering will likely allow for more efficient and less costly proton delivery systems in the near future. Therefore, it is critical to evaluate the potential benefits and techniques for a broad range of tumor types, such as breast cancer, in the setting of a clinical trial. Additionally, when the total costs of healthcare are considered, a prior analysis by Lundkvist et al (19) predicts that protons may be cost effective for selected patients with breast cancer. Overall, radiation is less expensive than many new cancer agents, and the use of protons for breast cancer warrants further study to determine whether it is indeed beneficial and cost effective for groups of patients at a higher risk for late morbidity. Despite several studies hypothesizing that protons will provide superior target volume coverage and a decrease in acute and late cardiopulmonary toxicities for advanced or left-sided breast cancer, to our knowledge, our study is the first to address this issue clinically (13 20).

Although we do not believe that proton radiation should become standard for all patients with locally advanced breast cancer, it may be appropriate for women with complex anatomy, including, but not limited to, patients with medial or inferior chest wall tumors, unfavorable cardiac anatomy, permanent bilateral
implants, evidence of internal mammary node metastasis, and underlying cardiopulmonary risk factors. We continue to offer proton PMRT on trial for these patients.

Conclusions

We report what is, to our knowledge, the first clinical experience with the use of protons for locally advanced breast cancer in a prospective clinical trial. Our study currently shows that proton radiation for PMRT is feasible, with acceptable early toxicities. Additional follow-up is needed to assess late complications and outcomes of proton RT.

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Conflict of interest: none.

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