Proton-Beam Therapy: At the Heart of Cardiac Dose-Sparing in Mediastinal Radiotherapy for Thymic Carcinoma

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An 88-year-old woman with a history of left-sided breast cancer, treated with lumpectomy and adjuvant whole-breast radiotherapy (RT), presented with abdominal pain and constipation for several days, for which chest and abdominal plain-film imaging was obtained and demonstrated a bowel obstruction. Incidentally, her chest radiograph revealed a new 8-cm, oblong upper thoracic mass. A computed tomography (CT) scan of the chest revealed a large, lobulated, anterior mediastinal mass measuring up to 10 cm, with a central heart-shaped calcification (Fig. 1). CT-guided mediastinal biopsy revealed an epithelial neoplasm, favored to represent thymic carcinoma. Further staging imaging was performed, including magnetic resonance imaging of the chest and positron emission tomography–CT, which confirmed localized disease. After obtaining multidisciplinary input, given her advanced age, poor performance status, and personal preferences, it was deemed she was not a candidate for systemic therapy, and definitive RT alone was recommended. Given that she had previously received whole-breast RT, which also delivered dose to the heart (and has been reported to increase the subsequent rate of ischemic heart disease for at least 20 years),[1] and the location of her current cancer, which abutted the heart, proton-beam therapy (PBT) was used to reduce the current and cumulative cardiac dose as compared to standard photon therapy with intensity-modulated RT (IMRT). Figures 2 and 3 reveal the reductions in the axial (Fig. 2) and sagittal (Fig. 3) dose distributions for comparative IMRT (left) and PBT (right) plans for this patient. Figure 4 is a dose-volume histogram that reveals the reduction in high, low, mean, and integral doses with PBT (boxes) compared with IMRT (triangles). She tolerated PBT without any acute grade 3 or higher toxicities. At 11.6 months after completion of PBT, she remains without clinical or radiographic evidence of disease or radiation-related cardiac toxicity. Figure 5 depicts her most recent chest CT revealing tumor regression with central necrosis.

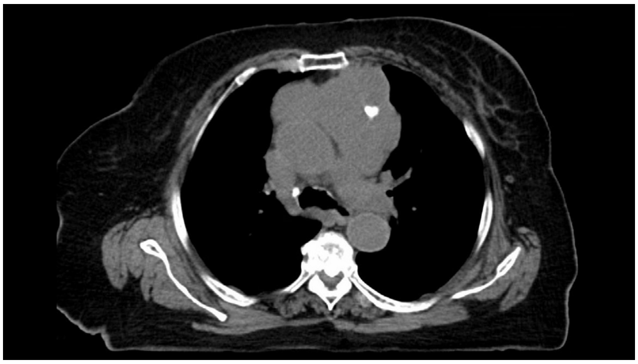

Figure 1. Computed tomography scan of the chest showing an 8 cm by 10 cm by 7 cm (sagittal, transverse, anterior-posterior) multilobulated, anterior mediastinal mass with a central heart-shaped calcification.

PBT has a unique physical property, the Bragg peak, in which protons lose energy quickly toward the end of their range, limiting energy deposition beyond the peak, and therefore, limiting dose beyond the target.[2] This

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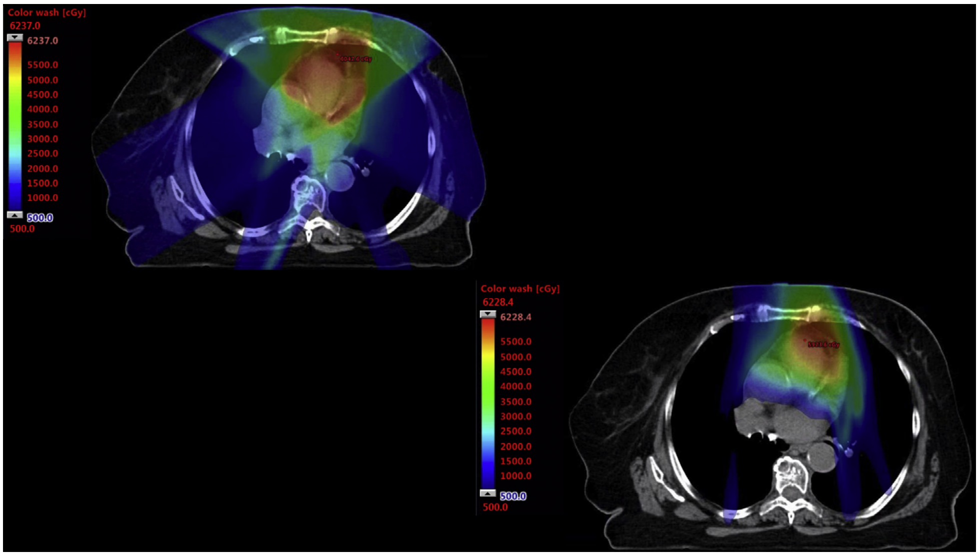

Figure 2. Comparative intensity-modulated radiotherapy (left) and proton-beam therapy (right) treatment plans for this patient demonstrating reductions in the axial dose distribution with protons.

offers a particular advantage in thoracic RT, in which published series have revealed increased risks of adverse cardiac events and mortality, with increases in the mean heart dose, heart V5 (volume of heart receiving at least 5 Gy), heart V30, and heart V50 delivered.[3–6] This has also been reported in a secondary analysis of a prospective, randomized controlled trial of dose escalation in definitive chemoradiotherapy for locally-advanced NSCLC, Radiation Therapy Oncology Group 0617, in which heart dose was associated with worse overall survival.[7] These data suggest that the dosimetric, cardiac-sparing benefits of mediastinal PBT may translate into improvements in cardiac toxicity, and potentially, survival, which is currently being tested prospectively in patients with unresectable NSCLC in Radiation Therapy Oncology Group 1308. Broadly speaking, in cases of unresectable thymic carcinomas, the 2020 National Comprehensive Cancer Network (NCCN) guidelines recommend concurrent chemoradiotherapy (similar to NSCLC), though multidisciplinary input for patient-specific recommendations is encouraged. NCCN recommends that RT be delivered using a three-dimensional conformal technique to reduce normal cardiac and lung doses, and also that IMRT may decrease the dose to normal tissues and that cardiac dose should be as low as reasonably achievable given the young age and long-term survival of many patients with thymic tumors.[8–10] Given the cardiac-sparing potential of PBT in mediastinal RT for thymic tumors, this modality may be consistent with the NCCN

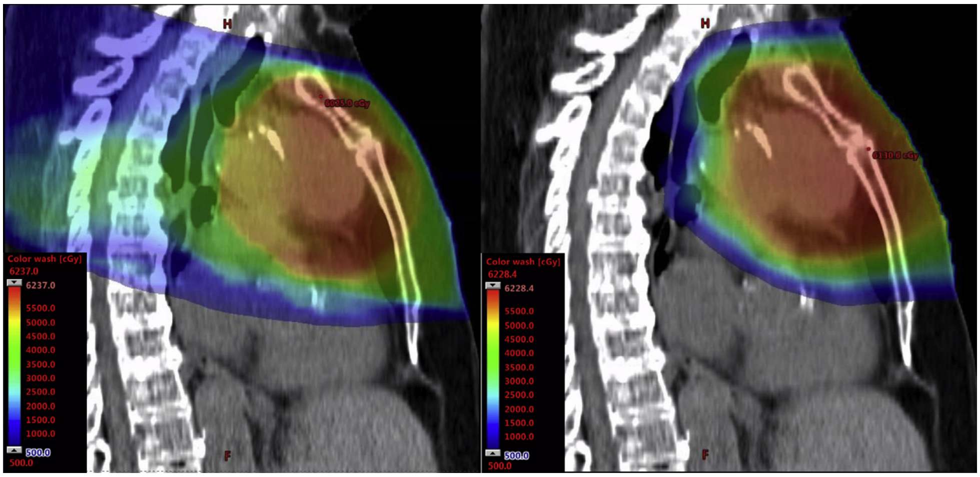

Figure 3. Comparative intensity-modulated radiotherapy (left) and proton-beam therapy (right) treatment plans for this patient demonstrating reductions in the sagittal dose distribution with protons.

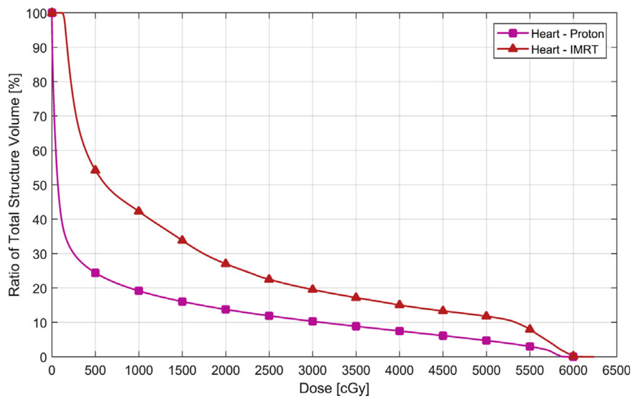

Figure 4. Dose-volume histogram radiation plan comparison conveying reductions of the high, low, mean, and integral cardiac dose parameters with proton-beam therapy (boxes) compared with intensity-modulated radiotherapy (triangles) in this patient.

recommendation. Still, mediastinal PBT may have a number of limitations. First, delivering PBT to moving targets surrounded by tissues with larger inhomogeneities (as in the thorax) can be technically challenging as small anatomical changes can lead to under- or over-dosing of target and nontarget tissues.[11] Second, although PBT seems promising, there are currently no published phase III data to reveal an improvement in oncologic outcomes using PBT in comparison with IMRT for mediastinal RT; although there are several that are ongoing. Finally, the use of PBT is controversial, as there are high costs associated with building and maintaining a proton facility.[12] We eagerly await the results of prospective investigations into the use of PBT, which may translate into similar improvements as in NSCLC in more rare malignancies such as thymic malignancies.

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Figure 5. Contrast-enhanced computed tomography scan of the chest obtained 11.6 months after completion of proton-beam therapy demonstrating tumor regression with central necrosis.

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