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ORIGINAL ARTICLE

Risk of major cardiac events following adjuvant proton versus photon radiation therapy for patients with thymic malignancies

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ABSTRACT

Background: While often managed with surgery alone, patients with thymic malignancies with high-risk features may benefit from adjuvant radiation therapy but are at risk for late toxicities. Previously, the risk of major cardiac events (MCEs) was reported to increase by 7% per one Gray (Gy) to the heart. In this study, we compare dose to organs at risk (OARs) with intensity-modulated (IMRT) versus proton beam therapy (PBT). We hypothesize a decrease risk of predicted MCEs with PBT.

Material and methods: Patients requiring adjuvant therapy for thymic malignancies were treated with double scattered proton beam therapy (DS-PBT). Clinical backup IMRT plans were generated. Predicted MCEs were calculated based on median dose to the heart. A Wilcoxon rank sum test was used for statistical comparisons.

Results: Twenty-two consecutive patients were evaluated. DS-PBT resulted in statistically significant decreases in dose to the heart, lungs, left ventricle, esophagus, and spinal cord (all $p \leq .01$). The increase in risk of MCEs from 0 to $\geq$20 years was lower with PBT (74% versus 135%, $p = .04$).

Discussion: DS-PBT results in decreased dose to OARs and may reduce the risk of MCEs compared with IMRT. Long-term follow-up is required to assess for clinical benefit from DS-PBT.

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Introduction

Thymoma is a rare malignancy, but accounts for approximately 20% of all tumors within the mediastinum [1]. Complete surgical resection is critical for curative treatment. Adjuvant radiation therapy has been demonstrated to reduce the risk of local recurrence and improve overall survival in high-risk patients with advanced stages or positive margins [2,3]. In addition, post-operative radiation therapy may also be considered for patients with stage II disease, especially in the setting of adverse pathologic features [2]. Guidelines suggest consideration of adjuvant radiation therapy for patients with stage II–IV thymoma and thymic carcinoma, as well as for all patients with positive margins or for gross residual disease. Doses generally range from 45 to 50 Gy for clear or close margins, 54 to 60 Gy for positive margins, and 60 Gy or more for patients with gross residual disease [4]. Prognosis for these patients is generally excellent, with 92%, 82%, and 68% 5-year overall survival anticipated for patients with I, II, and III disease, respectively [5].

Given the anticipated long-term survival, patients remain at risk for late toxicities from radiation therapy that may lower the therapeutic ratio of this modality following resection. In particular, radiation dose to the heart has been associated with increased risk ischemic heart disease, pericarditis, and valvular disease in patients treated for breast cancer and Hodgkins lymphoma [6,7]. Studies of breast cancer patients have demonstrated an increasing risk of major cardiac events (MCEs), defined as myocardial infarction, coronary revascularization, or death from ischemic heart disease, of 7% per one Gray (Gy) delivered to the heart from 0 to $\geq$20 years after radiation therapy [8].

Due to its characteristic dose deposition, proton beam therapy (PBT) may reduce dose to critical normal structures in the thorax and is well suited to treat the anterior mediastinum while sparing organs at risk (OARs) [9]. Dosimetric comparison studies exist for lung cancer demonstrating decreased doses to OARs [10,11]. In thymic malignancies, only a single study of four patients has evaluated dose to OAR using PBT as compared with intensity modulated radiation therapy (IMRT) [12]. In the present study, patients with thymic malignances were treated with adjuvant PBT. Comparison IMRT plans were generated and doses to OARs were quantified. We hypothesized a reduction in risk of predicted MCEs using PBT as compared with IMRT plans.

Material and methods

Patient population

All patients with thymoma or thymic carcinoma requiring adjuvant radiation therapy and treated with double scattering proton therapy between 2011 and 2016 were enrolled on an Institutional Review Board-approved proton registry study

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allowing prospective collection of treatment data, toxicity, and clinical outcomes.

Patient and treatment characteristics

Demographic and treatment data including age, sex, tumor size, radiation dose, and use of chemotherapy were abstracted from the electronic medical record. Operative and pathology reports were reviewed to determine resection and margin status. Surgical margins were defined as negative, close (defined as $\leq$2 mm from the inked margin), or positive based on post-operative pathologic reports. Histopathology was defined as per the 2004 WHO classification system [13]. Staging was assigned based on review of operative and pathology reports based on the Masaoka system.

Simulation and target contouring

A four-dimensional (4D)-computed tomography (CT) simulation was performed (Siemens Senation, Siemens, Munich, Germany and/or Philips GEMINI TF, Philips, Cambridge, MA, USA) using Varian Real-time Position Management (RPM) system (Varian Medical System, Palo Alto, CA, USA). All respiratory-phase images and the reconstructed averages were transferred into Eclipse planning system version 11.0 (Varian Medical System, Palo Alto, CA, USA).

In all cases, the planning scan was fused with pretreatment imaging to ensure coverage of the pre-operative mass and any residual disease. The ITV was created by expanding the pre-operative GTV by 1–2 cm, cropping out of normal structures, and adjusting for post-operative changes in anatomy and any motion of the operative bed. The ITV was expanded uniformly by 0.5 cm to create the planning target volume (PTV). Normal structures including the lung, esophagus, left ventricle (LV), left anterior descending coronary artery (LAD), and skin were contoured [14].

DS-PBT and IMRT treatment planning

The average 4D-CT, a pixel by pixel average of all 8 acquired phases of the breathing cycle, was used for plan optimization and dose calculation. All patients were treated with double-scatter proton beam therapy (DS-PBT). One to three DS-PBT fields were centered on the ITV, with beam angles optimized to maximize target coverage and minimize exposure to normal structures. Range uncertainty in the conversion of CT images to stopping power (3%) and patient setup (3 mm) were accounted for in distal and proximal margins of DS-PBT. Lucite compensators were manufactured for each beam and multi-leaf collimators were used for conformality. Smearing was used in the compensator design to incorporate motion and ensure target coverage along the beam [15].

For sliding-window IMRT plans, 3–6 gantry coplanar 6MV photon beams were used depending on patient anatomy. To meet planning constraints, 95% of the PTV was to be covered by at least 95% of the prescription dose, lung mean dose was constrained to $\leq$20 Gy, lung V20 $\leq$ 35%, lung V5 $\leq$ 60%, heart maximum the prescription dose, heart V45 $\leq$ 35%, and heart V30 $\leq$ 50%. Dose-volume histograms (DVHs) of the PTV and OARs were compared for DS-PBT and IMRT plans.

Statistical analysis

Predicted increases in MCEs were calculated based on mean dose to the heart for IMRT and DS-PBT plans. Risks were obtained from a previously published population-based case–-control study in which rates of major coronary events, defined as myocardial infarction, coronary revascularization, or death from ischemic heart disease in women treated for breast cancer were determined from a national cancer registry. Radiation therapy charts of matched patients with and without a diagnosis of MCEs were reconstructed on a CT scan of a woman with typical anatomy and the proportional increase in rate of MCEs per Gy of irradiation to the heart was estimated.

In that study, an increase in MCEs of 16% per Gy was anticipated for years 0–4 following mediastinal irradiation, 16% per Gy for years 5–9, 1% per Gy for years 10–19, and 8% per Gy for $\geq$20 years. Overall, for years 0 to $\geq$20, an increase in risk of 7% per Gy was anticipated [8]. The use of mean heart dose as the primary endpoint was further motivated by recent studies correlating mean heart dose with overall survival and cardiac events in non-small-cell lung cancer [16,17].

A Wilcoxon matched pair signed rank test was used for statistical comparisons. A p value $\leq$.05 was considered statistically significant. Statistical analyses were conducted using Stata Version 13 (STATA Inc., College Station, TX, USA).

Results

Twenty-two consecutive patients were analyzed for this study. Median patient age was 55 years (Table 1). Tumor histology was most commonly B1 (27%) and most patients were Masaoka stage II (72%). Margins were predominantly

Table 1. Patient characteristics.

Characteristic	Number of patients (%)
Age at diagnosis	
Median, years (range)	55 (25–77)
Sex	
Male	11 (50)
Female	11 (50)
Tumor Histology	
AB	4 (18)
B1	6 (27)
B2	1 (4)
B3	4 (18)
C	2 (10)
Unknown	5 (23)
Tumor size	
Median, cm (range)	5.2 (2.0–14.4)
Masaoka stage	
I	1 (4)
IIA–B	16 (72)
IIIA–B	3 (14)
IVA–B	2 (10)
Margin status	
Negative	4 (18)
Close	7 (32)
Positive	11 (50)
Radiation dose	
Median, Gy (range)	56.7 (50.4–70.0)

positive (50%) or close (32%). Median dose delivered was 56.7 Gy (range, 50.4–70.0 Gy) in 1.8 Gy daily fractions.

Coverage of the CTV and PTV did not vary significantly by modality ($p = .2$) (Table 2 and Figure 1). Compared with photon radiation, proton radiation resulted in statistically significant improvements in the mean lung dose (8.5 versus 11.8 Gy, $p \leq .01$) and lung V5 (26% versus. 49%, $p \leq .01$). Protons also achieved significant reductions in esophagus V30 (18% versus 41%, $p \leq .01$) and maximum cord dose (11.8 versus 40.0 Gy, $p \leq .01$).

Statistically significant decreases with DS-PBT were seen in mean heart dose (1.0 versus 18.2 Gy, $p \leq .01$), heart V5 (31% versus 50% $p \leq .01$), heart V30 (18% versus 29%, $p \leq .01$), mean left ventricle dose (5.4 versus 11.0 Gy, $p \leq .01$), and left ventricle V20 (11% versus 20%, $p \leq .01$). The median mean and maximum LAD doses were not significantly different.

A statistically significant increase in MCEs was predicted with photon compared with proton therapy (Table 3). Between years 0 and 4 following radiation, a 162% relative increase in risk was expected with DS-PBT compared with 297% with IMRT. Between years 5 and 9, a 154% increase in risk was expected with DS-PBT as compared with a 282% increase with IMRT. Between years 10 and 19, a 12% increase in risk was expected with DS-PBT compared with a 22% increase in risk with IMRT. Beyond 20 years, an 82% increase in risk was expected with DS-PBT as compared with 149% with IMRT. Overall, a 74% increase in risk was expected with DS-PBT as compared with 135% increase risk with IMRT ($p = .04$). At each time point, there was a 45% relative reduction in risk of MCEs with DS-PBT versus IMRT.

Table 2. OAR comparison between IMRT and DS-PBT studies.

	DS-PBT		Photon		
	Mean	Range	Mean	Range	*p*
PTV coverage (%)	98	93–100	99	95–102	NS
Mean lung (Gy)	8.5	1.1–20.5	11.8	4.0–23.7	**≤.01**
Lung V5 (%)	26	10–52	49	23–67	**≤.01**
Lung V20 (%)	17	0–37	21	3–56	**≤.01**
Heart mean (Gy)	1.0	2.6–33.5	18.2	6.0–38.8	**≤.01**
Heart V5 (%)	31	10–65	50	19–99	**≤.01**
Heart V30 (%)	18	0–50	29	6–83	**≤.01**
Mean left ventricle (Gy)	5.4	0–28.2	11.0	6–51.4	**≤.01**
Left ventricle V20 (%)	11	0–49	20	0–97	**≤.01**
LAD maximum (Gy)	52.0	7.1–75.6	54.6	7.9–77.8	NS
LAD mean (Gy)	26.1	0.2–53.8	29.1	0.3–53.0	NS
Esophagus maximum (Gy)	42.6	0–75.3	54.0	26.3–74.1	.11
Esophagus V30 (%)	18	0–70	41	0–69	**≤.01**
Skin maximum (Gy)	51.3	1.0–74.0	57.3	43.2–80.8	NS
Cord max (Gy)	11.8	0–55.4	40.0	10.9–56.4	**≤.01**

NS: non-significant ($p > .2$). Bold values represent statistically significant values ($p < .05$).

Discussion

PBT is a novel technology that has been shown to limit dose to normal tissues with low rates of acute toxicity in

Table 3. Predicted rates of MCEs between IMRT and DS-PBT studies.

	Increase in MCE			
Years since RT	Increase (%)/Gy [10]	Increase (%) with DS-PBT	Increase (%) with IMRT	Increase (%) with IMRT versus DS-PBT
0–4	16.3	162.0	296.8	134.8
5–9	15.5	154.1	282.3	128.2
10-19	1.2	12.0	21.8	9.8
≥20	8.2	81.5	149.3	67.8
0 to ≥20	7.4	73.6	134.7	61.1

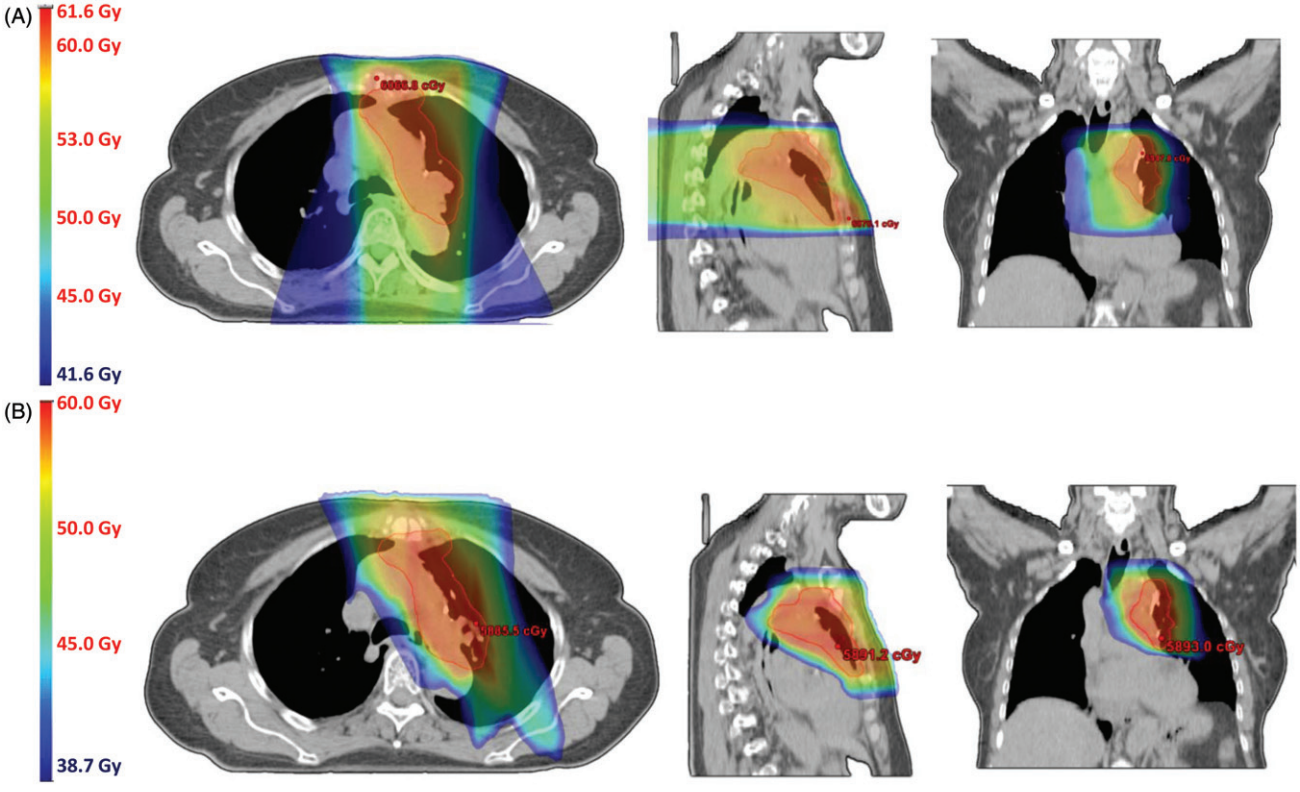

Figure 1. Comparison of four field IMRT (A) and two field DS-PBT (B) plans for adjuvant therapy for a patient with thymoma.

numerous settings [10,18–21]. In our study, we found a significant decrease in dose to the heart, lungs, and esophagus using DS-PBT as compared with IMRT plans. Similar reductions in mean heart, lung, and esophageal dose have also been demonstrated in a study comparing DS-PT and an alternative IMRT planning technique, volumetric modulated arc therapy, in adjuvant therapy for thymoma [22]. Using previously published data, we demonstrate a statistically significant decrease in predicted MCEs following adjuvant DS-PBT as compared with adjuvant IMRT treatments.

The magnitude of benefit of mediastinal irradiation may be limited by normal tissue toxicities, in particular cardiac complications which may occur months to years after treatment. Acute pericarditis, occurring shortly after radiation therapy, is rare; delayed chronic pericarditis and pericardial effusion commonly resolves spontaneously, but up to 20% of patients require pericardectomy [23]. Incidence of left-sided valvular regurgitation ranges from 16% to 40% [24,25]. Patients with left-sided breast cancer requiring radiation have an increased risk of ischemic heart disease, stress test abnormalities, and stenosis within the LAD [7,26].

Describing radiation dose–volume effects to the heart is limited by confounding patient and treatment-related factors, as well as lack of standardized definitions of normal structure contouring. Despite this, there is evidence that the dose and volume of heart which receives irradiation is important in predicting development of pericardial, myocardial, and arterial disease [27]. Darby et al. found the rate of MCEs was found to increase by 7% for each increase of one Gy in mean radiation dose to the heart, irrespective of cardiac risk factors at the time of breast-cancer diagnosis [8]. While patients in that study received radiation for breast cancer, with differing dose distributions as compared with patients on this study, the results of RTOG 0617 have shown that the mean heart-dose impacts overall survival for patients receiving irradiation for lung cancer [16]. Similarly, Wang et al. found that mean heart dose was significantly associated with radiation-associated cardiac injury in patients with non-small-cell lung cancer treated in the modern era. Two-year competing risk-adjusted event rates for patients with heart mean dose <10 Gy, 10–20 Gy, or ≥ 20 Gy were 4%, 7%, and 21% [17].

Patients with thymic carcinoma and thymoma with high-risk features including advanced stage and positive margins have an increased risk of recurrence after surgical management alone. There is a local control and overall survival benefit to adjuvant radiation therapy for patients with positive margins and stage III–IV disease [3,28]. The role of adjuvant radiation therapy for patients with stage II thymoma is less clear. Select studies have demonstrated an improvement in local recurrence rates for stage II patients alone, but others have demonstrated no benefit [29]. Proton therapy may serve to reduce the toxicity of treatment and increase the therapeutic ratio, especially in stage II thymoma patients for whom the benefit to risk therapeutic window for adjuvant radiotherapy may be smaller.

There are limitations of this study, including the use of DS-PBT. DS-PBT relies on physical scattering foils to spread the beam laterally and custom apertures and compensators to shape to the largest cross section of the treatment target. These extra irradiation areas limit normal tissue sparing. In contrast, pencil beam scanning (PBS) uses magnetic fields that deflect the beam and cover the target, allowing modulation of intensity throughout the entire range of the proton beam. Comparison plans with PBS-PT would have likely further reduced cardiac dose and risk of predicted MCEs. However, few thoracic patients to date have been clinically treated with PBS-PT due to concern of tumor motion and we, therefore, have elected to report on our clinical experience as opposed to a simple PBS-PT dosimetric analysis. DS-PT has negligible motion interplay effect compared to PBS-PT because beam delivery is repeated every 100 ms during treatment. Target coverage was also ensured by the limited motion for centrally located and caudal target volumes, with all patients on this study having <10 mm of motion on 4DCT and most having <5 mm of motion. However, both DS-PT and PBS are less robust than IMRT for dose distribution along the depth direction due to range uncertaininties and target motion along the beam path, patient setup, and CT Hounsfield to stopping power conversion. By developing tools to properly calculate the beam specific treatment margin and mitigate potential interplay effect with PBS-PT, the benefit derived from proton therapy for thoracic tumors may be even greater [30,31].

Additional photon technologies not studied here exist to treat the mediastinum. Deep inspiration breath hold photon techniques have been shown to limit dose to the heart in breast cancer and Hodgkins patients, and it may also reduce dose to the heart for thymoma patients [32,33]. However, given the size and location of thymic malignancies included in this study, we believe a much greater dosimetric benefit is to be gained from proton therapy.

There are specific limitations of the risk assessment previously reported by Darby et al. Their study limited the definition of MCEs to codes for myocardial infarction, coronary revascularization, or death from ischemic heart disease. This analysis may underestimate the magnitude of benefit given that valvular damage, chronic pericarditis, and congestive heart failure were not included. Their reconstruction of dose delivered to the heart was also limited, in that patients were treated radiation prior to the era of CT based planning, and that dose was reconstructed on a scan of a woman with "typical anatomy" when significant variation likely exists across patients clinically treated.

It remains unclear what clinical benefit will be afforded by reducing dose to the heart with proton therapy. Early clinical outcomes of a cohort of 27 patients treated with DS-PBT for thymoma and thymic carcinoma have been published [34]. While the dosimetric benefit from DS-PBT appears promising, cardic events are rare overall. Longer follow up of these patients will help to quantify the magnitude of any benefit and impact on risk of MCEs from PBT in this setting.

In this study, we demonstrate statistically significant reductions in dose to the lungs, heart, esophagus, and spinal cord using DS-PBT as compared with IMRT plans for patients requiring adjuvant radiation therapy for thymic carcinoma and thymoma. We show that the decrease in heart dose corresponds to statistically significant reductions in the risk of MCEs following proton radiation therapy as compared to

photon radiation. Long-term clinical follow up will be required to demonstrate if proton therapy allows for decreased rates of cardiac events and an improved therapeutic ratio in these patients.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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