Radiotherapy and Oncology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Dosimetric comparison to the heart and cardiac substructure in a large cohort of esophageal cancer patients treated with proton beam therapy or Intensity-modulated radiation therapy

Yutaka Shiraishi [a,b], Cai Xu [a], Jinzhong Yang [c], Ritsuko Komaki [a], Steven H. Lin [a,*]

[a] Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, United States; [b] Department of Radiology, Keio University School of Medicine, Tokyo, Japan; and [c] Department of Radiation Physics, The University of Texas MD Anderson Cancer Center, Houston, United States

ARTICLE INFO

Article history:
Received 28 March 2017
Received in revised form 3 June 2017
Accepted 28 July 2017
Available online xxxx

Keywords:
Esophageal cancer
Proton beam therapy
IMRT
Cardiac sparing

ABSTRACT

Purpose: To compare heart and cardiac substructure radiation exposure using intensity-modulated radiotherapy (IMRT) vs. proton beam therapy (PBT) for patients with mid- to distal esophageal cancer who received chemoradiation therapy.

Methods and materials: We identified 727 esophageal cancer patients who received IMRT ($n = 477$) or PBT ($n = 250$) from March 2004 to December 2015. All patients were treated to 50.4 Gy with IMRT or to 50.4 cobalt Gray equivalents with PBT. IMRT and PBT dose–volume histograms (DVHs) of the whole heart, atria, ventricles, and four coronary arteries were compared. For PBT patients, passive scattering proton therapy (PSPT; $n = 237$) and intensity-modulated proton therapy (IMPT; $n = 13$) DVHs were compared.

Results: Compared with IMRT, PBT resulted in significantly lower mean heart dose (MHD) and heart V5, V10, V20, V30, and V40 as well as lower radiation exposure to the four chambers and four coronary arteries. Compared with PSPT, IMPT resulted in significantly lower heart V20, V30, and V40 but not MHD or heart V5 or V10. IMPT also resulted in significantly lower radiation doses to the left atrium, right atrium, left main coronary artery, and left circumflex artery, but not the left ventricle, right ventricle, left anterior descending artery, or right coronary artery. Factors associated with lower MHD included PBT ($P < 0.001$), smaller planning target volume (PTV; $P < 0.001$), and gastroesophageal junction (GEJ) tumor ($P < 0.001$). Among PBT patients, factors associated with lower MHD included IMPT ($P = 0.038$), beam arrangement other than AP/PA ($P < 0.001$), smaller PTV ($P < 0.001$), and GEJ tumor ($P < 0.001$).

Conclusions: In patients with mid- to distal esophageal cancer, PBT results in significantly lower radiation exposure to the whole heart and cardiac substructures than IMRT. Long-term studies are necessary to determine how this cardiac sparing effect impacts the development of coronary artery disease and other cardiac complications.

One of the key aspects of esophageal cancer treatment is trimodality therapy that includes radiation therapy (RT), surgery, and chemotherapy. This approach has been associated with improvements in local disease control and patient survival [1,2]. However, thoracic RT planning for esophageal cancer patients remains challenging owing to the proximity of dose-limiting structures such as the heart and lungs to tumors in the mid- to distal esophagus [3]. Because RT can cause considerable cardiac toxicity in esophageal cancer patients, limiting the radiation dose to the heart is an important goal of thoracic RT planning [4]. As survival outcomes improve, an increased focus has been placed on improving treatment planning to minimize radiation exposure to surrounding normal structures.

The introduction of intensity-modulated RT (IMRT) for esophageal cancer has advanced efforts to spare normal tissue and improve dose conformity to the tumor. Dosimetric studies have shown that patients with distal esophageal cancer who receive IMRT have significantly lower radiation exposure to the heart and right coronary artery than patients who receive three-dimensional conformal RT (3DCRT) [5]. Proton beam therapy (PBT) can further limit the radiation exposure to normal tissue owing to the fact that protons can be manipulated to release their energy in a target volume, thereby eliminating the exit dose. Although planning studies have shown that PBT conveys a smaller mean radiation dose to the lungs and heart than conventional 3DCRT does [6,7], these studies enrolled few patients, and PBT's

* Corresponding author at: Department of Radiation Oncology, Unit 1422, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, United States.
E-mail address: SHLin@mdanderson.org (S.H. Lin).

http://dx.doi.org/10.1016/j.radonc.2017.07.034
0167-8140/

dose-sparing effects on cardiac substructures such as heart chambers and coronary arteries remain unclear.

In order to investigate PBT's dose-sparing effects on cardiac substructures, we retrospectively compared the radiation doses of PBT to the whole heart and cardiac substructures with those of IMRT in large groups of patients with mid- to distal esophageal cancer. In addition, although most esophageal cancer patients who undergo PBT in the United States receive passive scattering proton therapy (PSPT), intensity-modulated proton therapy (IMPT) is being considered to further improve critical normal organ sparing, especially for the heart. Therefore, we also compared the heart-sparing effect of IMPT with that of PSPT.

Methods and materials

Patients

The appropriate institutional review board approved the study. We searched a clinical database of esophageal cancer patients to identify those who received RT with or without surgical resection at our institution between March 2004 and December 2015. Inclusion criteria included pathologic confirmation of mid- to distal esophageal cancer, receipt of chemoradiation therapy using IMRT or PBT with curative intent, completion of a radiation dose of 50.4 Gy or 50.4 cobalt Gray equivalents in 28 fractions, and availability of RT plan. Patients with distant metastatic disease were excluded.

Treatment

Patients were treated with neoadjuvant or definitive chemoradiation therapy with or without induction chemotherapy. For treatment simulation, patients were in a supine position in an upper body cradle with their arms abducted overhead. Four-dimensional (4D) computed tomography (CT) simulation was used to track tumor motion throughout the respiratory cycle, as patients were treated in free-breathing mode. The gross tumor volume (GTV) was contoured based on the maximal intensity projection from the 4D CT scan, prior positron emission tomography imaging, and endoscopy results. The clinical target volume expansion was typically 3 cm superior and inferior and 1 cm radial, and the planning target volume (PTV) expansion was typically 1 cm. Daily kilovoltage imaging was used to reduce setup error. All normal structures were contoured on time-averaged CT scans. IMRT plans were generated using the Pinnacle treatment planning system (version 9.0, Philips, Andover, MA). PBT plans were generated using the Eclipse treatment planning system (Varian, Liverpool, NY), with a relative biological effectiveness assumed to be 1.1. An averaged 4D CT set (ie, assignment of maximum CT Hounsfield unit number from individual respiratory phases) was used to create all PSPT and IMPT plans. Next, we created 2 "verification" dose distributions by recalculating the dose on the 4D simulation CT scans at extreme breathing phases (the maximum inhale and maximum exhale) on the original plans. We then adjusted the original plan until the verification and original dose distributions all met the required prescription criteria including >95% CTV coverage and normal tissue dose–volume constraints. The dose–volume constraints used for both PBT and IMRT planning included a maximum dose to the spinal cord of <45 Gy; a mean lung dose of $\leq$20 Gy with a V20 of $\leq$35% (preferably a V20 of $\leq$30% if the patient was receiving chemoradiation therapy before surgery); a lung V5 of <55%; a heart V30 of $\leq$45% with a mean heart dose (MHD) of <26 Gy; and a liver V30 of $\leq$40% with a mean liver dose of <30 Gy.

Cardiac substructure contouring

Because cardiac substructures are almost indistinguishable on noncontrast CT images, PBT plans were exported to the Pinnacle treatment planning system, and the in-house Multi-Atlas Contouring Service (MACS) software program, which has a user interface in Pinnacle, was used to automatically delineate the cardiac structures on CT images for treatment planning. The details of MACS have been described previously, and its accuracy of auto-contouring has been validated [8]. An experienced radiation oncologist reviewed auto-contouring for each patient and, if necessary, modified the cardiac substructure contouring following detailed guidelines described previously [9]. The whole heart, atria, ventricles, and main coronary arteries were contoured on each treatment-planning axial CT slice.

Statistical analysis

For patient, tumor, and treatment characteristics, categorical data were compared using the chi-square test or Fisher's exact test as appropriate. The Student *t*-test and paired *t*-test were used to compare continuous data between groups and within groups, respectively. We defined outlier MHDs as greater than the mean MHD + 2 standard deviations or less than the mean MHD − 2 standard deviations. On the basis of outlier analyses, we hypothesized that smaller PTV, tumor location, and PBT are associated with low MHD. These patient and treatment-related characteristics were selected for multivariable linear regression analysis of MHD. The association of patient and treatment-related characteristics with MHD was assessed using multivariable linear regression. All statistical tests were two-sided with $P < 0.05$ used to confer statistical significance. SPSS version 23.0 software (IBM Corp, Armonk, NY) was used for statistical analyses.

Results

A total of 727 patients met the study criteria, including 477 who received IMRT and 250 who received PBT. The patient, tumor, and treatment characteristics are summarized in Table 1. Of the 250 patients who received PBT, 13 received IMPT.

IMRT versus PBT comparison

The average dosimetric indices of IMRT and PBT for the whole heart, individual cardiac structures, and four main coronary arteries (left main coronary artery [LMC], left anterior descending artery [LAD], left circumflex artery [LCX], and right coronary artery [RCA]) are given in Supplemental Table S1; dosimetric analyses for individual cardiac structures and for the four major coronary arteries are given in Fig. 1. DVH analysis revealed that PBT resulted in significantly lower mean radiation doses to the whole heart, individual cardiac structures, and major coronary arteries than IMRT did. The V5, V10, V20, V30, and V40 for the whole heart, individual cardiac structures, and major coronary arteries achieved with PBT were almost all significantly lower than those achieved with IMRT; only the RCA V30 and V40 did not differ significantly between PBT and IMRT.

PSPT versus IMPT comparison

The average dosimetric indices of PSPT and IMPT for the whole heart, cardiac structures, and main coronary arteries are given in Supplemental Table S2; dosimetric analyses for the individual cardiac structures and for the four coronary arteries are given in Fig. 2. DVH analysis revealed that IMPT resulted in significantly lower heart V20, V30, and V40, but not lower MHD or heart V5 or V10,

Please cite this article in press as: Shiraishi Y et al. Dosimetric comparison to the heart and cardiac substructure in a large cohort of esophageal cancer patients treated with proton beam therapy or Intensity-modulated radiation therapy. Radiother Oncol (2017), http://dx.doi.org/10.1016/j.radonc.2017.07.034