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Esophageal cancer

Multi-institutional analysis of radiation modality use and postoperative outcomes of neoadjuvant chemoradiation for esophageal cancer

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ABSTRACT

Purpose: Relative radiation dose exposure to vital organs in the thorax could influence clinical outcomes in esophageal cancer (EC). We assessed whether the type of radiation therapy (RT) modality used was associated with postoperative outcomes after neoadjuvant chemoradiation (nCRT).

Patients and methods: Contemporary data from 580 EC patients treated with nCRT at 3 academic institutions from 2007 to 2013 were reviewed. 3D conformal RT (3D), intensity modulated RT (IMRT) and proton beam therapy (PBT) were used for 214 (37%), 255 (44%), and 111 (19%) patients, respectively. Postoperative outcomes included pulmonary, GI, cardiac, wound healing complications, length of in-hospital stay (LOS), and 90-day postoperative mortality. Cox model fits, and log-rank tests both with and without Inverse Probability of treatment Weighting (IPW) were used to correct for bias due to non-randomization.

Results: RT modality was significantly associated with the incidence of pulmonary, cardiac and wound complications, which also bore out on multivariate analysis. Mean LOS was also significantly associated with treatment modality (13.2 days for 3D (95%CI 11.7–14.7), 11.6 days for IMRT (95%CI 10.9–12.7), and 9.3 days for PBT (95%CI 8.2–10.3) ($p < 0.0001$)). The 90 day postoperative mortality rates were 4.2%, 4.3%, and 0.9%, respectively, for 3D, IMRT and PBT ($p = 0.264$).

Conclusions: Advanced RT technologies (IMRT and PBT) were associated with significantly reduced rate of postoperative complications and LOS compared to 3D, with PBT displaying the greatest benefit in a number of clinical endpoints. Ongoing prospective randomized trial will be needed to validate these results.
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Neoadjuvant chemoradiation (nCRT) is the standard of care for the treatment of locally advanced esophageal cancer [1]. However, because of the distal location for the great majority of esophageal cancers in the western world, radiation can impart substantial doses to vital organs such as the heart and lungs, which may increase the risk of postoperative complications and diminish survival. Published studies have shown that utilizing advanced photon delivery methods like IMRT can improve outcomes over 3D conformal techniques (3D-CRT) [2–4]. A study evaluating postoperative complications after nCRT demonstrated a lower rate of postoperative pulmonary and GI complications in patients treated with IMRT compared to 3D-CRT [5]. This is likely due to reduced radiation dose to vital organs within the chest and upper abdomen [6,7].

The physical properties of charged particle interaction in matter allow for technologies such as PBT to potentially enhance the therapeutic index for esophageal cancer. Dosimetric studies have shown that PBT produces conformal dose distributions with substantially improved normal tissue sparing as compared to 3D-CRT or IMRT [8–10]. Preliminary reports on the clinical outcomes and toxicity of concurrent chemotherapy with PBT were

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encouraging [11,12]. Using multi-institutional data for patients treated with nCRT, either 3D-CRT, IMRT, or PBT within a concurrent, contemporary time period, we retrospectively assessed association between RT modality and postoperative outcomes.

Materials and methods

Patients

Institutional Review Board approval was obtained to assess clinical outcomes and normal tissue toxicities in patients treated with concurrent CRT using PBT, IMRT, or 3D-CRT. This study retrospectively examined 580 patients treated from January 2007 to June 2013 at 3 major academic institutions. All patients had initially non-metastatic esophageal cancer that was treated with neoadjuvant concurrent CRT and surgical resection. Staging was determined by the American Joint Committee on Cancer TNM staging system (6th edition, 2002); the initial workup of all patients included blood chemistries and hematology as well as thoracic computed tomography (CT) scans with contrast. Further workup included positron emission tomography – CT (PET-CT) scans, esophagogastroduodenoscopy (EGD), and endoscopic ultrasound (EUS).

After initial CRT with or without induction chemotherapy, most patients were restaged with PET-CT (96.5%) and evaluated by thoracic surgeons for resectability. Patients treated with upfront surgery (without nCRT) or patients who underwent salvage esophagectomy were not eligible for inclusion in this dataset. The most common surgical procedure was the Ivor-Lewis esophagectomy (84%), with other small subsets of patients such as transthoracic, transhiatal, partial or total gastrectomies, minimally invasive esophagectomies, and 3-field esophagectomies. After discharge, patients were followed-up with the surgical, medical, and/or radiation oncology teams on a routine basis with regular clinical and radiologic examinations. The most common follow-up schedule was every 3–4 months over the first two years, followed by every 4–6 months until the completion of the fifth year.

Chemotherapy

Chemotherapy regimens were given at the discretion of the treating oncologists. The most common indication for treatment with induction chemotherapy prior to CRT included participation on a prospective study or due to advanced nodal but non-metastatic disease. All patients who did not progress were then treated with nCRT.

Radiotherapy

Radiation treatment and planning was performed per techniques of each institution. Briefly, simulation was performed using a shoulder cradle created to immobilize the upper body and arms abducted and externally rotated above the head. Four-dimensional simulation, accounting for tumor and normal tissue displacement during respiration, was carried out in a subset of patients at centers where this was done routinely. Contouring and treatment planning were completed using Pinnacle (Phillips Medical System) or Eclipse (Varian Medical Systems) software. In all cases, the gross tumor volume (GTV) was contoured corresponding to clinically apparent disease on the simulation CT scan as well as fused PET images, with localization aided by the EGD/EUS report. The clinical target volume (CTV) corresponded to areas potentially involved by subclinical disease and respected anatomical planes, which generally corresponded to 3–4 cm superior and inferior margins added to the GTV along the mucosal surface. For 3D-CRT, the axial expansion is a 1 cm uniform expansion radially, whereas for IMRT and PBT planning, the 1 cm expansion is further trimmed to restrict to anatomic planes (i.e. vertebral bodies, vessels, heart). Supraclavicular lymph nodes were included electively for upper esophageal primary tumors and celiac lymph nodes were included for distal tumors accordingly to the discretion of the treating radiation oncologist. A 0.5–1 cm margin was added to the CTV uniformly to form the planning target volume. Fields were arranged uniquely for each patient, but most commonly included 4 fields for 3D-CRT, a forward planned IMRT technique utilizing 5–6 fields using the step-and-shoot technique, and a 2 field posterior/left posterior oblique for passive scattered PBT. Standard dose constraints were applied for all 3 modalities in the different institutions: total lung volume receiving greater than 20 Gy (V20) of <35%, mean lung dose < 20 Gy, heart V40 < 40%, liver V30 < 30%, and spinal cord dose maximum < 45 Gy. Custom brass blocking and Plexiglas tissue compensators were fabricated for each patient treated with PBT in order to shape the field and to optimally place the spread-out Bragg peak within the tumor. Beam energies of 6–18 MV photons and 150–250 MeV protons were used. Daily fractions of relative biologically effective (RBE) dose of 1.8 Gy were delivered for both proton and photon therapy, aided by daily setup kilovoltage imaging. The total photon and proton dose was typically 50.4 Gy and 50.4 cobalt Gray equivalent (cGE) assuming an RBE of 1.1.

Outcome measures

Postoperative complications were identified from hospital notes, discharge summary, and/or from a prospectively collected surgical database. Pulmonary complications included any development of pneumonia, pleural effusion, chylothorax, pulmonary embolism, acute respiratory distress syndrome (ARDS), or respiratory insufficiency requiring the use of oxygen or ICU admission. GI complications included the development of any anastomotic leak, ileus, fistula, bowel obstruction or necrosis. Cardiac complications included new onset of atrial fibrillation or any atrial or ventricular arrhythmias, myocardial infarction, or congestive heart failure. Wound complications included any surgical wound infection or dehiscence. Length of hospital stay (LOS) was scored from the date of hospital admission to the date of discharge.

Statistical analyses

Statistical computations were done using R, version 3.1.1. Descriptive statistics, including frequencies and percentages for categorical variables and the mean or median for quantitative variables were calculated to summarize the patient characteristics for each radiation modality group. Pairwise comparisons between radiation modalities were performed to evaluate imbalances in covariates using 2-sample t or Chi-square tests. The Chi-Square test was used to assess the association between treatment modality and pulmonary, GI, cardiac, wound healing complications, as well as 30, 60 and 90 day postoperative non-cancer-related mortality. The Kruskal–Wallis test was used to compare LOS in the hospital by RT modality. Univariate and multivariate logistic regression analyses were used to examine associations between clinicopathologic variables and binary outcomes. All covariates from univariate analysis with a cutoff p-value of ≤ 0.25 were included in the variable selection for multivariate logistic regression analyses.

Results

Patient characteristics

Table 1 summarizes the clinical characteristics of the study population, stratified by radiation modality. RT modality was