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Original article

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.

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

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Table 1
Clinical characteristics of the study population, stratified for radiotherapy modality.

	3D-CRT (n = 214, 36.9%)	IMRT (n = 255, 44.0%)	PBT (n = 111, 19.1%)	p-Value PBT vs. 3D-CRT	p-Value PBT vs. IMRT
Age (years)					
>65	77 (36.0%)	66 (25.9%)	36 (32.4%)	0.607	0.247
≤65	137 (64.0%)	189 (74.1%)	75 (67.6%)		
Gender					
Female	39 (18.2%)	34 (13.3%)	12 (10.8%)	0.114	0.619
Male	175 (81.8%)	221 (86.7%)	99 (89.2%)		
ECOG performance status					
0	208 (98.1%)	239 (94.8%)	110 (99.1%)	0.836	0.100
1	4 (1.9%)	13 (5.2%)	1 (0.9%)		
Institution					
Institution X	2 (0.9%)	221 (86.7%)	111 (100%)	**<0.001**	**<0.001**
Institution Y	194 (90.7%)	5 (2.0%)	0 (0%)		
Institution Z	18 (8.4%)	29 (11.3%)	0 (0%)		
Baseline FDG-PET					
No	3 (1.4%)	3 (1.2%)	1 (0.9%)	1.000	1.000
Yes	211 (98.6%)	252 (98.8%)	110 (99.1%)		
Location					
Upper/mid	25 (11.7%)	14 (5.5%)	2 (1.8%)	**0.004**	0.191
Lower/GEJ/cardia	189 (88.3%)	241 (94.5%)	109 (98.2%)		
Histology					
AC	191 (89.7%)	239 (93.7%)	106 (95.5%)	0.112	0.671
SCC	22 (10.3%)	16 (6.3%)	5 (4.5%)		
Differentiation					
Well/Moderate	34 (16.2%)	110 (44.4%)	59 (53.6%)	**<0.001**	0.132
Poor	176 (83.8%)	138 (55.6%)	51 (46.4%)		
Mean tumor length (SD) (cm)	5.2 (2.5)	5.2 (2.5)	5.3 (2.4)	0.230	0.698
Clinical Stage					
I/II	79 (36.9%)	91 (36.1%)	39 (36.1%)	0.985	1.000
III/IV	135 (63.1%)	161 (63.9%)	69 (63.9%)		
Induction Chemo					
No	206 (96.3%)	167 (65.5%)	68 (61.3%)	**<0.001**	0.511
Yes	8 (3.7%)	88 (34.5%)	43 (38.7%)		
History of HTN					
No	109 (50.9%)	130 (51.0%)	43 (38.7%)	**0.049**	**0.041**
Yes	105 (49.1%)	125 (49.0%)	68 (61.3%)		
History of CAD					
No	181 (84.6%)	221 (86.7%)	101 (91.0%)	0.148	0.320
Yes	33 (15.4%)	34 (13.3%)	10 (9.0%)		
Smoking at diagnosis					
No	151 (70.6%)	193 (76.3%)	91 (82.0%)	**0.035**	0.284
Yes	63 (29.4%)	60 (23.7%)	20 (18.0%)		

Two Sample T-tests were performed for continuous variables and Chi-square tests were used for categorical variables. Statistically significant values are in bold. 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; PBT, proton beam radiotherapy; ECOG, Eastern Cooperative Oncology Group; PET, positron emission tomography; GEJ, gastro-esophageal junction; AC, adenocarcinoma; SCC, squamous cell carcinoma; HTN, hypertension, CAD, coronary artery disease.

highly associated with institution. Of the 214 patients who received 3D-CRT, 194 (90.7%) were treated at institution Y, while PBT was performed only at institution X. Significant differences existed between the utilization of the various radiation modalities by institution, including relative location of the primary tumor (more patients in the 3D-CRT group had upper/mid esophagus located tumors), differentiation of the primary tumor (well/moderate vs. poor), the use of induction chemotherapy, history of hypertension, and smoking at the time of diagnosis. Otherwise, the groups stratified by radiation modality were balanced by patient and tumor characteristics, including the relative tumor lengths.

The 3 RT modalities differed in the radiation dose distribution to the surrounding lung and heart, which is evident from the dose plans in 3 representative patients with distal esophageal tumors (Fig. 1). For 3D-CRT, the dose intensity is greatest in the heart while the lung has relatively less dose, which is the planning approach used in order to reduce the mean lung dose at the expense of the heart dose. For IMRT, low dose scatter are seen in both lung and heart, whereas PBT has low to no dose anteriorly through the heart and relatively low lung doses, particularly to the right lung. This is reflective in the mean lung and heart doses when the 3 modalities were compared. Patients treated with 3D-CRT, the mean lung dose (standard deviation, SD) is 10.5 (3.9) Gy, IMRT 9.5 (3.2) Gy, and PBT 6.1 (2.6) Gy, all highly statistically significant (when compared to one another and as a whole ($p < 0.0001$). For mean heart dose (SD), 3D-CRT is 28.4 (7.4) Gy, IMRT is 22.4 (6.7) Gy, and PBT is 13.2 (5.2) Gy, also all highly statistically significant ($p < 0.0001$).

Postoperative outcomes based on radiation modality

Four categories of postoperative complications were assessed, stratified by radiation modality (Table 2). We found significant difference in the incidence of pulmonary, cardiac and wound complications, but not in GI complications. The incidence of pulmonary complications was lowest for PBT (16.2%), intermediate for IMRT (24.2%), and highest for 3D-CRT (39.5%). The rate of cardiac complications was identical for PBT and IMRT (11.7%) but highest for 3D-CRT (27.4%). For wound complications, the rate was similar between IMRT (14.1%) and 3D-CRT (15.3%) and lowest for PBT (4.5%).

We also assessed the rate of readmission within 60 days postoperatively or death during the same hospitalization, postoperative mortality rates, and LOS. The readmission rate within 60 days after discharge or dying in the hospital was not significantly different between the 3 radiation modalities, although there was a trend to be higher in the 3D-CRT group. For postoperative mortality within 30, 60 and 90 days, there were no significant differences between the radiation modalities, although the 90 day

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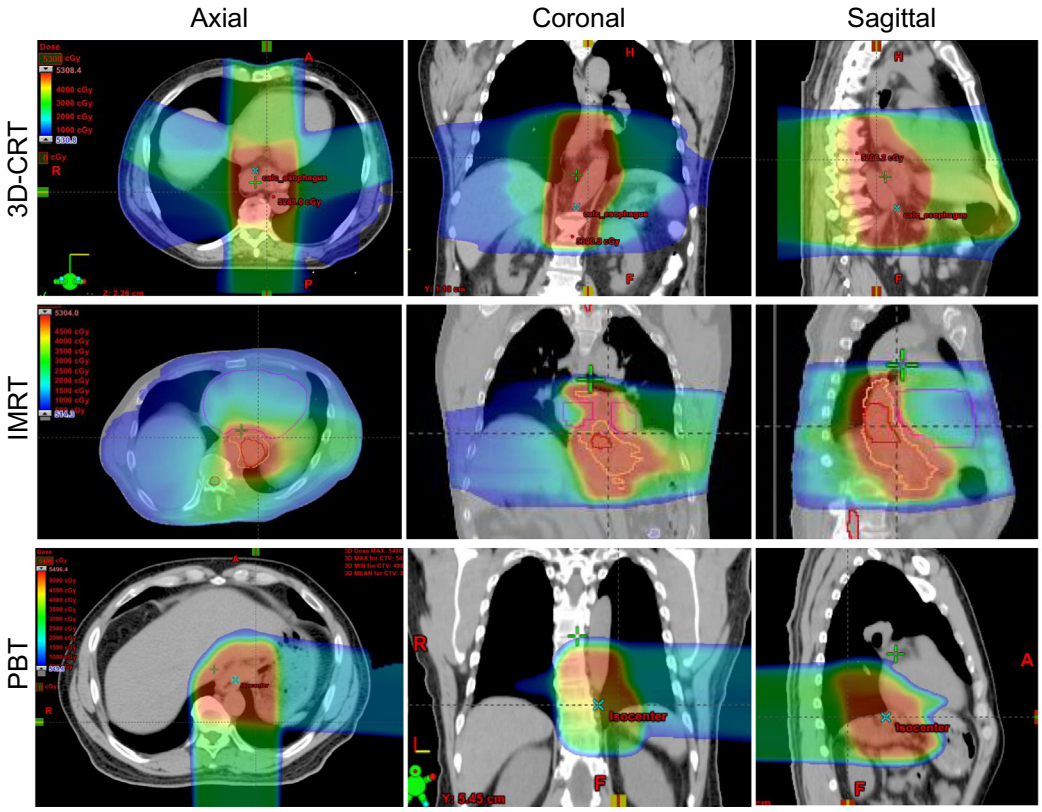

Fig. 1. Radiation dose distribution in 3 planes for 3D-CRT, IMRT or PBT in 3 patients with distal esophageal tumors.

Table 2
Postoperative outcomes stratified by treatment modality.

Complication Type	3D-CRT (n = 214, 36.9%)	IMRT (n = 255, 44.0%)	PBT (n = 111, 19.1%)	Chi-squared p-value
Postoperative complications				
Pulmonary				
Absent	130 (60.5%)	194 (75.8%)	93 (83.8%)	**<0.001**
Present	85 (39.5%)	62 (24.2%)	18 (16.2%)	
Gastrointestinal				
Absent	170 (79.1%)	197 (77.0%)	90 (81.1%)	0.656
Present	45 (20.9%)	59 (23.0%)	21 (18.9%)	
Cardiac				
Absent	156 (72.6%)	226 (88.3%)	98 (88.3%)	**<0.001**
Present	59 (27.4%)	30 (11.7%)	13 (11.7%)	
Wound				
Absent	182 (84.7%)	220 (85.9%)	106 (95.5%)	**0.014**
Present	33 (15.3%)	36 (14.1%)	5 (4.5%)	
Readmission within 60 days/died in hospital				
No	164 (76.3%)	216 (84.4%)	92 (82.9%)	0.070
Yes	51 (23.7%)	40 (15.6%)	19 (17.1%)	
Death within 30 days of surgery				
No	211 (98.1%)	253 (98.8%)	111 (100%)	0.425
Yes	4 (1.9%)	3 (1.2%)	0 (0%)	
Death within 60 days of surgery				
No	210 (97.7%)	249 (97.3%)	110 (99.1%)	0.590
Yes	5 (2.3%)	7 (2.7%)	1 (0.9%)	
Death within 90 days of surgery				
No	206 (95.8%)	245 (95.7%)	110 (99.1%)	0.264
Yes	9 (4.2%)	11 (4.3%)	1 (0.9%)	
Length of Hospital Stay (mean days & 95% CI)	13.2 (11.7–14.7)	11.8 (10.9–12.7)	9.3 (8.2–10.3)	**<0.001**

Statistically significant values are in bold. 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; PBT, proton beam radiotherapy.

mortality rate was numerically lower and clinically meaningful for PBT (0.9%, 1 of 111) compared to 3D-CRT or IMRT (~4% for each). The average LOS was significantly different in the 3 groups ($p < 0.001$), with the shortest LOS for PBT and longest for 3D-CRT patients.

In order to evaluate whether it was due to institutional biases that explained the differences in LOS rather than the use of a specific radiation modality, we stratified the LOS based on whether postoperative complications developed but didn't result in postoperative mortality, which will alter the true duration of the LOS. As a

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whole, 54% of the entire cohort had one or more postoperative complications. Patients who didn't have any complications had an average LOS (SD) of 7.9 days (2.1), and those who developed any complications had an average LOS of 11.9 days (10.9) ($p < 0.0001$). When LOS was evaluated by institution stratified for whether patients had developed any postoperative complications, patients from institution X had an average LOS of 7.5 days (1.7) without and 14.1 days (8.9) with complications. Patients from institution Y had an average LOS of 8.0 days (1.5) without and 16.3 days (14.1) with complications. Patients from institution Z had an average LOS of 13 days (2.8) without and 11.7 days (3.5) with complications. When we compared institution X with Y, we found no significant differences in the LOS whether patients did ($p = 0.114$) or did not ($p = 0.865$) have complications. However, when comparing institution Z with the others, it did have significantly longer LOS despite not having any complications ($p < 0.0001$). However, when comparing LOS in patients who had complications, there were no statistically significant differences comparing institution Z to the other institutions. We also evaluated this in the context of radiation modality. In patients treated with 3D-CRT, IMRT and PBT and didn't suffer complications, the average LOS (SD) were 8.1 days (1.8), 8.7 days (2.4), and 7.4 days (1.7), respectively. The small differences were significant as PBT patients did still have a reduced LOS compared to the other groups (vs 3D-CRT, $p = 0.01$; vs IMRT, $p = 0.0001$), although not different comparing 3D-CRT with IMRT ($p = 0.06$). However, in patients who had any complications, the average LOS (SD) for 3D-CRT, IMRT and PBT were 16.1 days (13.0), 12.8 days (1.9), and 12.0 days (7.7), respectively, but only the comparison of 3D vs PBT were marginally significant ($p = 0.05$). Taken together, this suggests that at least among the two largest centers that contributed the majority of the 3D-CRT, IMRT and PBT patients, it was not due to institutional bias that accounted for differences in LOS, as patients who did not develop complications had similar LOS, but rather the LOS was largely driven by the relative incidence of postoperative complications that were encountered.

Table 3
Multivariate analysis of factors associated with postoperative pulmonary, cardiac and wound complications.

Clinical Variable (Comparator vs. Reference)	*p*-Value	Odds Ratio (95% Confidence Interval)
Pulmonary Complications		
RT Modality		
IMRT vs. 3D-CRT	**0.009**	**0.577 (0.383–0.870)**
PBT vs. 3D-CRT	**<0.001**	**0.337 (0.187–0.610)**
PBT vs. 3D-CRT/IMRT	**0.005**	**0.447 (0.256–0.780)**
PBT vs. IMRT	0.077	0.584 (0.322–1.059)
Age at Diagnosis	**0.001**	**1.034 (1.014–1.054)**
History of COPD		
Yes vs. No	**0.032**	**2.075 (1.066–4.039)**
Tumor Location		
Distal vs. Proximal/Middle	0.071	0.534 (0.271–1.054)
Total Radiation Dose (Gray)		
≥50 vs. <50	**0.046**	**0.552 (0.307–0.990)**
Cardiac Complications		
RT Modality		
IMRT vs. 3D-CRT	**<0.001**	**0.388 (0.235–0.641)**
PBT vs. 3D-CRT	**0.002**	**0.336 (0.171–0.663)**
PBT vs. 3D-CRT/IMRT	**0.047**	**0.518 (0.271–0.990)**
PBT vs. IMRT	0.695	0.866 (0.423–1.774)
Age at Diagnosis	**0.002**	**1.039 (1.014–1.065)**
Gender		
Male vs. Female	0.061	0.577 (0.324–1.025)
History of CABG		
Yes vs. No	**0.022**	**3.140 (1.176–8.385)**
History of Atrial Fibrillation		
Yes vs. No	**0.005**	**3.791 (1.502–9.568)**
Wound Complications		
RT Modality		
IMRT vs. 3D-CRT	0.767	0.925 (0.551–1.551)
PBT vs. 3D-CRT	**0.006**	**0.255 (0.096–0.675)**
PBT vs. 3D-CRT/IMRT	**0.005**	**0.266 (0.104–0.677)**
PBT vs. IMRT	**0.009**	**0.276 (0.105–0.725)**
History of Coronary artery disease		
Yes vs. No	0.096	0.473 (0.195–1.143)
History of COPD		
Yes vs. No	0.060	2.166 (0.969–4.841)

Statistically significant values are in bold. IMRT, intensity-modulated radiotherapy; COPD, chronic obstructive pulmonary disease.

Predictors of postoperative complications

Univariate (Supplemental Tables 2–4) and multivariate analysis (Table 3) were conducted for factors that most significantly influenced the development of the 3 complications. Because radiation modality and institution are highly correlated, we did not include institution in the multivariate analysis. Age at diagnosis, radiation dose, and radiation modality were significantly associated with the risk of pulmonary toxicity. Both IMRT and PBT were associated with a reduced risk of pulmonary complications as compared to 3D-CRT ($p < 0.001$), whereas PBT had a trend to being superior to IMRT (OR 0.584, $p = 0.077$). For cardiac complications, older age and history of coronary artery bypass grafting or atrial fibrillation were associated with a greater risk of cardiac complications. IMRT or PBT was associated with a reduced risk of cardiac complications compared to 3D-CRT (OR 0.388, $p < 0.001$ and OR 0.336, $p = 0.002$, respectively). For wound complications, only PBT was significantly associated with reduced risk (OR 0.255, $p = 0.006$, PBT vs 3D-CRT; OR 0.276, $p = 0.009$, PBT vs IMRT), while there was no significant difference comparing IMRT and 3D-CRT. Surgical approaches were not associated with any of the toxicities.

Discussion

In this large retrospective multi-institutional analysis of patients treated with nCRT for esophageal cancer, we found that RT modality, along with other patient and clinical factors, was associated with postoperative morbidity and mortality and as a consequence, the length of hospitalization. Advanced radiation delivery technologies such as IMRT and PBT were associated with better outcomes compared to 3D-CRT, and PBT was superior to IMRT in some of clinical outcomes. We believe that the higher radiation dose to the heart and lungs is likely the reason for the higher rates of postoperative morbidity and mortality in the photon-based treatments, as described in other studies which have described the relationship of mean lung dose and postoperative pulmonary morbidities [5,13].

The utilization of advanced radiation technologies has been shown previously to have an impact on the clinical outcomes in esophageal cancer. In a single institution study, IMRT was associated with improved overall survival as compared to 3D-CRT. This difference appeared to be related to a lower rate of cardiac mortality in the patients treated with IMRT [2]. A SEER/TCR Medicare analysis also demonstrated that IMRT was associated with improved survival outcomes due in part to a lower risk of cardiac mortality compared to 3D-CRT treated patients [4]. These results suggest that the relatively good cardiac sparing effects of IMRT [6] may have long term clinical benefit for patients. For patients who undergo surgery after neoadjuvant chemoradiation, IMRT was also associated with a reduced risk of pulmonary and GI complications as compared to 3D-CRT [5]. A limitation of that particular study was that 3D-CRT patients were treated in an earlier era as compared to IMRT, potentially inaccurately portraying the absolute benefit of IMRT, a bias that the current study circumvents.

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PBT is a promising radiation modality for treatment of esophageal cancer, as PBT can drastically reduce radiation dose to the heart and lungs [10,14]. One of the first experiences was reported by Tsukuba University, where patients received PBT alone without systemic therapy delivered up to 98 CGE (median 79 cGE, range 62–98) [15] as definitive therapy. More recently, clinical experience of PBT with concurrent chemotherapy has been reported, with PBT associated with comparable efficacy (compared to photon based RT) and lower late effects such as pneumonitis, pleural and pericardial effusion [11,12]. There is limited published experience with the use of PBT as a component of trimodality therapy for esophageal cancer. A previous report showed lower rates of post-operative pulmonary complications with PBT or IMRT compared to 3D-CRT, likely due to the associated lower mean lung dose [5]. The present study further supports that PBT (compared to photon-based techniques) may reduce post-operative complications. Additionally, we demonstrate that PBT is associated with favorable long-term outcomes and is a promising treatment modality for this disease.

The strength of the current study is the size of the patient cohort treated with various modalities during the same period of time. However, a limitation of our study is the retrospective nature of this analysis, which potentially introduce bias in the data which could affect the results. One such bias is institutional, which we could not correct for since the use of the modalities was not evenly distributed across all 3 institutions. Postoperative morbidity and mortality could also be influenced by the experience and quality of medical care at a particular institution and not due to the type of radiation preferentially used at that institution [16]. However we believe this factor is unlikely to be a contributor to the observed complication rates, since all patients were treated at major academic centers with state-of-the-art surgery and postoperative care, in a fully-evolved multidisciplinary context. Although there appears to be institutional bias for longer LOS for institution Z regardless of whether patients developed complications or not, the policies for keeping patients in the hospital between the two major centers that contributed to >90% of the patients to this study appear similar, in that patients stay in the hospital due to postoperative complications that developed. We found that for the most part, patients who didn't develop complications had similarly short LOS regardless of which institutions the patients were treated at. Conversely, this was also true for patients who developed complications, as their LOS also were similarly long between institutions. Therefore, we believe the differences in the LOS were not due to institutional policies but due to the relative rates of complications seen at the respective institutions. While it is certainly possible that other factors contributed to the increased rate of complications seen in one institution versus another, radiation modality appears to be an important independent predictor of complications, along with other factors. We also don't believe that somehow the 3D-CRT cohort seen in our study did particularly bad, since the rates of post-operative complications (pulmonary, cardiac, and anastomotic) observed were equal or lower to those observed in patients receiving trimodality therapy on the Dutch CROSS trial [1], thereby ruling out "excess" morbidity in the 3D-CRT arm as a source of potential bias.

Conclusions

Advanced RT modalities appear to influence survival outcomes and reduce postoperative complications. Although randomized comparison between PBT and IMRT is ongoing, our data provide meaningful new evidence that supports the potential clinical benefit of PBT in the treatment of esophageal cancer.

Conflict of interest statement

MM has served as a consultant for Abbott, Bristol-Meyers-Squibb, Celldex, Cavion, Elekta, Novartis, Novocure, and Roche, has research funding from Novocure and Cellectar, and has served in a leadership capacity on the Pharmacyclics BOD (with stock options).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2017.04.013.

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