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Scientific Article

Dosimetry and Acute Toxicity Profile of Patients With Esophageal Cancer Treated With Proton Beam Radiation Therapy: Outcomes From the Proton Collaborative Group REG001-09 Trial

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Abstract

Purpose: Concurrent chemoradiation plays an integral role in the treatment of esophageal cancer. Proton beam radiation therapy has the potential to spare adjacent critical organs, improving toxicity profiles and potentially improving clinical outcomes.

Methods and Materials: We evaluated the REG001-09 registry for patients undergoing proton radiation therapy for esophageal cancer. Demographic, clinicopathologic, toxicity, and dosimetry information were compiled.

Results: We identified 155 patients treated at 10 institutions between 2010 and 2019. One hundred twenty (77%) had adenocarcinoma and 34 (22%) had squamous cell carcinoma. One hundred thirty-seven (88%) received concurrent chemotherapy. The median delivered dose was 50.51 Gy-equivalent (GyE; range, 41.4-70.1). Grade ≥3 toxicities occurred in 22 (14%) of patients and were most commonly dysphagia (6%), esophagitis (4%), anorexia (4%), and nausea (2%). There were no episodes of grade ≥4 lymphopenia and no grade 5 toxicities. The average mean heart, lung, and liver doses and average maximum spinal cord dose were 10.0 GyE, 4.8 GyE, 3.8 GyE, and 34.2 GyE, respectively. For gastroesophageal junction tumors, 8% of patients developed acute grade ≥3 toxicity and the mean heart, liver, right kidney, and left kidney doses were 10.5 GyE, 3.9 GyE, 0.4 GyE, and 4.9 GyE, respectively. Gastroesophageal junction location was protective against development of grade ≥3 toxicity on univariate ($P = .0009$) and multivariate ($P = .004$) analysis.

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The data sets generated and analyzed during the present study are not publicly available but are available from the corresponding author on reasonable request.

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Conclusions: Proton beam radiation therapy affords excellent dosimetric parameters and low toxicity in patients with esophageal cancer treated with curative intent. Prospective trials are underway investigating the comparative benefit of proton-based therapy.

Introduction

Esophageal cancer is relatively rare but has one of the worst prognoses among all malignancies. The Chemoradiotherapy for Esophageal Cancer Followed by Surgery Study (CROSS) established trimodality therapy as the standard of care for resectable esophageal cancer, with 5-year overall survival (OS) of 47% representing a considerable improvement relative to historical series.[1-3] However, such treatment may incur significant cardiopulmonary, hematologic, and postoperative complications that may predict poor outcomes.[4,5] Radiation therapy (RT) plays an integral role in this treatment paradigm, but the proximity of the esophagus to dose-limiting critical structures, such as the heart and lung presents a unique challenge. To date, a number of studies have demonstrated that intensity modulated RT (IMRT) may result in a significant benefit relative to 3-dimensional conformal RT (3DCRT) by virtue of an improved toxicity profile as a result of more conformal dosimetry and superior sparing of adjacent organs-at-risk.[6-8]

Proton beam therapy (PBT) has the potential to further improve dose conformity and spare normal tissues.[9] Indeed, the physical characteristics of particle therapy offer the potential for improved target coverage while reducing dose to surrounding critical structures compared with photon-based therapy.[10] In contrast to photon-based therapy, proton therapy sharply deposits dose at the Bragg peak, yielding a localized high-dose region around the target volume without exit dose to significantly spare nearby healthy tissue. Several retrospective studies have demonstrated a clinical and dosimetric advantage with this approach.[11-13] Xi et al suggested an OS benefit with the use of PBT compared with IMRT, and Lin et al suggested that the clinical benefit of PBT may derive from an improved cardiopulmonary toxicity profile.[11,12] More recently, a phase 2B trial comparing IMRT and PBT demonstrated an improved toxicity profile with PBT with similar clinical endpoints.[14] In particular, this study used a novel toxicity endpoint, total toxicity burden (TTB), which encompassed 13 possible instances of 11 distinct adverse events, which were either postoperative or deemed secondary to chemoradiation. Before closure upon activation of the NRG-GI006 phase 3 randomized PBT versus IMRT trial, mean TTB was found to be lower for PBT than IMRT, with similar rates of 3-year progression free survival and OS. Further prospective investigation is required before PBT can be considered a standard of care. The present study is a multi-institutional prospective registry evaluation of patients receiving definitive PBT for locally advanced esophageal cancers, with a focus on acute toxicity and dosimetry profiles.

Methods and Materials

The REG001-09 trial is a prospective, multi-institutional registry study of patients undergoing PBT; beginning in 2017 patients treated with photon therapy alone or in addition to PBT were also permitted to enroll. Written informed consent was obtained from all patients before they were enrolled on the registry study. Institutional review board approval was granted for each of the participating institutions.

The registry trial was queried for the subset of patients undergoing PBT for esophageal cancer to the intact esophagus. Patients were treated with pencil beam scanning (PBS) or passive scattering/uniform scanning (PS). Patients undergoing photon therapy were excluded. Only patients treated to at least 41.4 dose unit Gy-equivalent (GyE) were included in the present analysis (patients with limited metastatic disease treated with definitive intent were allowed per treating physician discretion). Patients receiving esophageal reirradiation were not eligible. Patient, tumor characteristics, radiation treatment details, toxicity, and dosimetric information were all collected.

Patients generally underwent 4-dimensional computed tomography (CT) simulation with intravenous contrast. Gross tumor volume was defined as all disease as seen on positron emission tomography/computed tomography and esophagogastroduodenoscopy, and clinical target volume included all areas of potential disease spread. Optimal beam arrangements were determined on a case-by-case basis. The relative biologic effectiveness was set at 1.1 per institutional standard of all participating institutions. GyE was proton dose in Gy multiplied by relative biologic effectiveness. Fractionation schemes were at the discretion of participating institutions. Acute toxicity was physician-graded and documented at on-treatment visits and at up to 3-month clinical follow-up. Follow-up beyond 3 months is not reported in the present study. Toxicity was recorded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

The actuarial rates of toxicity were calculated using the Kaplan-Meier method, starting from the first day of radiation. The log-rank test was used to analyze intergroup differences. Univariable analysis was conducted using the

Cox proportional hazards regression model, and prognostic factors with univariate significance of $P < .1$ where further tested in multivariate analysis to determine hazard ratios (HR). Two-sample t tests were conducted to compare dosimetric means based on patient baseline characteristics. Statistical analyses were performed using R version 3.6.2. Statistical significance was set to $P < .05$.

Results

Patient characteristics

In total, 161 patients signed consent forms and were enrolled on the registry trial. A total of 155 patients were treated to at least 41.4 GyE. These patients were treated across 10 institutions between 2010 and 2019. The median number treated per institution was 11 (range, 1-39). Of the 155, 120 (77%) had adenocarcinoma, 34 (22%) had squamous cell carcinoma, and 1 (1%) had mixed adenocarcinoma/neuroendocrine. Patient characteristics are listed in Table 1. The logistics of surgery and surgical postoperative toxicity were not collected on the registry and are not reported herein. The vast majority of patients underwent concurrent systemic therapy (88%). Of patients receiving systemic therapy, 97 (71%) received carboplatin/paclitaxel, 5 received capecitabine (4%), 4 received paclitaxel/cisplatin/fluorouracil (3%), 4 received fluorouracil monotherapy (3%), 5 received cisplatin/fluorouracil (4%), 6 received docetaxel-based regimens (4%), 1 received leucovorin/fluorouracil/oxaliplatin (1%), 1 received paclitaxel/ carboplatin /fluorouracil (1%), and 13 received unknown regimens (9%). One hundred fifteen (74%) had tobacco histories, 38 did not (25%), and 2 had unknown status (1%).

Table 1 Patient characteristics

Characteristic	n = 155% (no.) or median (range)
Age, y	68.2 (24-91)
Sex	
Male	77% (120)
Female	23% (35)
Race/ethnicity	
White	76% (118)
Black	0% (0)
Hispanic	17% (27)
Other	1% (1)
Unknown	6% (9)
ECOG	
0	48% (75)
1-3	37% (58)
Unknown	14% (22)
Histology	
Adenocarcinoma	77% (120)
Squamous cell carcinoma	22% (34)
Other	1% (1)
Grade	
1-2	43% (67)
3	30% (46)
Undetermined	27% (42)
Tumor dimension, cm	4.5 (1-10)
Stage	
I-II	39% (60)
III-IV	54% (83)
Unknown	8% (12)
T category	
T1-T2	26% (41)
T3-T4	60% (93)
TX	6% (9)
Unknown	8% (12)
N category	
N0	30% (46)
N+	61% (94)
NX	1% (2)
Unknown	8% (13)
M category	
M0	75% (116)
M1	7% (11)
Unknown	18% (28)
Chemotherapy	
Induction	12% (19)
Concurrent	88% (137)

Abbreviation: ECOG = Eastern Cooperative Oncology Group.

Radiation and dosimetry

Ninety-three patients (60%) were treated with PBS, 53 were treated with PS (34%), and 9 (6%) were treated with unknown technique. The median dose delivered was 50.51 GyE (range, 41.4-70.1). One hundred forty-nine patients (96%) completed treatment as planned, whereas 2 stopped due to toxicity (2%), 1 stopped due to patient preference (1%), 1 died due to reasons not related to treatment toxicity (1%), and 2 stopped for other unspecified reasons (1%). Of those patients finishing treatment as planned, 51 required a treatment break (34%). Twenty-seven (18%) had a break due to equipment issues, 13 (9%) had a break per patient preference, and 11 (7%) had a break due to toxicity (either radiation, systemic therapy, or a combination). The average maximum spinal cord dose was 34.2 GyE (range, 11.5-44.3 GyE), the average mean heart dose was 10.0 GyE (range, 1.4-25.9), the average mean total lung dose was 4.8 GyE (range, 1.4-13.4), and the average mean liver dose was 3.8 GyE (range, 0.59-16.7). When evaluating only patients with gastroesophageal junction (GEJ) tumors, the average mean heart dose was 10.5 GyE, the average mean liver dose was 3.9 GyE, the average mean right kidney dose was 0.4 GyE, and the average mean left kidney dose was 4.9 GyE. The presence of T3/T4 disease (versus T1/T2),

Table 2 Treatment-related toxicity

Toxicity			
CTCAE category	CTCAE term	Any grade% (no.)	grade 3+% (no.)
Cardiac	Atrial fibrillation	1% (1)	
Gastrointestinal	Diarrhea	19% (30)	
	Dry mouth	3% (5)	
	Dyspepsia	16% (25)	
	Dysphagia	29% (45)	6% (10)
	Esophageal obstruction	1% (1)	
	Esophageal pain	16% (25)	1% (2)
	Esophagitis	40% (62)	4% (6)
	Oral mucositis	3% (4)	
	Nausea	56% (87)	2% (3)
	Gastric obstruction	1% (1)	
	Stomach pain	1% (1)	
	Vomiting	21% (32)	
General	Fatigue	60% (93)	1% (1)
	Noncardiac chest pain	1% (1)	
	Pain	23% (36)	1% (1)
Infections	Stoma site infection	1% (1)	
Injury/procedural	Radiation dermatitis	65% (101)	1% (2)
Investigations	Neutropenia	1% (1)	1% (1)
	Lymphopenia	0	0
	Thrombocytopenia	0	0
	Weight loss	10% (15)	
Metabolism	Anorexia	43% (66)	4% (6)
	Dehydration	17% (26)	
Musculoskeletal	Back pain	1% (1)	
Nervous system	Dizziness	1% (2)	
	Dysgeusia	3% (5)	
	Peripheral sensory neuropathy	4% (6)	
Respiratory	Aspiration	1% (2)	
	Cough	26% (40)	
	Dyspnea	10% (15)	
	Hoarseness	16% (25)	
	Laryngitis	1% (1)	
	Pharyngitis	2% (3)	
	Pharyngolaryngeal pain	1% (2)	
	Sore throat	2% (3)	
Skin	Erythema multiforme	3% (5)	
	Hyperpigmentation	3% (5)	
Vascular	Hypotension	1% (1)	

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events (version 4).

N + disease (versus N0), or GEJ location were not associated with higher mean heart, mean lung, mean liver, or maximum spinal cord doses by 2-sample *t* tests ($P > .05$ for all).

Toxicity

Acute toxicities are presented in Table 2. The most common toxicities of any grade were radiation dermatitis (101/155, 65%), fatigue (93/155, 60%), nausea (87/155, 56%), anorexia (66/155, 43%), esophagitis (62/155, 40%), and dysphagia (45/155, 29%). Grade ≥3 toxicities included dysphagia (10/155, 6%), esophagitis (6/155, 4%), anorexia (6/155, 4%), nausea (3/155, 2%), esophageal pain (2/155, 1%), and radiation dermatitis (2/155, 1%). There was in addition one grade ≥3 episode of each of the following: fatigue, pain, and neutropenia. There were no episodes of grade 4 leukopenia. Postoperative complications and long-term cardiopulmonary sequelae were not comprehensively available. As depicted in Fig. 1, the 3-month actuarial freedom from grade ≥3 toxicity was 81.8% (95% CI [confidence interval], 74.8%-89.4%). Univariate and multivariate analysis were

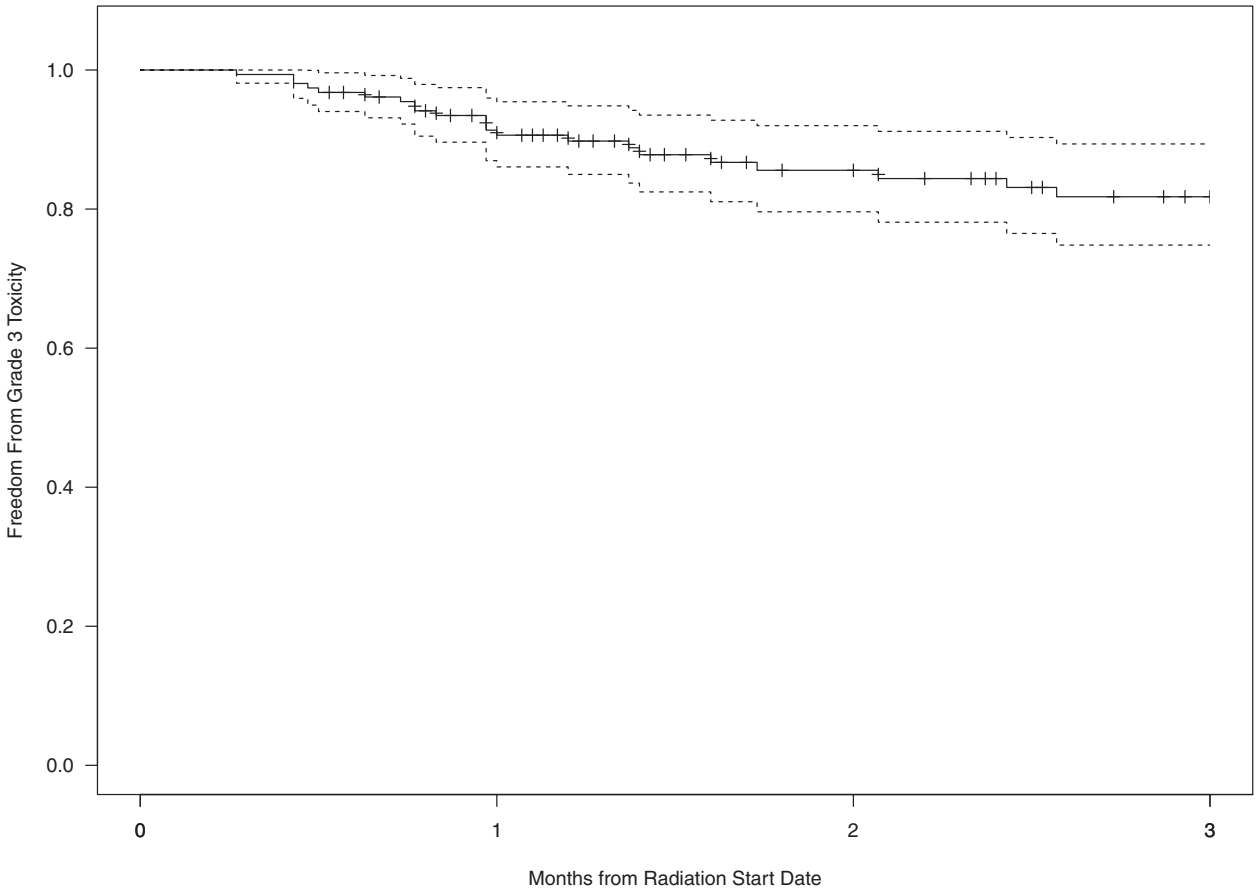

Figure 1 Kaplan-Meier freedom from grade ≥3 toxicity from the start of radiation therapy.

Table 3 Univariate and multivariate analysis for development of grade ≥3 toxicity

Univariate					Multivariate			
Variable	Level	HR	95% CI	*P* value	Variable	HR	95% CI	*P* value
Age		1.05	1.003-1.10	.037	Age	1.05	0.96-1.14	.29
ECOG	1-3 vs 0	0.79	.31-2.04	0.63				
Size, cm		1.23	.81-1.86	0.34				
T stage	T3/T4 vs T1/T2	0.77	.32-1.89	0.57				
N stage	N+ vs N0	0.98	.39-2.45	0.97				
Dose, GyE		0.97	0.88-1.07	.57				
Modality	PBS vs PS	1.03	.42-2.54	0.95				
Location	GEJ vs other	0.074	.016-.34	0.0009	Location	0.10	.02-.48	0.004
Mean heart dose		0.81	0.62-1.05	.11				
Mean lung dose		0.78	0.45-1.33	.36				
Mean liver dose		1.1	0.89-1.35	.38				
Maximum cord dose		1.27	0.95-1.70	.11				

Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; GEJ = gastroesophageal junction; HR = hazard ratio; PBS = pencil beam scanning; PS = passive scattering.

performed to determine prognostic factors for the development of grade ≥3 toxicity (Table 3). The presence of GEJ location was associated with lower rates of grade ≥3 toxicity on univariate (HR 0.074; 95% CI, 0.016-0.34; *P* = .0009) and multivariate (HR 0.10; 95% CI, 0.02-0.48; *P* = .004) analyses. The presence of T3/T4 disease versus T1/T2 disease (*P* = .57) and N + disease versus N0 disease (*P* = .97) was not associated with less grade ≥3

toxicity. In addition, the use of PBS versus PS technique ($P = .95$) was not associated with lower rates of grade ≥3 toxicity.

Discussion

To our knowledge, this is the largest prospective report of patients undergoing proton beam therapy for esophageal cancer. We report very low rates of acute toxicity and dosimetric parameters, consistent with other recently published particle-based series.[14,15] Our acute toxicity profile also compare favorably to acute events during chemoradiation on the CROSS trial, despite the fact that those patients only received 41.4 Gy.[3] In particular, we report only a single patient with grade ≥3 hematological toxicity (1 of 155, 1%), compared with a 7% (12 of 171) rate of grade ≥3 hematological toxicity on the CROSS trial. In terms of nonhematological toxicity, 14% (22 of 155) of our patients experienced grade ≥3 toxicity, compared with 13% on the CROSS trial.

The impetus for increasing conformality in esophageal radiation planning stems from the central location of the esophagus in the thorax and its proximity to the heart and lungs. Although 3DCRT technically remains the standard-of-care, intensity modulated radiation therapy (IMRT) is now commonly used based on retrospective evidence suggesting dosimetric and clinical benefit. By virtue of decreased cardiac dosing with IMRT, there is suggestion that patients have lower cardiac morality with IMRT that may translate to an overall survival advantage.[7,8] IMRT may also significant reduce the V_{10} (volume receiving 10 Gy), V_{20}, and mean dose to the total lung volume.[6] With the increasing prevalence of proton therapy centers in the United States, there is now a concerted effort to use particle-based therapies to further improve outcomes via additional normal tissue sparing.

Until recently, these efforts were from single institutions and retrospective in nature. In one of the initial reports on PS proton beam therapy at MD Anderson, patients treated to 50.4 GyE in 28 fractions experienced low rates of grade 3 esophagitis (9.7%), dysphagia (9.7%), nausea/vomiting (8.1%), radiation dermatitis (3.2%), fatigue (8.1%), and anorexia (4.8%).[15] There were also 2 episodes of grade 5 toxicity. Our corresponding toxicities compare very favorably to these results, which could be attributed to the exclusive use of PS technique in that study, in contrast to the PBS used in a majority of our patients. PBS uses magnets to "paint" the target volume layer by layer, allowing for potentially more conformal dose distributions.[9] However, drawing comparisons between retrospective series must be undertaken with caution. Moreover, PBS did not significantly predict for lower grade ≥3 toxicity on statistical analysis ($P = .95$). Other retrospective series have similarly suggested meaningful reductions in dose to heart, lung, and liver afforded by proton therapy along with modest rates of grade ≥3 toxicity.[16]

More recently, in a phase 2B randomized trial comparing protons with IMRT, Lin et al demonstrated that patients receiving proton therapy had improved TTB.[14] TTB was created as a novel toxicity index to evaluate the total patient experience throughout their treatment as an alternative to more conventional National Cancer Institute Common Terminology Criteria for Adverse Events-based methods. Three-year progression-free survival and OS rates were similar on the study between the proton and photon-based groups. For the PBT group, they reported average mean lung, average mean heart, average mean liver, and average maximum spinal cord doses of 4.8 Gy, 11.3 Gy, 2.4 Gy, and 38.3 Gy, respectively. Among their IMRT patients, the respective values were 8.4 Gy, 19.8 Gy, 12.1 Gy, and 38.4 Gy. Our respective values of 4.8 GyE, 10.0 GyE, 3.8 GyE, and 34.2 GyE are similar to these parameters, and highlight the improvement in heart, lung, and liver dosimetry when using protons. In general, 3DCRT therapy yields even higher doses to organs-at-risk than IMRT, with mean heart doses up to 28.3 Gy in 3DCRT series.[7] Among the 11 distinct adverse events encompassed by TTB, we report only a single episode of atrial fibrillation (although follow-up was limited, and our results are limited to acute toxicity).

There were no episodes of grade ≥4 lymphopenia in our series, and only a single case of grade ≥3 hematological toxicity. In general, lymphocyte counts decline during chemoradiation, which in part is due to the extreme radio-sensitivity of lymphocytes. Lymphocytes are the most radiosensitive cell in the human body, with a D50 (dose required to kill 50% of the population) of approximately 1 Gy.[17] Davuluri et al demonstrated that a grade 4 absolute lymphocyte count nadir was associated with worse overall survival in patients with esophageal cancer.[4] In that series, 59% of patients had a grade 3 absolute lymphocyte count nadir and 27% of patients had a grade 4 nadir. The lower rates of lymphopenia observed with proton therapy are likely secondary to lower integral dose and thereby less dose to circulating blood cells and potentially precursor blood cells in the bone marrow. Unfortunately, bone marrow was not routinely contoured in the present study. The lack of cytotoxic T lymphocytes in these patients may weaken host defense,[18] thus adversely affecting clinical outcomes. Put together, the alleviation of toxicity burden and reduction in lymphopenia nadir offer 2 potential pathways via which proton therapy may improve clinical outcomes in patients with locally advanced esophageal cancer (NRG-GI006 protocol).

Among our patients, the presence of T3/T4 or N + disease did not predict for the development of grade ≥3 toxicity, which suggests that with PBT, dose conformity is achievable even in patients with very locally advanced disease. Based on RTOG 9404, radiation dose escalation beyond 50.4 Gy is not considered standard.[2]

However, that trial was based on outdated radiation techniques, was prematurely closed, and 7 out of 11 treatment-related deaths occurred in patients receiving less than 50.4 Gy. With improved technical capabilities, there has recently been renewed interest in dose escalation, particularly in patients who are not operative candidates. In fact, more recent evidence suggests that there might be a dose-response and benefit for dose-escalation.[19] This is currently being investigated with a phase 1 dose-escalation trial of neoadjuvant proton beam radiation therapy at the University of Pennsylvania (NCT02213497). Moreover, the ART DECO trial (NRT3532) is a randomized phase 3 trial comparing standard-dose (50.4 Gy) to high-dose (61.6 Gy via a simultaneous integrated boost) chemoradiation. Preliminary results do not suggest a local control benefit with dose-escalation as measured by 3-year local-progression free survival,[20] although this has not been published in manuscript form. Furthermore, our results also suggest that distal esophageal location is protective against grade ≥3 toxicity. This is likely a result of normal esophageal physiology, wherein the proximal portion of the esophagus is more sensitive and less compliant than the distal portions.[21] It is also possible that patients with GEJ tumors are more likely to have comorbid gastroesophageal reflux, which limits esophageal sensitivity along the entire tract of the organ.[22] Finally, GEJ tumors may better spare the heart and lung, though we did not find improved dosimetry in this analysis with GEJ tumors.

Shortcomings of this report includes incomplete information on which patients underwent definitive esophagectomy after chemoradiation. Accordingly, we do not report clinical outcomes herein. In addition, we do not report long-term toxicity and we are thus unable to capture potential late cardiopulmonary sequelae of treatment and correlate this with our dosimetry data. Removing patients receiving less than 41.4 GyE may have introduced selection bias into our analysis. Moreover, because toxicity was collected in radiation oncology departments, hematological toxicity may be underreported. The population presented is heterogeneous due to the multi-institutional nature of this report and the fact that patients were not treated on a strictly defined protocol. Conversely, this represents the largest proton experience on dosimetry and acute toxicity in patients with esophageal cancer to date and is prospective in nature.

We conclude that treatment with proton-based therapy with curative intent in patients with esophageal cancer affords promising normal tissue sparing and rates of non-hematological acute grade ≥3 toxicity that compare favorably to photon-based historical controls, contributing to the growing body of evidence showing that PBT is safe and feasible. The presence of distal esophageal location predicts protection from acute grade ≥3 toxicity. Prospective evaluation of the comparative efficacy of proton therapy compared with photon-based therapy is the basis for the ongoing NRG-GI006 study.

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