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Scientific Article

A Prospective Pilot Study of Pencil Beam Scanning Proton Radiation Therapy as a Component of Trimodality Therapy for Esophageal Cancer

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Purpose: To evaluate the safety and efficacy of pencil beam scanning (PBS) proton radiation therapy (RT) in trimodality therapy for esophageal cancer.

Methods and Materials: This prospective pilot study was planned to accrue 30 patients with locally advanced esophageal or gastroesophageal junction carcinoma medically suitable for chemoradiation therapy (CRT) followed by esophagectomy. PBS proton RT consisted of 25 fractions, 50 Gy to tumor + 1 cm and 45 Gy to a 3.5 cm mucosal expansion and regional lymph nodes. Chemotherapy included weekly carboplatin (area under the curve, 2 mg/mL/min) and paclitaxel (50 mg/m^2). At 4 to 8 weeks after CRT, patients underwent restaging and potential esophagectomy. The primary endpoint was acute grade 3+ adverse events (AEs) attributed to CRT. Overall survival and progression-free survival were assessed using the Kaplan-Meier methodology; local-regional recurrence and distant metastases rates were assessed using the cumulative incidence methodology. The Functional Assessment of Cancer Therapy−Esophagus assessed quality of life.

Results: Thirty eligible patients were enrolled from June 2015 to April 2017. Median age was 68 years. Histology was adenocarcinoma in 87%, and location was distal esophagus/gastroesophageal junction in 90%. Stage was T3 to T4 in 87% and N1 to N3 in 80%. All patients completed the planned RT dose. Acute grade 3+ AEs occurred in 30%, most commonly leukopenia and neutropenia. Acute grade 3+ nonhematologic AEs occurred in 3%. Esophagectomy was performed in 90% of patients (R0 in 93%). Pathologic complete response rate was 40%. Major postoperative complications (Clavien-Dindo score, ≥3) occurred in 34%. Postoperative mortality at 30 days was 3.7%. Median follow-up was 5.2 years. Five-year outcome estimates were overall survival at 46%, progression-free survival at 39%, local-regional recurrence at 17%, and distant metastases at 40%. Functional Assessment of Cancer Therapy−Esophagus scores

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(medians) at baseline, at the end of CRT, before esophagectomy, at 12 months, and at 24 months were 145, 136 (p = .0002 vs baseline), 144, 146 and 157, respectively.

Conclusions: PBS proton RT is feasible and safe as a component of trimodality therapy for esophageal cancer.

Introduction

For patients with resectable nonmetastatic thoracic esophageal cancer, the current standard of care is trimodality therapy consisting of preoperative concurrent chemoradiation therapy (CRT) followed by esophagectomy. Trimodality therapy is associated with significant treatment-related adverse effects (AEs). In the ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) trial, a majority of patients experienced fatigue, cytopenia, anorexia, and nausea during CRT and approximately 20% experienced serious or life-threatening AEs.[1] Additionally, a significant proportion of patients experienced major postoperative complications, including pulmonary, cardiac, anastomotic, and wound complications and/or late cardiopulmonary AEs.[1] In patients with esophageal cancer, several studies have reported a significant direct correlation between radiation therapy (RT) dose to the lungs and heart and risk of pulmonary or cardiac AEs.[2-6]

For esophageal cancer, retrospective dosimetric studies have reported that proton RT can deliver a similar dose to the target volume compared with photon-based techniques, with a significantly lower dose delivered to adjacent organs, including the heart, lungs, uninvolved stomach, bowel, liver, and kidneys.[7] By reducing the RT dose delivered to normal organs, proton RT may reduce the acute, perioperative, and late toxicities associated with CRT for esophageal cancer. When this trial was initiated in 2015, there were limited published retrospective clinical data evaluating proton RT for esophageal cancer, and existing studies used passive scatter (PS) techniques.[8,9] Furthermore, in 2015, there were no published prospective trials evaluating proton RT for esophageal cancer and no published data regarding the use of pencil beam scanning (PBS) or intensity modulated proton RT. Although intensity modulated proton RT offers significant dosimetric advantages over PS proton RT for esophageal cancer (specifically superior heart and lung sparing), concern exists regarding its use related to dosimetric robustness and motion interplay effects.[10,11]

This prospective observational pilot study was designed to assess the AE profile and efficacy of PBS proton RT in patients with esophageal cancer to be treated with trimodality therapy. We hypothesized that PBS proton RT would be associated with a favorable AE profile and similar disease control outcomes relative to historical comparisons of patients treated with photon RT. Disease control outcomes were assessed as a secondary endpoint.

Methods and Materials

Eligibility

This was a single-institution, single-arm prospective observational pilot study. Eligibility criteria were (1) age ≥18 years; (2) histologically confirmed adenocarcinoma or squamous cell carcinoma arising from the esophagus (middle or distal) or gastroesophageal junction, with ≤5 cm of tumor extension into the stomach/cardia (Siewert type I-II); (3) American Joint Committee on Cancer seventh edition clinical stage T1N1-3M0 or T2-4N0-3M0; (4) Eastern Cooperative Oncology Group performance status score of 0, 1, or 2; and (5) evaluation by radiation oncology, medical oncology, and thoracic surgery and deemed medically suitable for neoadjuvant CRT followed by esophagectomy. Exclusion criteria were (1) tumors arising from the cervical or upper esophagus with any part of the tumor <24 cm from the incisors, (2) prior chemotherapy or RT for esophageal cancer, (3) history of RT to the thorax, and (4) severe concurrent or comorbid illness. All patients underwent basic laboratory assessment, esophagogastroduodenoscopy, endoscopic ultrasound, and fluorodeoxyglucose positron emission tomography/computed tomography within 30 days prior to registration. All patients provided written informed consent for enrollment in this study. The protocol, protocol amendments, and informed consent documents were approved by the institutional review board.

Treatment

PBS proton RT consisted of 50 Gy in 25 fractions, 1 treatment per day, 5 days per week, over 5 weeks. Patients underwent 4-dimensional computed tomography (4DCT) simulation in the supine position, preferably with arms above the head in a custom vacuum immobilization device, although arms at the side were acceptable. Clinical target volume (CTV) 5000 consisted of the internal margin of gross tumor volume, including primary tumor and involved lymph nodes, + 1 cm geometric expansion, cropped from anatomic barriers of spread, including bone, lung, and heart. CTV4500 consisted of a 3.5 cm mucosal expansion on the primary tumor, as well as elective regional lymph nodes including the adjacent periesophageal, perigastric, and celiac lymph nodes. Treatment was administered with 2 posterior oblique beams, single field optimization, with isolayer

repainting to mitigate potential motion interplay effect. If target motion exceeded 10 mm, patients were treated with phased-based respiratory gating or breath hold. A planning target volume was not explicitly defined; rather, robust optimization was used with uncertainty parameters of ±5mm in axial, coronal, and sagittal directions and range uncertainty of ±3%. The goal was for 98% of the CTVs to be covered by the prescription dose on the base plan and for 95% of the CTVs to be covered by 95% of the prescription dose under uncertainty parameters. The treatment plan was cast on the 0 and 50 phases of the 4DCT to ensure robustness at the extremes of respiratory motion. 4DCT verification scan was performed once per week to confirm the integrity of the dose distribution, with adaptive replanning performed at the discretion of the treating radiation oncologist. Prior to initiation of PBS, all patients had a volumetric modulated arc therapy (VMAT) plan generated and prepared for treatment as backup in case of a proton center outage. A 5 mm planning target volume expansion was applied to the CTVs. Figure 1 shows a representative patient planned with PBS proton and VMAT photon.

Patients received concurrent weekly carboplatin (dose titrated to achieve an area under the curve of 2 mg/mL/min) and paclitaxel (50 mg/m^2 of body surface area) by intravenous infusion for planned 5 doses.

Patients were reassessed at 4 to 6 weeks after completion of CRT with history and physical examination, positron emission tomography/computed tomography, and pulmonary function tests. Esophagectomy was to be performed between 4 and 8 weeks after completion of CRT. A variety of surgical approaches were employed at the discretion of the individual surgeon's preference.

Outcomes assessment

The primary endpoint of this trial was to assess the rate of acute grade 3+ AEs possibly attributed to neoadjuvant CRT, occurring within 90 days after registration or until the patient underwent surgery, whichever occurred first. AEs were described and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. This pilot study did not use a formal statistical design or power calculation; the AE rates and secondary endpoints were to be assessed in the context of other published data. Specifically, in the CROSS trial, the observed rate of acute grade 3+ AEs during CRT was 20%; thus, we decided that a rate ≤20% may be of particular interest.[1] The sample size was 30 evaluable patients, allowing enrollment of up to 40 patients to account for dropout due to ineligibility or insurance denial of coverage for proton therapy.

Dose-volume histogram (DVH) parameters from the PBS proton and VMAT photon plans were compared using the Wilcoxon signed-rank test with paired p values.

Postoperative complications were defined as those occurring within 30 days after surgery. Complications were categorized as pulmonary, cardiac, gastrointestinal, infection/wound, or other, as outlined by the Esophagectomy Complications Consensus Group.[12] Severity of all

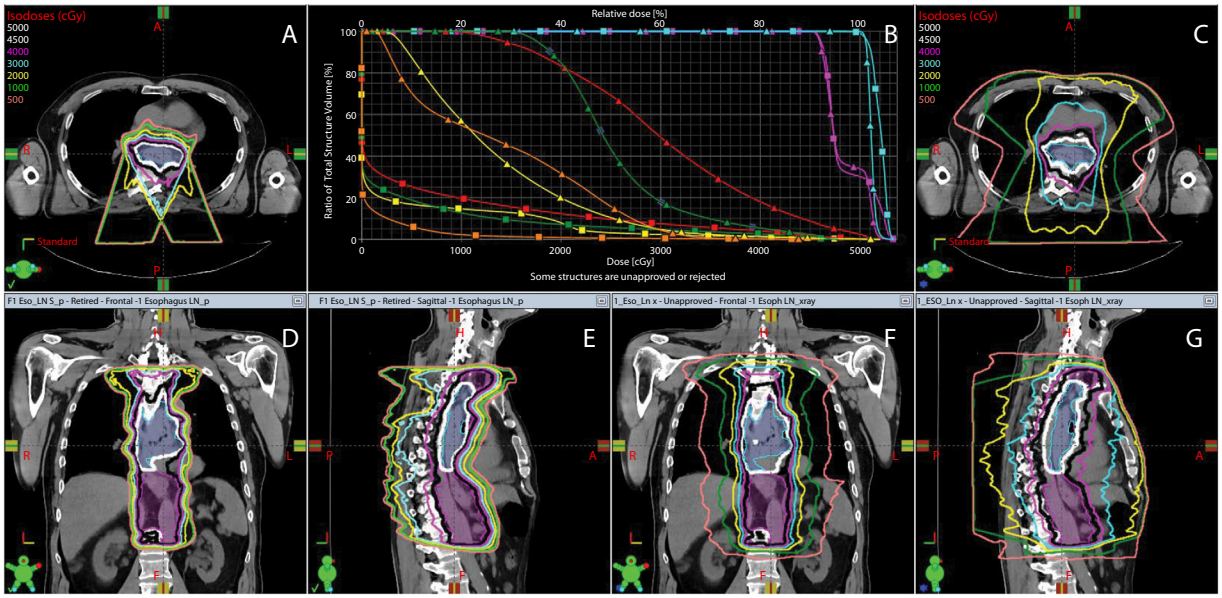

Figure 1 Pencil beam scanning (PBS) proton radiation therapy and volumetric modulated arc therapy (VMAT) photon radiation therapy plans for a patient with esophageal cancer enrolled in the study. PBS proton plan (A) axial, (D) coronal, and (E) sagittal slices. VMAT photon plan (C) axial, (F) coronal, and (G) sagittal slices. (B) In the dose-volume histogram, triangles represent the VMAT photon plan and squares represent the PBS proton plan. Cyan indicates clinical target volume 5000, and magenta indicates clinical target volume 4500. Red indicates the heart, green indicates the liver, and yellow and orange indicate the lungs.

postoperative complications was graded using the Clavien-Dindo classification.[13]

Patient-reported health-related quality of life (HRQOL) was assessed using the Functional Assessment of Cancer Therapy—Esophagus (FACT-E) prior to RT, weekly during RT, 42 days post-RT (at the presurgical visit), and every 6 months up to 2 years after enrollment. The FACT-E has a maximum score of 176, with higher values representing better HRQOL. The FACT-E is composed of the Functional Assessment of Cancer Therapy general questionnaire with a maximum score of 108 and the Esophageal Cancer Subscale with a maximum score of 68. The 95% CIs for the means were generated using bootstrap estimation. Change in HRQOL from baseline was assessed using the Wilcoxon signed-rank test with paired p values.

The median follow-up time was estimated using the reverse Kaplan-Meier method. Local-regional recurrence (LRR) was defined as disease recurrence within the CTV, which includes the primary tumor and regional lymphatics. Distant metastases (DMs) were defined as disease recurrence outside of the CTV. Progression-free survival (PFS) was defined as freedom from disease recurrence at any site and/or death from any cause. Overall survival (OS) was defined as freedom from death from any cause. PFS and OS were estimated from the time of registration using the Kaplan-Meier method, along with 95% CI. LRR and DMs were estimated using the cumulative incidence methodology, with death considered a competing risk. The α level was set at 0.05 for statistical significance.

Results

Enrollment and patient characteristics

A total of 35 patients were enrolled between June 2015 and April 2017; 3 patients were withdrawn because of insurance denial of proton therapy, and 2 were deemed to be ineligible prior to initiating treatment (screening failure), leaving 30 evaluable patients. Table 1 shows patient characteristics. No patient received induction chemotherapy prior to initiation of CRT. Two patients had percutaneous jejunostomy tubes placed prior to initiation of CRT because of tumor-related severe dysphagia and malnutrition.

Table 1 Patient characteristics

Characteristic	Patient data
Age (y), median (range)	68 (54-86)
Sex (%)*	
Male	90
Female	10
Race (%)	
White	100
Other	0
ECOG performance status (%)	
0	57
1	43
Tumor histology (%)	
Adenocarcinoma	87
Squamous cell carcinoma	13
Tumor location (%)	
Middle esophagus	10
Lower esophagus or GEJ	90
Clinical T stage (%)	
1-2	13
3-4	87
Clinical N stage (%)	
0	20
1-3	80
Tumor length on EGD (cm), median (range)	5 (1.1-12)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; EGD = esophagogastroduodenoscopy; GEJ = gastroesophageal junction.
*Sex was self-reported.

DVH parameters for proton versus VMAT plans

Figure 2 shows DVH parameters. Mean doses (in Gray) to all relevant organs at risk (OARs) were lower with PBS proton RT versus VMAT, including heart (6.5 vs 23.1; $p < .01$), lungs (3.3 vs 10.7; $p < .01$), stomach minus CTV4500 (12.1 vs 27.4; $p < .01$), bowel (small + large, 1.1 vs 11.7; $p < .01$), liver (2.3 vs 15.9; $p < .01$), and kidneys (0.9 vs 4.9; $p < .01$). On a per-patient level for all 30 patients, the mean heart and lung doses were lower with PBS proton RT.

Treatment characteristics and acute AEs

All patients completed the planned number of RT fractions and total dose. Median number of days from the start to end of CRT was 34 (range, 33-37). Respiratory management strategy was free-breathing with internal target volume and repainting (28 patients) or breath hold (2 patients). Five patients (17%) had adaptive replan performed (at fractions 8, 15, 20, 20, and 21) owing to anatomical change and/or tumor shrinkage. Reasons for replan were baseline diaphragm shift impacting proton range at the lung-diaphragm interface (3 patients), tumor shrinkage (1 patient), and change in tumor location due to large hiatal hernia (1 patient). For all 5 patients, treatment with the original plan was continued until the replan was ready (1-2 business days).

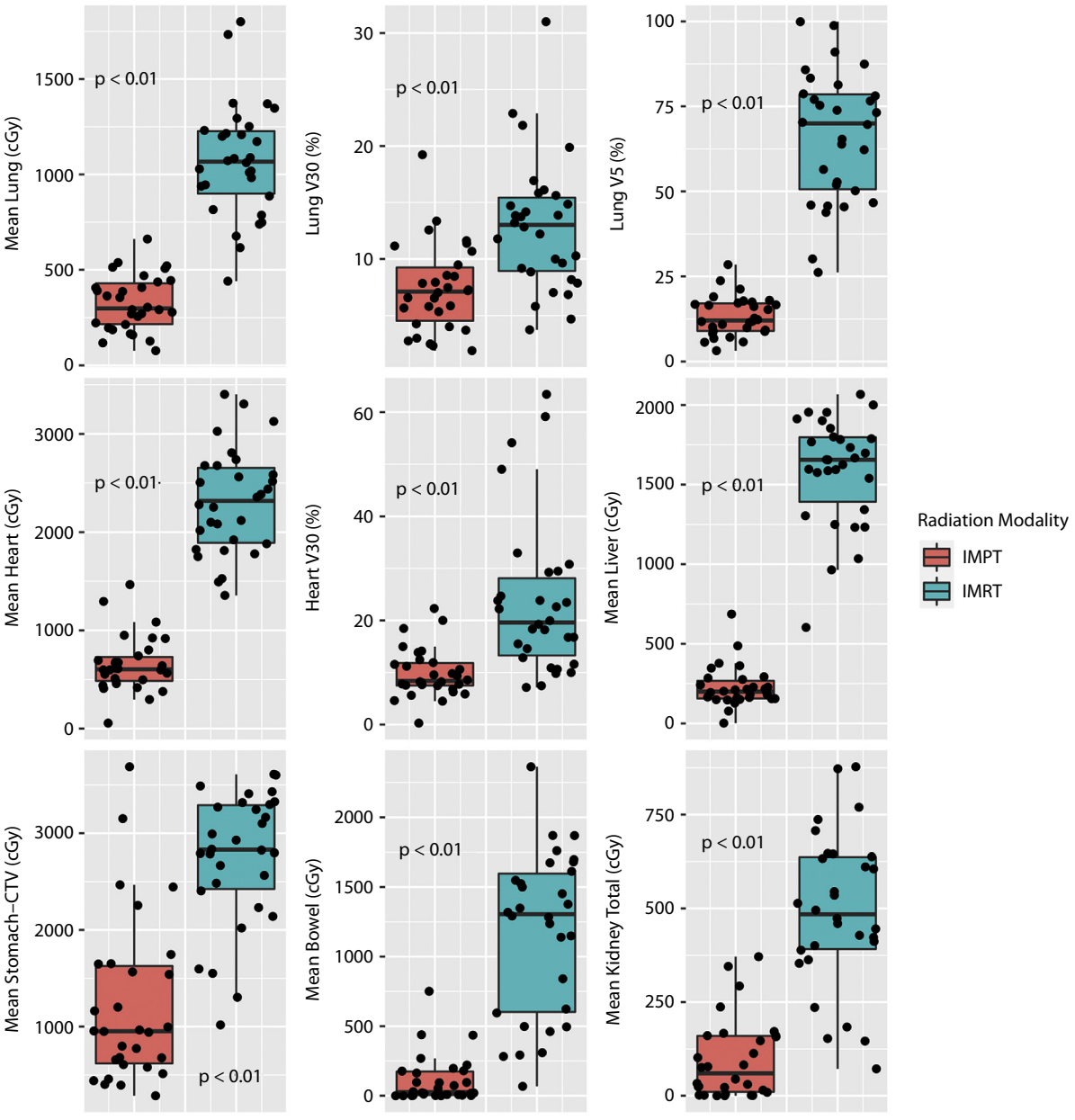

Figure 2 Comparative dosimetric parameters for all 30 patients enrolled in the study.
Abbreviations: CTV = clinical target volume; IMPT = intensity modulated proton radiation therapy; IMRT = intensity modulated radiation therapy.

Acute AEs are described in Table 2. Acute grade 3+ AEs occurred in 10 patients (30%). Individual grade 3+ AEs were leukopenia (20%), neutropenia (10%), and dehydration (3%). No patients required placement of an enteral feeding tube or total parenteral nutrition during or immediately after CRT.

Surgical outcomes

Twenty-seven patients (90%) underwent esophagectomy. Three patients (10%) did not undergo esophagectomy because of metastatic disease on restaging (1 patient), patient refusal (1 patient), and technical inoperability on exploration owing to adhesions from prior surgery (1 patient). Esophagectomy was transthoracic (59%), tri-incisional (30%), or transhiatal (11%) and was performed as an entirely open (85%) or minimally invasive/hybrid procedure (15%). Surgical margins were negative (R0) in 93% and positive (R1) in 7%. Pathologic T stage (ypT) was 0 (48%), 1 (19%), 2 (26%), or 3 (7%). Pathologic N stage (ypN) was 0 (70%) or 1 to 3 (30%). Pathologic complete response (pCR) was observed in 12 patients (40% of all patients, 44% of those undergoing surgery).

Table 2 Acute adverse events as scored by National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0

	Maximum grade				
Adverse event	**0**	**1**	**2**	**3**	**4**
Diarrhea	28	2	0	0	0
Dysphagia	7	10	13	0*	0
Esophageal pain	8	16	6	0	0
Nausea	13	14	3	0	0
Vomiting	22	8	0	0	0
Fatigue	3	23	4	0	0
Pain	14	11	5	0	0
Radiation dermatitis	13	16	1	0	0
Anorexia	16	7	7	0*	0
Dehydration	18	5	6	1	0
Anemia	4	25	1	0	0
White blood cell decrease	4	3	16	6	1
Neutrophil decrease	12	7	8	2	1
Platelet decrease	14	14	2	0	0
Creatinine increase	28	2	0	0	0

*Two patients had grade 3 tumor-related dysphagia and anorexia requiring percutaneous jejunostomy at baseline before enrollment. These patients were scored as having grade 2 treatment-related adverse effects.

Median hospital length of stay was 11 days (range, 5-50). During the initial hospitalization, the maximum severity of postoperative complication per patient by Clavien-Dindo score was 2, 3 (requiring surgical, endoscopic, or radiologic intervention), and 4 (life-threatening or requiring intensive care unit management) in 44%, 19%, and 15%, respectively. Individual grade 3 to 4 complications by category were pulmonary (19%), wound (15%), gastrointestinal (15%), and cardiac (4%). The 30- and 90-day postoperative mortality rates were 3.7% and 7.4%, respectively.

Survival and recurrence outcomes

Median follow-up was 5.2 years (IQR, 4.8-5.3 years). For the 18 patients who were deceased, cause of death was esophageal cancer (12), unknown (2), respiratory failure (1), renal failure (1), sepsis (1), and cerebrovascular (1). Disease recurrence occurred in 13 patients, with the initial site of recurrence being DMs only (9), LRR only (1), and both DMs and LRR (3). Figure 3 shows survival and recurrence estimates, including all 30 evaluable patients. The 5-year estimates (95% CI) were as follows: OS 46% (30%-68%), PFS 39% (24%-92%), LRR 17% (7%-41%), and DMs 40% (26%-62%).

HRQOL

Figure 4 shows HRQOL outcomes. FACT-E scores at baseline, at end of CRT, before esophagectomy, at 12 months, and at 24 months were 145, 136 (p = .0002 vs baseline), 144, 146, and 157, respectively. For the FACT-E and Functional Assessment of Cancer Therapy general questionnaire, significant decline from baseline was observed at weeks 3 to 5, with recovery at the pre-esophagectomy visit. For the Esophageal Cancer Subscale, a significant decline from baseline was observed at week 5, with recovery at the pre-esophagectomy visit.

Discussion

To our knowledge, this is the first reported prospective study assessing PBS proton RT for esophageal cancer. Key findings include the following: (1) for all patients, the PBS proton plan resulted in superior sparing of the heart and lungs compared with photon VMAT plans; (2) favorable tolerance in this cohort, with an acute nonhematologic grade 3+ AE rate of 3%; (3) favorable pCR rate of 40%; and (4) mature follow-up with 5-year OS of 46%. In summary, these data support the feasibility and safety of PBS proton RT for the treatment of esophageal cancer.

There are limited published series documenting the safety and efficacy of proton RT for esophageal cancer (Table 3).[8,14–17] Limitations of these series include retrospective design, small patient numbers, heterogeneous patient cohorts and treatments, use of older PS proton RT techniques, and short-duration patient follow-up. Our study overcomes some of these limitations and expands on the promising initial outcomes observed with PBS proton RT for esophageal cancer. Notably, OAR doses in the present series using advanced PBS proton techniques (heart mean, 6.5 Gy; lung mean, 3.3 Gy) are lower than those reported with older PS proton RT techniques (heart mean, 11-13 Gy; lung mean, 5-6 Gy).[8,17] Furthermore, all 30 patients had lower mean heart and lung doses with PBS proton RT versus VMAT. Given the "linear no-threshold" relationship between mean heart and lung dose and AEs, our data suggest that all patients with esophageal cancer (not just a subset) may benefit from PBS proton RT compared with VMAT.[2-6]

The observed rate of acute grade 3+ AEs possibly related to CRT (30%) was modestly higher than that observed in the Dutch CROSS trial (20%), driven primarily by the higher rate of acute hematologic grade 3+ AEs (30% vs <10%). The higher rate of hematologic grade 3+ AEs observed may be related to differences in patient characteristics in the present study (older age and worse performance status) versus CROSS. Additionally, the RT dose was higher (50 vs 41.4 Gy), and the CTV included elective coverage of the celiac lymph nodes (not included

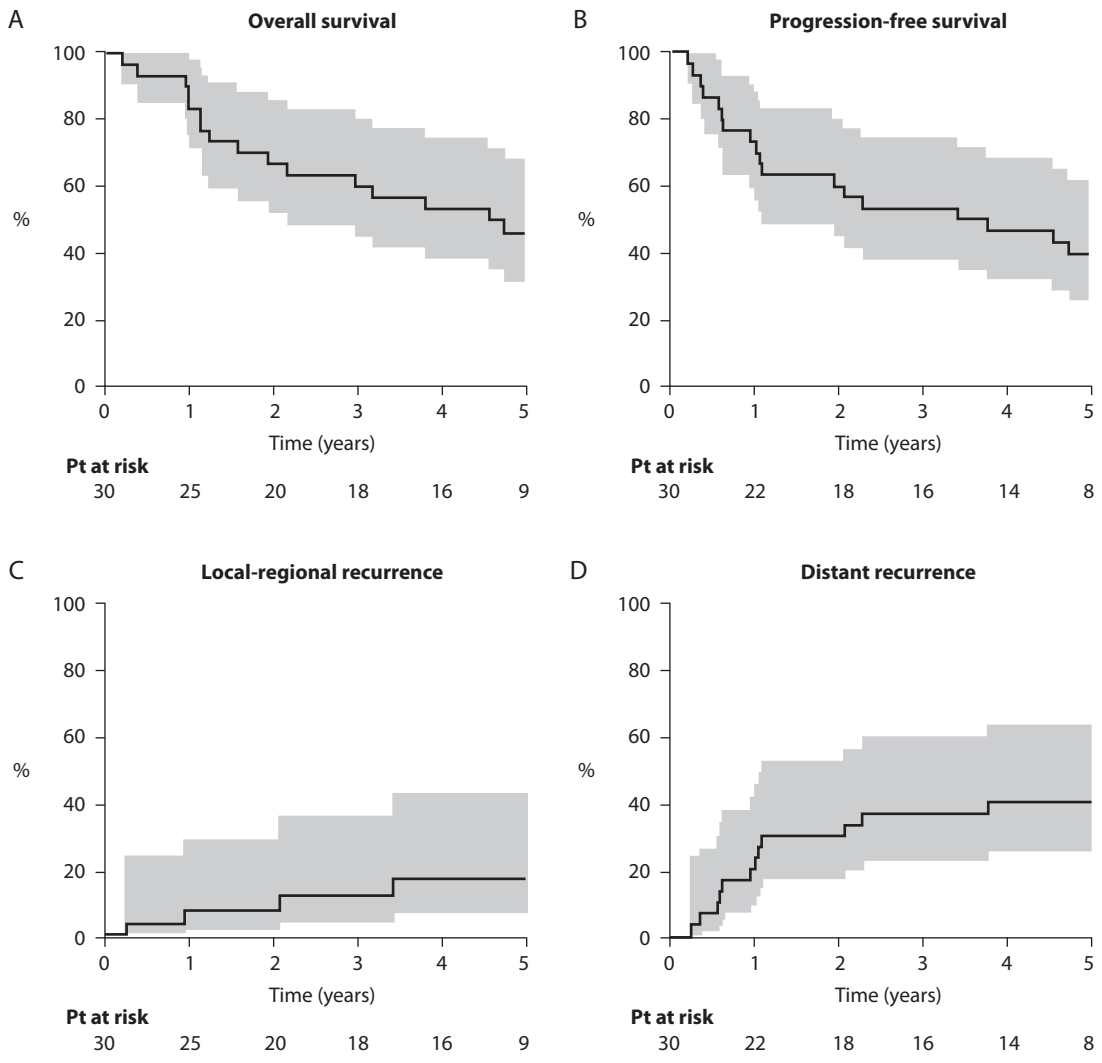

Figure 3 Survival and recurrence estimates. (A) Overall survival, (B) progression-free survival, (C) local-regional recurrence, and (D) distant metastasis estimates with 95% CIs.
Abbreviation: Pt = patients.

in CROSS). Importantly, rates of acute nonhematologic grade 3+ AEs, including gastrointestinal AEs, were similar between our study and the CROSS trial (all <10%).

Among those who underwent surgery, the pCR rate in the present trial was higher than that observed in the CROSS trial (44% vs 29%) despite more adverse risk features for patients in the present trial.[18] This may be related to the higher effective RT dose (50 Gy at 2 Gy/fraction) in the present study versus that delivered in CROSS (41.4 Gy at 1.8 Gy/fraction), as previous studies have observed a correlation between neoadjuvant RT dose and pCR rate.[19,20]

Mature oncologic outcomes in the present series are comparable with those observed in the CROSS trial using photon-based neoadjuvant CRT and esophagectomy, including 5-year OS (46% vs 47%), LRR (17% vs 21%), and DMs (40% vs 40%). These outcomes are encouraging, considering the patients treated in the present trial were significantly older (median age, 68 vs 60 years) and frailer (performance status score of 1 in 43% vs 19%), related in part to the CROSS trial excluding patients >75 years of age. Additionally, baseline tumor characteristics appeared less favorable in the present trial versus the CROSS trial, including squamous cell carcinoma histology (13% vs 23%), positive lymph nodes (80% vs 65%), T3 to T4 disease (87% vs 84%), and tumor length (5 vs 4 cm).

Preliminary data suggest that trimodality therapy incorporating neoadjuvant proton RT (instead of photon RT) may be associated with a lower risk of postoperative complications, which is hypothesized to be related to lower heart and lung doses.[17,21] Congruent with this hypothesis, we observed relatively low rates of severe postoperative cardiac and pulmonary complications and mortality despite the relatively advanced age of the cohort. Additional contributing factors may include patient selection, preoperative medical optimization, and an

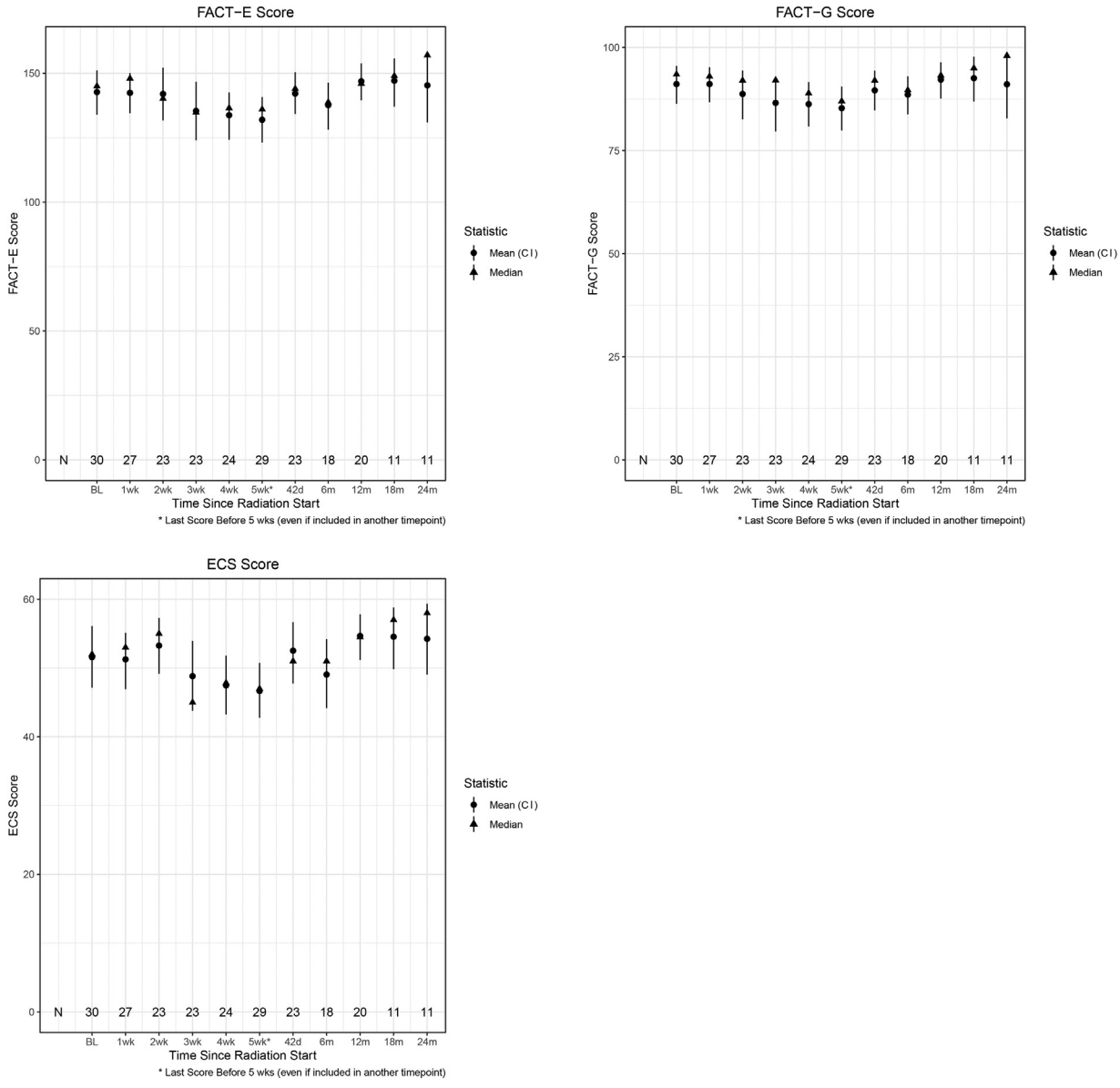

Figure 4 Patient-reported quality of life. Assessed using the Functional Assessment of Cancer Therapy—Esophagus (FACT-E; maximum score, 176), the Functional Assessment of Cancer Therapy general questionnaire (maximum score, 108), and the Esophageal Cancer Subscale (maximum score, 68), with higher scores indicating better quality of life. Lines represent 95% CIs for the mean.
Abbreviations: CI = confidence interval; Pt = patients.

experienced surgical team at a high-volume center. Further efforts to reduce postoperative complications include prehabilitation, minimally invasive surgical techniques, and postoperative enhanced recovery pathways. Ongoing prospective randomized controlled trials of proton versus photon RT (NCT03801876 and NCT05055648) are specifically evaluating the potential impact of radiation modality on postoperative complications.

In the present trial, we observed a decline in HRQOL during trimodality therapy, with subsequent recovery greater than baseline at 1 year. A similar observation was made in the CROSS trial using a different HRQOL measure.[22] A previous study that included patients treated in the present trial assessed change in HRQOL specifically during CRT (either neoadjuvant or definitive) for esophageal cancer and observed less decline in the FACT-E score for patients who received proton (vs photon) CRT.[23] Given the significantly reduced dose to OARs observed in the present trial with proton (vs photon) CRT, further randomized studies are needed to assess longitudinal HRQOL between modalities to determine if there is a clinically meaningful benefit with proton CRT.

There are limitations to the present trial. This was a single-arm pilot study with no randomization or comparison arm, which limits the strength of the conclusions that

Table 3 Published clinical outcomes of proton therapy for esophageal cancer from North America

Series	Design	No. of Pts	Neoadj/ definitive	RT dose (Gy)	Proton technique	Mean heart and lung doses	Chemotherapy agents	Med. f/u	Grade 3+ nonhematologic AEs with incidence >10%	Survival
Lin et al[8]	R	62	47%/53%	50.4	Passive scatter	Heart, 13 Gy Lung, 6 Gy	Not reported	20 mo	None	3 y, 52%
Prayongrat et al[15]	R	19	79%/21%	41.4-50.4	PBS	Heart, 7.9 Gy Lung, 4.9 Gy	Docetaxel + 5-FU or capecitabine (73%)	17 mo	Esophagitis, 16% Fatigue, 16% Nausea/vomiting, 11%	2 y, 88%
Zeng et al[14]	R	13	100%	50.4	PBS	Heart, 14 Gy Lung, 5 Gy	Carboplatin + paclitaxel	11 mo	None	NR
Bhangoo et al[16]	R	32	72%/23%	50	PBS	Heart, 8.1 Gy Lung, 3.9 Gy	Carboplatin + paclitaxel (91%)	10 mo	Dysphagia, 28%	1 y, 74%
Lin et al	P	46	83%/17%	50.4	Passive scatter	Heart, 11.3 Lung, 4.8 Gy	Docetaxel + 5-FU or capecitabine (61%)	44 mo	Dysphagia, 17% Esophagitis, 13% Anorexia, 11%	3 y, 45%
Current	P	30	100%	50	PBS	Heart, 6.5 Gy Lung, 3.3 Gy	Carboplatin + paclitaxel	5.2 y	None	5 y, 46%

Abbreviations: 5-FU = 5-fluorouracil; AE = adverse event; f/u = follow-up; Med. = median; Neoadj = neoadjuvant; NR = not reported; P = prospective; PBS = pencil beam scanning; Pts = patients; R = retrospective; RT = radiation therapy.

can be drawn. The sample size was relatively small (30 patients); thus, CIs for event rates and survival are large, which should be considered in comparison with the CROSS trial (178 patients in the neoadjuvant CRT arm).[1] All patients were treated at a tertiary care center that sees a high volume of patients with esophageal cancer, so it is unclear if outcomes would be generalizable to a community setting. Patients with upper thoracic or cervical esophageal cancer and those with Siewert type III gastroesophageal junction cancers were not eligible, and it remains unclear if such patients would benefit from proton RT, as dose to heart and lung are usually low with photon-based techniques. For esophageal cancer patients treated with trimodality therapy, the standard of care now includes adjuvant immunotherapy for those not achieving pCR, impacting potential comparisons of data from our trial with future trials.[24]

Conclusion

Our data suggest that PBS proton RT is safe and feasible in the multimodal treatment of esophageal cancer. The 3% rate of nonhematologic acute grade 3+ AEs suggests a favorable side-effect profile, and all patients had lower mean heart and lung doses with PBS proton RT. Ongoing phase 3 randomized controlled trials in the United States (NRG-GI006, NCT03801876) and Europe (PROTECT, NCT05055648) are comparing proton RT with photon RT for esophageal cancer, with primary endpoints of survival and severe AEs. These trials will help further define the role of proton RT for esophageal cancer.[3]

Disclosures

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A1; and leadership or fiduciary role in the Society of Thoracic Surgeons, Southern Thoracic Surgery Association, Women in Thoracic Surgery, American Association of Thoracic Surgeons, and European Society of Thoracic Surgeons (none directly relates to this work).

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