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Esophageal Cancer Outcomes After Definitive Chemotherapy With Intensity Modulated Proton Therapy

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ABSTRACT

Purpose: The effectiveness of intensity-modulated proton therapy (IMPT) for esophageal cancer treated with definitive concurrent chemoradiation therapy remains inadequately explored. We investigated long-term outcomes and toxicity experienced by patients who received IMPT as part of definitive esophageal cancer treatment.
Patients and Methods: We retrospectively identified and analyzed 34 patients with locally advanced esophageal cancer who received IMPT with concurrent chemotherapy as a definitive treatment regimen at The University of Texas MD Anderson Cancer Center from 2011 to 2021. The median IMPT dose was 50.4 GyRBE in 28 fractions; concurrent chemotherapy consisted of fluorouracil and/or taxane and/or platinum. Survival outcomes were determined by the Kaplan-Meier method, and toxicity was scored according to the Common Terminology Criteria for Adverse Events version 4.0.
Results: The median age of all patients was 71.5 years. Most patients had stage III (cT3 cM0) adenocarcinoma of the lower esophagus. At a median follow-up time of 39 months, the 5-year overall survival rate was 41.1%; progression-free survival, 34.6%; local regional recurrence-free survival, 78.1%; and distant metastasis-free survival, 65.0%. Common acute chemoradiation therapy-related toxicities included hematologic toxicity, esophagitis (and late-onset), fatigue, weight loss, and nausea (and late-onset); grade 3 toxicity rates were 26.0% for hematologic, 18.0% for esophagitis and 9.0% for nausea. No patient had grade ≥3 wt loss or radiation pneumonitis, and no patients had pulmonary fibrosis or esophageal fistula. No grade ≥4 events were observed except for hematologic toxicity (lymphopenia) in 2 patients.
Conclusion: Long-term survival and toxicity were excellent after IMPT for locally advanced esophageal cancer treated definitively with concurrent chemoradiation therapy. When available, IMPT should be offered to such patients to minimize treatment-related cardiopulmonary toxicity without sacrificing outcomes.

Introduction

Photon-based radiation therapy has had well-documented beneficial effects on survival for patients with esophageal cancer. Specifically, trimodality therapy in which neoadjuvant concurrent chemoradiation is followed by esophagectomy has been shown to yield higher rates of pathologic complete response, negative margins, and better overall survival relative to surgery alone.[1–4] Other studies of trimodality therapy versus definitive concurrent chemoradiation therapy have shown conflicting results in terms of mortality rates.[5–7] Nevertheless, in

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all these studies, most of the patients were treated with photon radiation therapy techniques, such as 3-dimensional conformal radiation therapy, intensity-modulated radiation therapy (IMRT), or volumetric modulated arc therapy.

Through its ability to deliver the highest dose of radiation at the Bragg peak followed by rapid dose fall-off thereafter, proton beam therapy (PBT) has improved the safe delivery of tumoricidal radiation doses to esophageal cancer with better sparing of the heart and lungs compared with photon delivery techniques.[8–10] To date, most reported PBT studies have involved passive scatter proton therapy (PSPT). A retrospective study at our institution demonstrated better 5-year rates of overall survival (OS), progression-free survival (PFS), distant metastasis-free survival (DMFS), and treatment-related toxicity among patients treated with PSPT rather than IMRT.[11] A study published by the Mayo Clinic and the University of Florida reported good outcomes at 3 years for 17 patients, 16 of whom received PSPT.[12] However, numerous studies have shown that PBT can still lead to significant toxicity, with grade 3 esophagitis experienced by 22% of the patients after doses of 66 to 75.6 GyE,[13] and grade 2 to 3 esophageal ulcers in 35%, pneumonitis in 15%, esophageal stenosis in 10%, and pleural effusion in 10% after 66 to 74.8 GyE.[14]

The advent of intensity-modulated proton therapy (IMPT, also known as pencil beam proton therapy) represented a new era of advanced radiation therapy that further improves dose conformality around targets and dose distribution around organs at risk. The improved conformality is realized from a combination of sweeping magnet modulation of dose distribution along the x and y axes, and range shifter–adjusted plane-by-plane dose delivery along the z axis. Despite this apparent benefit, only a few studies have been published on outcomes and toxicity after definitive concurrent chemoradiation therapy with IMPT for esophageal cancer, and most had either very few patients or short-term outcomes. We published an early but short-term follow-up report on 19 patients who received IMPT for esophageal cancer with good outcomes and few grade 3 toxicities at 2 years.[15] A comparative study of IMPT versus IMRT by the Mayo Clinic group in Arizona reported outcomes at 1 year for 32 patients who received IMPT.[16] A University of Washington group published a feasibility study with 13 PBT patients, 5 of whom received IMPT; after a median follow-up time of 11 months, median OS and PFS times had not been reached, and only toxicity experienced during treatment was reported.[17] To date, no reports have been published on long-term outcomes and toxicity after definitive concurrent chemoradiation therapy (dCRT) with IMPT for relatively large numbers of patients with esophageal cancer. Given that dCRT is typically offered to patients with poorer prognosis, we wanted to investigate the long-term benefit of IMPT in such patient group. Here, we present the first such study of a relatively large number of patients with esophageal cancer from The University of Texas MD Anderson Cancer Center who were treated exclusively with IMPT as part of dCRT in which survival outcomes and toxicity are reported at 5 years.

Patients and methods

Patients

This study was approved by The University of Texas MD Anderson Cancer Center Institution Review Board. The population analyzed in this retrospective study consisted of 34 patients with esophageal cancer who completed definitive concurrent chemoradiation with IMPT at our institution from 2011 to 2021; patient data were included in a REDCap database.[18] Study data were collected and managed by using REDCap research electronic data capture tools hosted at The University of Texas MD Anderson Cancer Center.[19,20] REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources. Exclusion criteria included enrollment in the phase III NRG-GI006 trial, presentation with *de novo* diffuse metastases, treatment with palliative intent, or receipt of planned surgery within 4 months after completion of radiation therapy. Imaging at baseline, for restaging, and for treatment assessment for all patients consisted of either computed tomography (CT) or fluorodeoxyglucose positron emission tomography (PET)/CT. The clinical T category was assigned after esophagogastroduodenoscopy with endoscopic ultrasound; the N category with endoscopic ultrasound-guided fine-needle aspiration or CT or PET/CT; and the M category with either CT or PET/CT. The American Joint Committee on Cancer's Cancer Staging Manual 7th edition (2010) was used to assign summary staging for both adenocarcinoma and squamous cell carcinoma histologic subtypes.

Treatments and toxicities

All patients received IMPT as dCRT. The median IMPT dose was 50.4 GyE (range: 39.6-63.05 GyE; 3 patients received < 50 GyE due to prior chest RT or toxicity; 6 patients received > 54 GyE on a dose-escalation protocol using a simultaneous integrated boost), delivered in 28 fractions of 1.8 GyE. Twelve patients received induction systemic chemotherapy that consisted of a platinum-based drug, with or without a fluoropyrimidime (typically 5-fluorouracil), with or without a taxane, and with or without a topoisomerase I inhibitor. Concurrent chemotherapy consisted of a fluoropyrimidime (typically 5-fluorouracil) with or without a taxane, and with or without a platinum-based drug. Four-dimensional CT scans that accounted for respiratory motion, obtained after patients had fasted for at least 3 hours, were used for IMPT treatment planning on an Eclipse treatment planning system (Varian Medical Systems Inc, Palo Alto, California). Patients were immobilized by means of a thermoplastic mask over the head and shoulders (for cervical primary tumors) or a cradle (for primary tumors at other locations). Clinical target volumes consisted of a 3-cm mucosal margin expansion around the gross tumor volume and an additional internal margin of 1 cm and included nodal regions at risk. The planning tumor volumes were 0.5-cm expansions of the clinical target volumes. Organs at risk were contoured, and the doses they received were limited to the constraints used at the authors' institution.[21] Single- or multifield optimization with 2 or 3 beams was used as described elsewhere.[15] Digitally reconstructed radiographs, from the initial CT images acquired at simulation, were used as reference for image-guided radiation therapy by bony alignment of orthogonal kilovoltage radiographs acquired daily before treatment. All chemoradiation therapy-induced acute and late toxicities were graded according to version 4.0 of the Common Terminology Criteria for Adverse Events. Anemia, lymphopenia, neutropenia or thrombocytopenia were grouped under hematologic toxicity. Arrythmias, cardiac arrest, congestive heart failure, or myocardial infarction were grouped under cardiac toxicity.

Statistical analyses

Descriptive statistics were used to report patient, tumor, and treatment characteristics. The Kaplan-Meier method was used to calculate OS, PFS (time to any recurrence event, death, or last follow-up), local regional recurrence-free survival (LRFS), and DMFS from the last date of IMPT. All statistical analyses were done with IBM SPSS Statistics version 28.0.0.0 and GraphPad Prism version 9.2.0.

Results

Baseline patient, tumor, and treatment characteristics

The cohort was predominantly white patients (30 [88%]) with Eastern Co-Operative Group performance status scores of 0 to 1 (31 [91%]). Most patients had lower esophageal disease (16 patients

Table 1
Patient and treatment characteristics.

	Value or no. of patients (%)
Total number of patients	34 (100)
Age, years, median (IQR)	71.5 (66.7-79.0)
Sex	
Female	7 (21)
Male	27 (79)
Race/ethnicity	
Black	1 (3)
Latino	2 (6)
Asian	1 (3)
White	30 (88)
BMI, kg/m^2, median (IQR)	26.3 (23.9-30.3)
ECOG score	
0	9 (26)
1	22 (65)
2	3 (9)
Other malignancy	
Yes	17 (50)
No	17 (50)
Location	
Cervical	1 (3)
Upper	8 (24)
Middle	9 (26)
Lower	16 (47)
Histology	
AC	19 (56)
SCC	15 (44)
EUS T status	
1	1 (3)
2	1 (3)
3	31 (91)
4	1 (3)
N status	
0	11 (32)
1	9 (26)
2	11 (32)
3	3 (9)
M status	
0	31 (91)
1	3 (9)
Overall clinical disease stage[a]	
I	2 (6)
II	9 (26)
III	20 (59)
IV	3 (9)
Induction chemo	
Yes	12 (35)
No	22 (65)

Abbreviations: AC, adenocarcinoma; BMI, body mass index; ECOG, Eastern Co-operative Oncology Group; EUS, endoscopic ultrasound; IQR, interquartile range; SCC, squamous cell carcinoma.

[a] Overall clinical stage was assigned according to the 7th edition of the American Joint Committee on Cancer's Cancer Staging Manual after a combination of endoscopic ultrasound and CT or PET/CT for TNM staging.

[47%]); disease in most cases was adenocarcinoma (19 patients [56%]), T3 (31 [91%]), M0 (31 [91%]), and clinical stage III (20 [59%]). Only 12 patients (35%) received induction chemotherapy (Table 1).

Survival outcomes

The median follow-up time was 39 months; the median OS time was 37 months, the 3-year OS rate was 52.8%, and the 5-year OS rate was 41.1% (Figure 1A). The median PFS time was 24 months, the 3-year PFS rate was 41.6%, and the 5-year PFS rate was 34.6% (Figure 1B). The median LRFS time was not reached, and the 3- and 5-year LRFS rates were both 78.1% (Figure 1C). The local regional control rate was 82%, with 6 patients developing local regional recurrence. Three of those patients had recurrence within the RT field, while the other 3 reoccurred outside the field. The median DMFS time was not reached, the 3-year DMFS rate was 72.2%, and the 5-year DMFS rate was 65.0% (Figure 1D).

Toxicity

The most common chemoradiation therapy-related toxic effects were acute hematologic (30 patients [88%] mostly with lymphopenia), acute and late esophagitis (26 patients [76%]), acute fatigue (19 [56%]), acute weight loss (18 [53%]), and acute and late nausea (13 [38%]). No pulmonary fibrosis or esophageal fistulae were reported, and fewer than 10% of the patients developed late radiation pneumonitis (2 patients), late esophageal stricture (3 patients), or any late cardiac toxicity (3 patients) (Table 2). Grade 3 toxicities were hematologic (9 [26%]), esophagitis (6 [18%]), nausea (3 [9%]), fatigue (2 [6%]), esophageal stricture (2 [6%]) and any cardiac toxicity (1 [3%]) (Table 2). Two patients developed acute grade 4 lymphopenia. No other grade ≥ 4 toxicities were experienced.

Discussion

We retrospectively analyzed survival and disease control outcomes and toxicity among patients who received IMPT as part of dCRT for locally advanced esophageal cancer and observed very good 5-year OS, LRFS, and DMFS rates with minimal rates of grade 3 toxicity and only 2 (hematologic) grade 4 toxicity. This study represents one of the largest cohorts, with the longest follow-up, reported to date among patients with esophageal cancer who received IMPT.

Previously, we published 2-year outcomes for 19 patients with esophageal cancer treated with IMPT (all 15 dCRT patients are included in the current update); in that study, the OS rate was 87.5%, PFS 50.6%, LRFS 74%, and DMFS 72.9%.[15] We subsequently reported longer-term outcomes in a retrospective comparative analysis of IMRT versus PBT (125 patients received PSPT and 7 IMPT) and found a 5-year OS rate of 41.6% among the PBT patients,[11] which is similar to the 5-year OS rate of 41.1% for the 34 IMPT patients in the current report. The 5-year PFS rate (34.9%) and DMFS rate (64.9%) in that comparative review were also very similar to those in the current report (PFS 34.6%, DMFS 65.0%). However, the patients in the current analysis seemed to have better 5-year LRFS rates than those in our previous report (78.1% vs 59.9%). Another analysis, this one of a randomized phase II trial comparing PBT with IMRT for locally advanced esophageal cancer, revealed 3-year OS and PFS rates for 46 PBT patients (9 IMPT) of 51.2% (vs 52.8% in the current series) and 44.5% (vs 41.6% in the current series).[9] These findings, and our collective institutional experience, seem to suggest that PSPT and IMPT, in particular, produce similar survival outcomes in all measures except for LRFS, and the findings from this current report may better represent the outcomes for patients treated with dCRT using IMPT. A similar study comparing IMPT with IMRT from the Mayo Clinic in Arizona showed 1-year OS, PFS, and DMFS rates of 74%, 71%, and 87% in 32 patients treated with IMPT.[16] The corresponding 1-year OS, PFS, and DMFS rates for the 34 IMPT patients in the current study were 71.5%, 62.5%, and 83.3% (not shown). The likely reason for the differences is that the proportion of patients who received dCRT, which is typically offered to patients with a poorer prognosis, was only 28% in the Mayo study (9 patients) compared 100% in our report. Despite this potential difference in overall patient prognosis between both reports, the differences in between both reports for the 1-year OS and DMFS are both only about 4%.

In our earliest IMPT report, the only grade 3 toxicities observed were acute-onset esophagitis and fatigue in 3 patients, and late-onset esophageal stricture and pleural effusion in 1 patient each.[15] The phase II trial conducted by our group showed worse total toxicity burden as well as more cardiopulmonary toxicities and postoperative complications with IMRT than with PBT, presumably because of the significantly better heart, lung, and liver dosimetry with PBT.[9] The Arizona Mayo Clinic IMPT study, which assessed toxicity before and immediately after treatment, reported grade 3 toxicity rates of 28% for dysphagia, 3% for nausea, and 3% for esophagitis.[16] Another study involving only 5 IMPT patients in which toxicity was documented only during the treatment

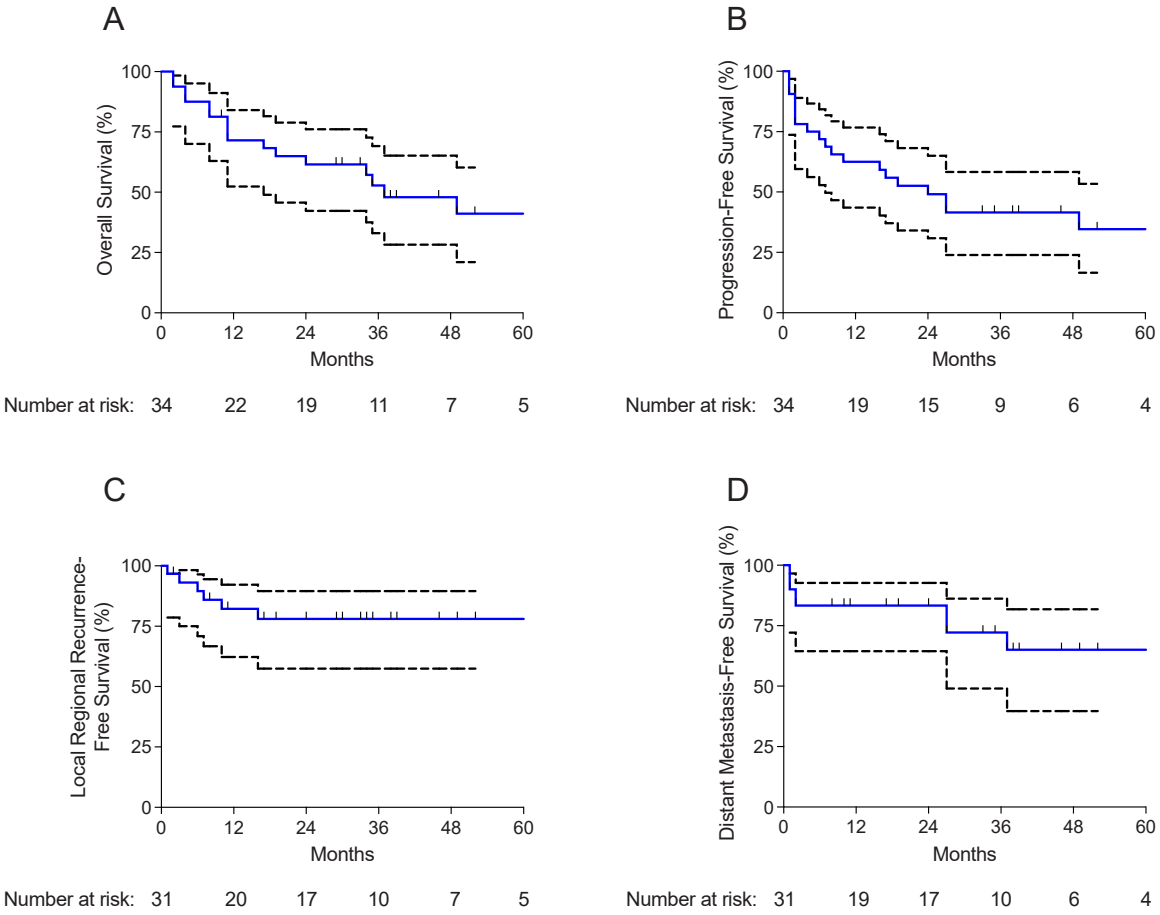

Figure 1. Survival outcomes after intensity-modulated proton therapy for esophageal cancer for A: Overall survival; B: Progression-free survival; C: Local regional recurrence-free survival; D: Distant metastasis-free survival. 95% upper and lower confidence intervals are displayed in the black dashes above and below each survival curve, respectively.

Table 2
Rates and grades of chemoradiation therapy-related toxicity.

Toxicity	Absent	Present	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic toxicity	4 (12)	30 (88)	10 (29)	9 (26)	9 (26)	2 (6)
Esophagitis	8 (24)	26 (76)	1 (3)	18 (53)	6 (18)	0 (0)
Weight loss	16 (47)	18 (53)	14 (41)	0 (0)	0 (0)	0 (0)
Fatigue	15 (44)	19 (56)	12 (35)	5 (15)	2 (6)	0 (0)
Nausea	21 (62)	13 (38)	7 (21)	3 (9)	3 (9)	0 (0)
Radiation pneumonitis	32 (94)	2 (6)	1 (3)	1 (3)	0 (0)	0 (0)
Esophageal stricture	31 (91)	3 (9)	1 (3)	0 (0)	2 (6)	0 (0)
Cardiac toxicity	31 (91)	3 (9)	2 (6)	0 (0)	1 (3)	0 (0)
Pulmonary fibrosis	34 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Esophageal fistula	34 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Values are number of patients (%).

period led to no grade 3 events.[17] In contrast, and as expected, the 5-year toxicity assessment in the current cohort showed higher cumulative incidences of acute and late grade 3 esophagitis (18%) and nausea (9%), as well as acute hematologic toxicity (26%).

Our study had several notable limitations. Although our cohort was larger than other published reports on dCRT with IMPT in esophageal cancer, that cohort still consisted of only 34 patients. Presumably, analyses of larger numbers of patients will bolster our findings. Another shortcoming is that this was a retrospective series and was prone to the associated biases. The most objective demonstration of survival, disease control, and toxicity associated with IMPT versus PSPT would come from a randomized trial. However, a combination of factors, including the low incidence of esophageal cancer and the rarity of IMPT, coupled with long wait times when it is available, makes the planning, execution, and completion of such a trial challenging. As a result, clinical trials of PBT in esophageal cancer to date focus mostly on comparing PBT with IMRT. One example, the ongoing NRG-GI006 phase III randomized trial, is assessing whether dCRT or neoadjuvant concurrent chemoradiation therapy with PBT yields better outcomes than dCRT or neoadjuvant concurrent chemoradiation therapy with IMRT; that trial is still occurring in patients at this time and the subset of patients treated with IMPT were excluded from this series. Further, the single-institution approach of our current report may limit its applicability. Other institutions with IMPT capability presumably are also collecting long-term data on patients with esophageal cancer, and a meta-analysis of long-term outcomes and toxicity, when available, would provide perhaps more widely applicable findings.

This report on the use of IMPT for radiation delivery to patients with

locally advanced esophageal cancer receiving dCRT demonstrated excellent 5-year survival outcomes and a good toxicity profile, with no grade ≥ 4 toxic events except for 2 patients with severe lymphopenia. A larger cohort of patients, and a comparative study between IMPT and PSPT, are still needed to validate our observations and to demonstrate the clinical benefits from the improved conformality of particle delivery afforded by IMPT. Nevertheless, our study demonstrates that IMPT can be safe and effective over the long term for treating patients with esophageal cancer.

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Author Contributions

Chike O. Abana: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review and editing. **Pim J. Damen**: Data curation, Validation. **Peter S. van Rossum**: Data curation, Validation. **Pablo Lopez Bravo**: Data curation. **Xiong Wei**: Software. **Julianne M. Pollard-Larkin**: Data curation. **Paige L. Nitsch**: Data curation. **Mariela Blum Murphy**: Data curation. **Wayne L. Hofstetter**: Conceptualization, Writing – review and editing. **Zhongxing Liao**: Data curation, Writing – review and editing. **Steven H. Lin**: Conceptualization, Methodology, Data curation, Funding acquisition, Supervision, Writing – review and editing.

Declaration of Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper: Dr Steven H. Lin discloses grant funding from Beyond Spring Pharmaceuticals, Nektar Therapeutics, STCube Pharmaceuticals, and IntraOp Corporation; serving on advisory board for Beyond Spring Pharmaceuticals, STCube Pharmaceuticals, Creatv Microtech, and AstraZeneca; being a consultant for XRAD Therapeutics; and a co-founder of SEEK Diagnostics. Dr Zhongxing Liao discloses a strategic alliance with Zhengdong. All other authors: none.

Data availability

All data generated and analyzed during this study are stored in an institutional repository and will be shared upon request to the corresponding author.

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