Advances in Radiation Oncology (2020) **5**, 871-879

advances
in radiation oncology

www.advancesradonc.org

Scientific Article

Acute Toxicities and Short-Term Patient Outcomes After Intensity-Modulated Proton Beam Radiation Therapy or Intensity-Modulated Photon Radiation Therapy for Esophageal Carcinoma: A Mayo Clinic Experience

Ronik S. Bhangoo, MD,[a] Todd A. DeWees, PhD,[b] Nathan Y. Yu, MD,[a] Julia X. Ding, BA,[a] Chenbin Liu, PhD,[a] Michael A. Golafshar, MS,[b] William G. Rule, MD,[a] Sujay A. Vora, MD,[a] Helen J. Ross, MD,[c] Daniel H. Ahn, DO,[c] Staci E. Beamer, MD,[d] Dawn E. Jaroszewski, MD,[d] Christopher L. Hallemeier, MD,[e] Wei Liu, PhD,[a] Jonathan B. Ashman, MD, PhD,[a] and Terence T. Sio, MD, MS[a,*]

[a]Department of Radiation Oncology, Mayo Clinic Hospital, Phoenix, Arizona; [b]Biostatistics, Mayo Clinic, Scottsdale, Arizona; [c]Division of Hematology and Medical Oncology, Mayo Clinic Hospital, Phoenix, Arizona; [d]Division of Thoracic Surgery, Mayo Clinic Hospital, Phoenix, Arizona; and [e]Department of Radiation Oncology, Mayo Clinic, Rochester, Minnesota

Received 20 December 2019; revised 2 April 2020; accepted 7 April 2020

Abstract

Purpose: Intensity modulated proton beam radiation therapy (IMPT) has a clinically significant dosimetric advantage over intensity modulated photon radiation therapy (IMRT) for the treatment of patients with esophageal cancer, particularly for sparing the heart and lungs. We compared acute radiation therapy–related toxicities and short-term clinical outcomes of patients with esophageal cancer who received treatment with IMPT or IMRT.

Methods and Materials: We retrospectively reviewed the electronic health records of consecutive adult patients with esophageal cancer who underwent concurrent chemoradiotherapy with IMPT or IMRT in the definitive or neoadjuvant setting from January 1, 2014, through June 30, 2018, with additional follow-up data collected through January 31, 2019. Treatment-related toxicities were evaluated per the Common Terminology Criteria for Adverse Events, version 4. Survival outcomes were estimated with the Kaplan-Meier method.

Results: A total of 64 patients (32 per group) were included (median follow-up time: 10 months for IMPT patients vs 14 months for IMRT patients). The most common radiation therapy regimen was 45 Gy in 25 fractions, and 80% of patients received a simultaneous integrated

Sources of support: The authors have no outside funding to disclose.

Research data are not available at this time.

Disclosures: Dr. Terence T. Sio provides strategic and scientific recommendations as a member of the Advisory Board and speaker for Novocure Inc. Dr. Daniel Ahn receives consultancy fees from Eisai, Genetech, and Exelixis. Dr. Dawn Jaroszewski receives consultancy, patent, and royalty compensation from Zimmer Biomet. None of these disclosures are related to this manuscript. None of the other authors have any conflicts of interest to disclose.

This study was presented at the Annual Meeting of the American Society of Radiation Oncology in Chicago, Illinois on September 15 to 18, 2019, and subsequently published in abstract form in the International *Journal of Radiation Oncology • Biology • Physics*.

* Corresponding author: Terence T. Sio, MD, MS; E-mail: sio.terence@mayo.edu

https://doi.org/10.1016/j.adro.2020.04.026

boost to a median cumulative dose of 50 Gy. Similar numbers of IMPT patients (n = 15; 47%) and IMRT patients (n = 18; 56%) underwent surgery ($P = .07$), with no difference in pathologic complete response rates (IMPT: n = 5; 33% vs IMRT: n = 7; 39%; $P = .14$). At 1 year, the clinical outcomes also were similar for IMPT and IMRT patients, respectively. Local control was 92% versus 84% ($P = .87$), locoregional control 92% versus 80% ($P = .76$), distant metastasis–free survival 87% versus 65% ($P = .08$), progression-free survival 71% versus 45% ($P = .15$), and overall survival 74% versus 71% ($P = .62$). The rate of acute treatment–related grade 3 toxicity was similar between the groups ($P = .71$).

Conclusions: In our early experience, IMPT is a safe and effective treatment when administered as part of definitive or trimodality therapy. Longer follow-up is required to evaluate the effectiveness of IMPT.

Introduction

Approximately 17,000 new cases of esophageal cancer and 16,000 deaths due to esophageal cancer occur every year in the United States.[1] Locally advanced esophageal cancer is an aggressive disease and is treated with neoadjuvant chemoradiotherapy (CRT) and surgical resection.[2] Definitive CRT is also a treatment of choice for patients who are unable to undergo surgery or have unresectable disease or squamous cell carcinoma in the upper esophagus.[3]

Because the esophagus is adjacent to the heart and lungs, advanced radiation therapy techniques are needed to limit the dose administered to these normal tissues. Late cardiopulmonary toxicity occurs in approximately 5% to 10% of patients receiving CRT, and the administration of radiation therapy increases the probability of cardiac death by 22% according to a database analysis by the Surveillance, Epidemiology, and End Results Program.[4,5]

Compared with intensity modulated photon radiation therapy (IMRT), proton beam therapy has a substantially lower exit dose.[6] Proton beam therapy does entail challenges related to range uncertainty and target motion,[7] but advances in proton-based treatments have produced more-conformal dose distributions that facilitate the delivery of therapeutic doses to the target organ while minimizing the dose administered to the surrounding organs at risk.[7-9] Dosimetric comparisons have shown that, compared with IMRT, proton beam therapy delivers lower doses to the heart and lungs of patients with esophageal cancer.[10,11] Furthermore, proton beam therapy can be administered with a spot-scanning technique, allowing for intensity modulated proton beam radiation therapy (IMPT), which is not possible with older passive-scattering technology. Passive-scattering proton therapy delivers a uniform dose to the target, as determined by its maximum depth; however, this approach can increase the dose delivered to adjacent normal tissues. In contrast, IMPT delivers the dose to individual points within the target, as determined by each layer of the tumor. Thus, IMPT delivers a more-conformal dose to the target and better spares the adjacent normal tissues (eg, spinal cord, heart, lungs). A recent dosimetric comparison by our institution showed that patients who underwent IMPT received reduced mean liver, heart, and lung doses compared with those received by patients who received IMRT.[12]

To date, most published studies on proton beam therapy for esophageal cancer describe passive-scattering technology,[8,13] and the reported clinical experiences with IMPT for esophageal cancer are limited.[14-16] One retrospective series from the MD Anderson Cancer Center reported that IMPT resulted in reasonable 1-year outcomes (89% of patients had locoregional recurrence-free survival) and acute toxicities (63% of patients had grade $\geq$3 toxicity).[17] A larger retrospective series from the same institution reported increased overall survival (OS) among patients treated with definitive proton beam therapy (primarily passive scattering) compared with that of patients treated with IMRT, and toxicity rates were similar between the groups.[18]

To add to the limited published data on IMPT for the treatment of esophageal cancer, we report our clinical comparison of acute radiation therapy–related toxicities and short-term outcomes between patients treated with IMRT and IMPT. We hypothesized that IMPT is a well-tolerated treatment modality with short-term clinical outcomes and toxicity profiles that are similar to those of IMRT.

Methods and Materials

Patient selection

We obtained Mayo Clinic Institutional Review Board approval to retrospectively review the electronic health records (EHRs) of consecutive patients with esophageal cancer who were treated with radiation therapy at our institution between January 1, 2014, and June 30, 2018. We collected follow-up data through January 31, 2019, because patients generally underwent standard clinical evaluations every 3 months during the first year of treatment. We included adult patients (age $\geq$18 years) with a pathologic diagnosis of esophageal adenocarcinoma or

squamous cell carcinoma who underwent neoadjuvant or definitive CRT with curative intent (as determined by the treating physician) and received IMPT or IMRT. We included patients with cervical, thoracic, and gastroesophageal junction carcinoma (Siewert type I or II). Patients were excluded if they had received prior radiation therapy for esophageal cancer.

Patients were selected for IMPT or IMRT by their treating physician, and treatment was subject to insurance approval. Patients treated through 2015 received IMRT, and those who started treatment in 2016 (when the Mayo Clinic Proton Beam Therapy Program opened in Phoenix, Arizona) generally received IMPT. Detailed patient, disease, treatment, and outcome characteristics were retrospectively extracted from the EHRs. Demographic and clinical characteristics included smoking history, comorbid conditions, dysphagia at the time of presentation, pretreatment feeding tube placement, Eastern Cooperative Oncology Group performance status score, cardiac ejection fraction (before and after treatment), and pulmonary function (before and after treatment). Pre- and posttreatment maximum esophageal standardized uptake values were obtained with positron emission tomography (PET)–computed tomography (CT). We also recorded tumor location, histologic characteristics, *HER2* status, and cancer stage (per the American Joint Committee on Cancer's *Cancer Staging Manual*, 7th edition).

Oncologic treatments

We collected data on prior induction chemotherapy, chemotherapy regimen, and completion status. Chemotherapy regimens were chosen at the discretion of the treating medical oncologist. Radiation therapy characteristics were extracted from a prospectively maintained departmental database of clinical outcomes and toxicities. We collected data on radiation therapy modality (proton or photon), dose, fractionation, boost method (if used), treatment breaks, and completion status from the database, and these data were separately confirmed in the EHRs. IMPT doses were recorded in grays, and a relative biological effectiveness of 1.1 was assumed.

The radiation therapy modality and treatment-planning techniques were determined by the treating physician. Generally, for treatment simulation, all patients were placed in the supine position and underwent 4-dimensional CT. With their arms secured overhead, patients were immobilized with a wing board (CIVCO Medical Solutions) and vacuum cushion (BlueBag, Elekta Instrument AB). In our commercial treatment-planning system (Eclipse version 13, Varian Medical Systems Inc.), pretreatment PET images were aligned with the averaged 4-dimensional CT scan. The coregistered PET-CT images and endoscopy findings were used to contour the gross tumor volume (GTV) on the averaged 4-dimensional CT scan or a CT scan of a single breathing phase. A 3- to 4-cm longitudinal expansion of the GTV along the mucosal surface and a 1- to 1.5-cm anatomically adjusted radial expansion were used to create the appropriate clinical target volumes (CTVs). Alternatively, for some patients, an internal target motion volume was contoured on the basis of the GTV motion on the 4-dimensional CT scan, and an additional 1- to 2-cm margin was added to create the CTV. For setup consideration, volumetric modulated arc therapy plans were generated with Eclipse, and planning target volumes were created with an additional 5-mm uniform expansion of the CTVs. Two or 3 coplanar arcs were commonly used.

For IMPT treatment planning, we uniformly expanded the CTVs by 5 mm to create the optimized target volume, and robust planning was used. Posterior left-right oblique and superior-inferior oblique beam arrangements were commonly used.[12] For targets that have considerable longitudinal expansion and substantial mediastinal involvement, anterior and posterior beam arrangements were also used. Organs at risk were contoured, and we complied with the following institutional dose constraints: The volume of normal lung receiving 20 Gy was <20%; mean lung dose was <15 Gy; the volume of heart receiving 40 Gy was <30%; mean heart dose was <26 Gy; mean liver dose was <25 Gy; and maximum spinal cord dose was <45 Gy.

Among patients who underwent surgery, the surgical approach was determined by the treating surgeon. Laparoscopic and thoracoscopic approaches were defined as minimally invasive surgery, and laparotomy, thoracotomy, or hybrid approaches were considered open procedures. Detailed pathologic and postoperative complication data were extracted from the EHRs. The patient's cancer status was considered downstaged if either the tumor (T) or nodal (N) stage was downstaged (without upstaging of the other) compared with the status at the time of presentation.[19] A complication was considered postoperative if it occurred within 30 days of surgery without an identified nonsurgical cause.

Clinical outcomes

Pre- and posttreatment toxicities were prospectively noted in the departmental database and evaluated per the Common Terminology Criteria for Adverse Events, version 4. We also retrospectively and independently verified all toxicities in all patients. Local control (LC), locoregional control (LRC), distant metastasis–free survival (DMFS), progression-free survival (PFS), and OS outcomes were recorded. For DMFS, survival outcomes were determined from the date of diagnosis until the date of distant failure or death; for PFS, until the date of first failure or death; and for OS, until the date of death or last known follow up. A treatment failure was considered

local if it occurred within the esophagus, regional if within the regional lymph nodes, and distant if outside the local or regional sites.

Statistical methods

We compared the unmatched IMPT and IMRT cohorts and used a subgroup analysis to compare patients in each cohort who underwent surgery. The Fisher exact test was used to assess associations between categorical variables and treatment modality and the Wilcoxon rank sum test to assess associations between continuous variables and treatment.

Survival outcomes were estimated with the Kaplan-Meier method. A univariate Cox regression analysis was used to determine associations between patient characteristics and clinical time-to-event outcomes. Multivariate analyses of clinical outcomes and acute toxicity were conducted in a stepwise manner to take into account clinically and statistically significant univariate factors and underlying models. A 2-sided P value $< .05$ was considered statistically significant for the univariate and multivariate analyses.

Results

Patient, tumor, and treatment characteristics

We identified 64 consecutive patients who were treated with IMPT (n = 32) or IMRT (n = 32). The median follow-up time was 10 months for IMPT patients (12 months for patients who were alive at the time of the data analysis) and 14 months for IMRT patients (29 months for those who were alive at the time of the analysis). Significantly more IMPT patients had dysphagia at the time of presentation (27 IMPT [84%] vs 20 IMRT [63%] patients; $P = .04$), but significantly fewer IMPT patients had adenocarcinoma (20 IMPT [63%] vs 29 IMRT [91%] patients; $P = .02$; Table 1).

Treatment intent at the time of diagnosis was most commonly neoadjuvant (23 IMPT [72%] vs 26 IMRT [81%] patients; $P = .24$; Table 1). Most patients received concurrent carboplatin and paclitaxel (29 IMPT [91%] vs 32 IMRT [100%] patients; $P = .24$). For both groups, the median radiation therapy dose was 45 Gy (range, 41.4-50.4 Gy) in 25 fractions, and 80% of patients received a simultaneous integrated boost to a median cumulative dose of 50 Gy (range, 50-56 Gy). The dosimetric analysis showed that the mean heart dose, volume of heart receiving <30 Gy, and mean lung dose were significantly lower in the IMPT group than the IMRT group (all $P < .01$).

Patient outcomes

We did not observe a significant difference in the maximum esophageal standardized uptake values (with PET-CT) before and after treatment (4.7 for IMPT vs 4.2 for IMRT patients; $P = .57$). At 1 year, both treatment groups had similar outcomes (IMPT vs IMRT, respectively): LC, 92% versus 84% ($P = .87$); LRC, 92% versus 80% ($P = .76$); DMFS, 87% versus 65% ($P = .08$); PFS, 71% versus 45% ($P = .15$); and OS, 74% versus 71% ($P = .62$; Figs. 1 and 2). On multivariate analysis, surgery was a significant predictor of LC ($P = .02$) and LRC ($P = .01$). To determine the additive effect of IMPT, we included all significant variables from the univariate analysis as confounders in the multivariate analysis of OS. When we controlled for pretreatment feeding tube placement, tumor stage, surgery, and total planned dose, IMPT patients did not have improved OS compared with IMRT patients (hazard ratio: 0.57; 95% confidence interval, 0.19-1.74; $P = .57$; Table 2).

Fifteen IMPT (47%) and 18 IMRT (56%) patients underwent surgery ($P = .07$), with no difference in pathologic complete response rates (5 of 15 IMPT patients [33%] vs 7 of 18 IMRT patients [39%]; $P = .14$; Table 3). Postoperative complication rates were also similar between the groups, including those for pneumonia, anastomotic leak, anastomotic stricture, and cardiac arrhythmia (all $P > .06$).

Treatment-related toxicities

Placement of a pretreatment feeding tube was considered indicative of grade 3 dysphagia at baseline, and a pretreatment feeding tube had been placed in 9 IMPT patients (28%) versus 4 IMRT patients (13%; $P = .21$). At the end of treatment, only 2 patients (6.2%) per treatment group had grade 3 toxicities other than dysphagia (esophagitis and nausea in IMPT, dehydration and anemia in IMRT; Table 4). The rate of acute treatment-related grade 3 toxicity (including dysphagia) was not significantly different between the 2 groups (5 IMPT [16%] vs 3 IMRT [9%] patients; Fisher exact test, $P = .71$). Fewer IMPT patients had grade 4 lymphopenia (6 IMPT [19%] vs 9 IMRT [28%] patients; $P = .37$).

Discussion

Locally advanced esophageal cancer is an aggressive disease that is ideally treated with trimodality therapy. We report our initial clinical experience with administering IMRT and IMPT to patients with esophageal cancer in the neoadjuvant and definitive settings. This is one of the few retrospective analyses to compare clinical outcomes and acute toxicities between cohorts of IMRT and IMPT patients.

Table 1 Demographic, clinical, tumor, and treatment characteristics of IMPT and IMRT patients

Characteristic	IMPT (n = 32)*	IMRT (n = 32)*	*P*-value
Demographic			
Age, median (IQR), y	71.5 (29.7-84.3)	71.4 (55-90.0)	.69†
Male sex	24 (75)	29 (91)	.18‡
Race/ethnicity			.17‡
White	29 (91)	31 (97)	
Other	3 (9)	1 (3)	
Clinical			
Year of diagnosis, mode (range)	2017 (2016-2018)	2016 (2014-2018)	…
Smoking history			.77‡
Nonsmoker	10 (31)	12 (38)	
Current	3 (9)	4 (13)	
Past	19 (59)	16 (50)	
ECOG performance status score			.87‡
0	15 (47)	18 (56)	
1	14 (44)	11 (34)	
2	3 (9)	3 (9)	
Barrett esophagus	13 (41)	18 (56)	.32‡
Dysphagia at presentation			.04‡
None	5 (16)	12 (38)	
Solids	24 (75)	20 (63)	
Solids and liquids	3 (9)	0 (0)	
Pretreatment feeding tube	9 (28)	4 (13)	.21‡
Maximum pretreatment SUV on PET-CT, median (IQR)	9.5 (3.0-25.4)	8.2 (2.8-22.9)	.57†
Difference between pretreatment and posttreatment maximum SUV on PET-CT, median (IQR)	4.7 (1.3-5.2)	4.2 (1.1-5.6)	.57†
Tumor			
Location			.15‡
Distal esophagus or gastroesophageal junction	25 (78)	30 (94)	
Cervical, midthoracic, or upper thoracic	7 (22)	2 (6)	
Clinical stage§			
T stage			.82‡
1	3 (9)	5 (16)	
2	9 (28)	9 (28)	
3	20 (63)	18 (56)	
N stage			.51‡
0	7 (22)	5 (16)	
1	15 (47)	19 (59)	
2	8 (25)	8 (25)	
3	2 (6)	0 (0)	
Histologic diagnosis			.02‡
Adenocarcinoma	20 (63)	29 (91)	
Squamous	11 (34)	3 (9)	
Adenosquamous	1 (3)	0 (0)	
Pathology grade			.44‡
Not reported	3 (9)	1 (3)	
Well	0 (0)	1 (3)	
Moderate	15 (47)	12 (38)	
Poor	14 (44)	18 (56)	
HER2 status			.60‡
Not reported	14 (44)	12 (38)	
Negative or indeterminate	17 (53)	17 (53)	
Positive	1 (3)	3 (9)	
Treatment			
Intent			.24‡

(*continued on next page*)

Table 1 (*continued*)

Characteristic	IMPT (n = 32)*	IMRT (n = 32)*	*P*-value
Neoadjuvant	23 (72)	26 (81)	
Definitive	9 (28)	6 (19)	
Induction chemotherapy	5 (16)	3 (9)	.46‡
Chemotherapy regimen			.24‡
Carboplatin + paclitaxel	29 (91)	32 (100)	…
Carboplatin + capecitabine	3 (9)	0 (0)	…
Completed planned cycles of neoadjuvant chemotherapy	25 (78)	27 (84)	.75‡
Radiation therapy			
Primary dose, median (IQR), Gy	45.0 (41.4-50.4)	45.0 (41.4-50.4)	.24†
Cumulative boost dose, median (IQR), Gy	50.0 (50.0-56.0)	50.0 (50.0-56.0)	.10†
Fractions, median (IQR)	25.0 (23.0-28.0)	25.0 (23.0-28.0)	.46†
Completed	31 (97)	29 (91)	.61†
Mean heart dose, median (IQR), Gy	8.1 (5.0-10.1)	19.3 (15.7-23.5)	<.01†
Volume of heart receiving <30 Gy, median (IQR), %	12 (10-17)	19 (14-30)	<.01†
Mean lung dose, median (IQR), Gy	3.9 (3.3-5.2)	9.2 (4.0-12.0)	<.01†
Volume of lung receiving <20 Gy, median (IQR), %	10 (7-13)	12 (9-16)	.07†

Abbreviations: ECOG = Eastern Cooperative Oncology Group; *HER2* = human epidermal growth factor receptor 2; IMPT = intensity modulated proton beam therapy; IMRT = intensity modulated radiation therapy; IQR = interquartile range; PET-CT = positron emission tomography-computed tomography; SUV = standardized uptake value

* Values are shown as n (%) of patients, unless stated otherwise.

† Wilcoxon rank sum test

‡ Fisher exact test

§ Per the American Joint Committee on Cancer's *Cancer Staging Manual, 7th edition*.

Compared with the IMRT group, the IMPT group had improved (although not significantly) LC, LRC, DMFS, PFS, and OS. In a smaller IMPT series, researchers at the MD Anderson Cancer Center noted similar clinical outcomes, including a 1-year locoregional recurrence-free survival rate of 89% and a DMFS rate of 73%.[17] In a larger series by the same institution,[18] compared with IMRT patients, patients treated with proton beam therapy had improved 5-year OS rates (32% vs 42%; $P = .01$) and improved PFS rates (20% vs 35%; $P < .01$). These patients were treated in the definitive setting, and most patients received passive-scattering proton therapy. Only 7 patients underwent IMPT.

In our study, more IMPT patients had a pretreatment feeding tube than IMRT patients. After adjustment for this baseline characteristic, the 2 groups had similar rates of grade 3 toxicity (only 4 patients [6.2%] were affected in the entire cohort). This compares favorably to the rate of approximately 20% for grade 3 toxicity reported in the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study.[2] Researchers at the MD Anderson Cancer Center reported 12 acute grade ≥3 toxicity events in their series of 19 IMPT patients.[17] In the larger comparative

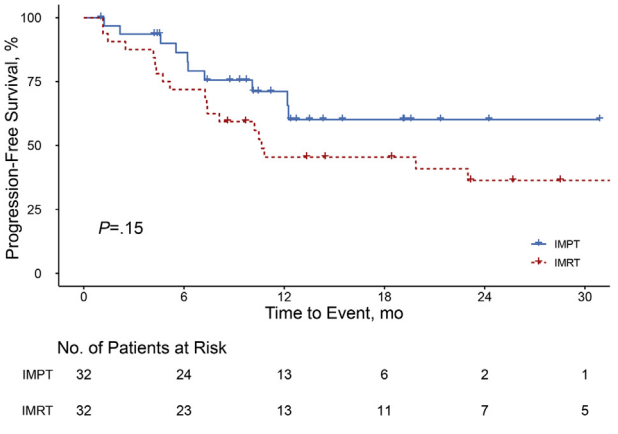

Figure 1 Progression-free survival of intensity modulated proton beam and intensity modulated photon radiation therapy patients. The *P* value was calculated for the difference in survival at 1 year.

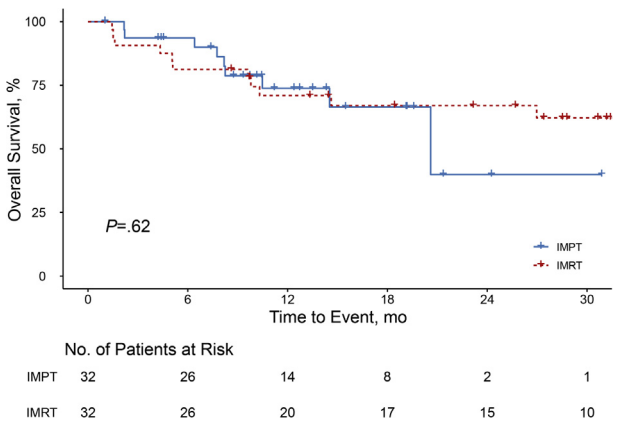

Figure 2 Overall survival of intensity modulated proton beam and intensity modulated photon radiation therapy patients. The *P* value was calculated for the difference in survival at 1 year.

Table 2 Univariate Cox analysis of overall survival*

Characteristic (selected)	Hazard ratio (95% CI)	*P*-value
Male (vs female)	0.55 (0.18-1.67)	.29
Smoking history (vs nonsmoker)	1.20 (0.27-5.38)	.81
Dysphagia at presentation (vs no dysphagia)	1.15 (0.44-2.96)	.77
Pretreatment feeding tube (vs no tube)	3.11 (1.27-7.58)	.01
T3 (vs T1-2 stage)	2.35 (0.88-6.23)	.09
Neoadjuvant (vs definitive intent)	0.69 (0.09-5.26)	.72
Completed concurrent chemotherapy (vs incomplete chemotherapy)	0.30 (0.12-0.71)	<.01
IMPT (vs IMRT)	1.25 (0.52-3.03)	.62
No treatment break during radiation therapy (vs treatment break)	0.29 (0.11-0.81)	.02
Completed radiation therapy (vs incomplete radiation therapy)	0.16 (0.05-0.56)	<.01
Surgery (vs no surgery)	0.48 (0.21-1.14)	.09
Primary radiation dose (per Gy)	1.24 (1.04-1.48)	.02
Boost dose (per Gy)	1.17 (0.90-1.51)	.24

Abbreviations: CI = confidence interval; IMPT = intensity modulated proton beam therapy; IMRT = intensity modulated photon radiation therapy.
* Conducted with Cox regression analysis.

Table 3 Pathologic findings and postoperative complications of IMPT and IMRT patients who underwent surgery

Characteristic	IMPT (n = 15)*	IMRT (n = 18)*	Total (n = 33)*	*P*-value†
Surgical approach				.08
Minimally invasive	12 (80)	18 (100)	30 (91)	
Open	3 (20)	0 (0)	3 (9)	
Pathologic stage‡				
T stage				.06
0	6 (40)	7 (39)	13 (39)	
1	3 (20)	3 (17)	6 (18)	
2	4 (27)	0 (0)	4 (12)	
3	2 (13)	8 (44)	10 (30)	
N stage				.04
0	12 (80)	16 (89)	28 (85)	
1	3 (20)	0 (0)	3 (9)	
2	0 (0)	2 (11)	2 (6)	
Margin status				.42
Not reported	2 (13)	0 (0)	2 (6)	
Negative	12 (80)	18 (100)	30 (91)	
Margin	1 (7)	0 (0)	1 (3)	
Invasion				>.99
Not reported	2 (13)	0 (0)	2 (6)	
None	12 (80)	16 (89)	28 (85)	
Perineural	1 (7)	1 (6)	2 (6)	
Lymphovascular	0 (0)	1 (6)	1 (3)	
Pathologic complete response	5 (33)	7 (39)	12 (36)	.42
Downstaged status	13 (87)	13 (72)	26 (79)	.20
Postoperative complication				
Pneumonia	2 (13)	5 (28)	7 (21)	.40
Acute respiratory distress syndrome	0 (0)	3 (17)	3 (9)	.23
Esophageal stricture	1 (7)	2 (11)	3 (9)	>.99
Anastomotic leak	3 (20)	4 (22)	7 (21)	>.99
Anastomotic stricture	4 (27)	7 (39)	11 (33)	.47
Tracheoesophageal fistula	2 (13)	0 (0)	2 (6)	.20
Cardiac arrhythmia	8 (53)	3 (17)	11 (33)	.06

Abbreviations: IMPT = intensity modulated proton beam therapy; IMRT = intensity modulated radiation therapy.
* Values are shown as n (%) of patients, unless stated otherwise.
† Fisher exact test.
‡ Per the American Joint Committee on Cancer's *Cancer Staging Manual, 7th edition*.

Table 4 Grades 2 and 3 toxicities in IMPT and IMRT patients*

Toxicity	IMPT (n = 32)†,‡		IMRT (n = 32)†,‡		*P*-value§
	Grade 2	Grade 3	Grade 2	Grade 3	
Esophagitis	12 (38)	1 (3)	8 (25)	0 (0)	>.99
Dysphagia	17 (53)	9 (28)	8 (25)	4 (13)	.01
Nausea	8 (25)	1 (3)	4 (13)	0 (0)	>.99
Lymphopenia‖	5 (16)	27 (84)	4 (13)	26 (81)	.65
Vomiting	1 (3)	0 (0)	0 (0)	0 (0)	…
Radiation therapy–related dermatitis	5 (16)	0 (0)	0 (0)	0 (0)	…
Fatigue	12 (38)	0 (0)	12 (38)	0 (0)	…
Dehydration	7 (22)	0 (0)	5 (16)	1 (3)	>.99
Anemia	6 (19)	0 (0)	1 (3)	1 (3)	…

Abbreviations: IMPT = intensity modulated proton beam therapy; IMRT = intensity modulated photon radiation therapy.

* Grade was assessed according to the Common Terminology Criteria for Adverse Events, version 4.

† Values are shown as n (%) of patients, unless stated otherwise.

‡ No grade 4 or 5 toxicities were reported, except for lymphopenia.

§ Grade 3 toxicities due to IMPT vs IMRT, determined with the Fisher exact test.

‖ Grade 3 toxicity included grade ≥3 lymphopenia (6 IMPT and 9 IMRT patients had grade 4 lymphopenia). Lymphopenia toxicity was graded according to Common Terminology Criteria for Adverse Events, version 4: Grade 1, < lower limit of normal - 800/mm^3; grade 2, <800-500/mm^3; grade 3, <500-200/mm^3; grade 4, <200/mm^3.

study,[18] patients who received proton beam therapy or IMRT had similar rates of grade ≥3 toxicity (38% vs 45%; $P = .19$). Furthermore, recent studies have shown that the incidence of grade 4 lymphopenia, a marker of poorer survival outcomes, was significantly decreased among IMPT patients.[15,20]

Both cohorts had increased rates of grade ≥3 lymphopenia by the end of treatment, but the difference between IMPT and IMRT patients was not significant (likely because of the small number of patients). Recently, researchers at the MD Anderson Cancer Center published results from their randomized phase 2b study, comparing proton beam therapy with IMRT for locally advanced esophageal cancer.[21] Patients treated with proton beam therapy had a decreased total toxicity burden and similar oncologic outcomes compared with patients treated with IMRT. The composite toxicity score used in their study incorporated acute and late radiation toxicities, which may help to determine the value of proton beam therapy over the course of cancer care. Again, similar to other studies, most patients (80%) received passive-scattering proton treatment and the other patients received IMPT.

Among patients who underwent surgery in our cohort, pathologic outcomes and postoperative complications were also similar between the IMPT and IMRT groups. These 2 groups had pathologic complete response rates of 33% and 39%, respectively, which are similar to those reported in the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study.[2] In a larger multi-institutional analysis of radiation therapy modalities for neoadjuvant CRT for esophageal cancer, passive-scattering proton beam therapy resulted in significantly lower risks of postoperative pulmonary, cardiac, and wound complications compared with those of 3-dimensional conformal radiation therapy. However, proton beam therapy resulted in only a lower risk of postoperative wound complications (the risk of pulmonary complications was not significantly lower) compared with that of IMRT.[22]

Our study has several limitations. The inherent biases of a retrospective study should be kept in mind. Although most pretreatment characteristics were similar between the groups, IMPT patients more commonly had dysphagia at the time of presentation and squamous cell carcinoma; therefore, we may not have accounted for an underlying selection bias in our analysis. Insurance approval may also have been a factor.[23] Our sample size was small, and the follow-up period was short. An analysis of dose-volume histogram data of normal tissues would also help to elucidate clinical differences between the IMPT and IMRT cohorts.

IMPT appears to be a safe and effective treatment for esophageal cancer. We did not find significant differences between the clinical outcomes of IMPT and IMRT patients, possibly because of the short-term follow-up and small cohort size. However, this report supports the need for prospective studies comparing survival, toxicity, and patient-reported outcomes between patients receiving IMPT or IMRT for esophageal cancer.[24] NRG Oncology is currently conducting a randomized phase 3 trial of proton beam therapy (passive-scattering therapy or IMPT) versus IMRT for esophageal cancer (NRG Oncology identifier NRG-GI006; Clinical Trials Reporting Program Identifier NCI-2018-03378; ClinicalTrials.gov identifier NCT03801876).

Conclusions

We report on the preliminary, promising retrospective evidence of the safety and effectiveness of IMPT and IMRT when administered as definitive or neoadjuvant therapy for esophageal cancer. Prospective studies comparing IMPT versus IMRT are crucial to define the ideal patient populations for each treatment modality.

Supplementary Data

Supplementary material for this article can be found at https://doi.org/10.1016/j.adro.2020.04.026.

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