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Scientific Article

Reirradiation With Proton Therapy for Recurrent Malignancies of the Esophagus and Gastroesophageal Junction: Results of the Proton Collaborative Group Multi-Institutional Prospective Registry Trial

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Purpose: Treatment options for recurrent esophageal cancer (EC) previously treated with radiation therapy (RT) are limited. Reirradiation (reRT) with proton beam therapy (PBT) can offer lower toxicities by limiting doses to surrounding tissues. In this study, we present the first multi-institutional series reporting on toxicities and outcomes after reRT for locoregionally recurrent EC with PBT.

Methods and Materials: Analysis of the prospective, multicenter, Proton Collaborative Group registry of patients with recurrent EC who had previously received photon-based RT and underwent PBT reRT was performed. Patient/tumor characteristics, treatment details, outcomes, and toxicities were collected. Local control (LC), distant metastasis-free survival (DMFS), and overall survival (OS) were estimated using the Kaplan-Meier method. Event time was determined from reRT start.

Results: Between 2012 and 2020, 31 patients received reRT via uniform scanning/passive scattering (61.3%) or pencil beam scanning (38.7%) PBT at 7 institutions. Median prior RT, PBT reRT, and cumulative doses were 50.4 Gy (range, 37.5-110.4), 48.6 Gy (relative biological effectiveness) (25.2-72.1), and 99.9 Gy (79.1-182.5), respectively. Of these patients, 12.9% had 2 prior RT courses, and 67.7% received PBT with concurrent chemotherapy. Median follow-up was 7.2 months (0.9-64.7). Post-PBT, there were 16.7% locoregional only, 11.1% distant only, and 16.7% locoregional and distant recurrences. Six-month LC, DMFS, and OS were 80.5%, 83.4%, and 69.1%, respectively. One-year LC, DMFS, and OS were 67.1%, 83.4%, and 27%, respectively. Acute grade ≥3 toxicities occurred in 23%

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of patients, with 1 acute grade 5 toxicity secondary to esophageal hemorrhage, unclear if related to reRT or disease progression. No grade ≥3 late toxicities were reported.

Conclusions: In the largest report to date of PBT for reRT in patients with recurrent EC, we observed acceptable acute toxicities and encouraging rates of disease control. However, these findings are limited by the poor prognoses of these patients, who are at high risk of mortality. Further research is needed to better assess the long-term benefits and toxicities of PBT in this specific patient population.

Introduction

Esophageal cancer (EC) is the eighth most common type of cancer worldwide and the sixth leading cause of cancer death.[1] In the United States, there is an estimated 21,560 new cases of EC and 16,120 attributed deaths in 2023.[2] The majority of patients with EC present with locally advanced disease. Unfortunately, the prognosis for this patient population remains poor, with a 10-year overall survival (OS) rate of 38%.[3]

In patients with locally advanced esophageal and gastroesophageal junction (GEJ) cancers, treatment is generally multimodal, with patients often receiving chemotherapy, radiation therapy (RT), and/or surgery. However, even with a tri-modality approach, between 20% to 40% of patients will experience locoregional recurrence.[4-8] To date, outcomes in patients with recurrent EC are poor. Additionally, recurrent disease can lead to a profound deterioration in a patient's quality of life due to sequelae such as severe pain, bleeding, vomiting, obstruction, dysphagia, and/or weight loss.

Salvage treatment options for locoregionally recurrent esophageal and GEJ cancers previously treated with RT are limited and largely consist of salvage systemic therapy, surgical resection, or reirradiation (reRT). Unfortunately, many patients are not surgical candidates because of a prior history of esophagectomy or limited performance status. Moreover, additional RT to a previously irradiated field can pose a significant challenge because of the dosimetric constraints of adjacent critical structures and is associated with an increased incidence of treatment-related toxicity, especially with photon-based reRT.[9,10]

Proton beam therapy (PBT) has the unique ability to deposit dose at a specific depth corresponding with the Bragg peak, beyond which there is essentially no further dose deposition, allowing significant reduction of distal normal tissue exposure to unnecessary radiation.[11] This allows for more conformal dose delivery and improved surrounding organs-at-risk sparing with PBT,[12] advantages that may permit safer dose reRT escalation and thus provide patients with locally recurrent disease an opportunity to receive curative, rather than palliative, salvage reRT.[13,14] Although proton therapy is increasingly being used in the setting of reirradiation for esophageal cancer, to date, data on outcomes in this patient population are limited to small retrospective[15] and prospective studies,[16] with the largest study reporting outcomes on 17 patients.[17] In this study, we report on outcomes and toxicities from a multi-institutional series of patients with locoregionally recurrent esophageal and GEJ cancers who underwent reRT with PBT.

Methods and Materials

This retrospective analysis of a prospective, multi-institutional registry from the Proton Collaborative Group was approved by the institutional review board, and patient consent was obtained at time of enrollment. Forty consecutive patients who underwent PBT with definitive intent for locoregionally recurrent esophageal and GEJ cancer in a previously irradiated field between May 21, 2012, and March 11, 2021, to allow time for adequate follow-up were identified from 7 proton centers across the United States. Additionally, initial RT doses needed to be higher than 30 Gy for patients to be included in this study. Five patients with no initial radiation treatment information, 3 with a lack of post-reRT follow-up data, and 1 patient who only received 10.6 Gy in 6 fractions at initial diagnosis were excluded from our study, leaving 31 patients treated at 7 institutions for analysis.

All patients underwent computed tomography simulation, and positron emission tomography scans were fused when available for target delineation. Target delineation was specific for each patient as determined by the treating radiation oncologist. Concurrent systemic therapy was administered at the discretion of the treating oncologist. PBT was delivered using uniform scanning/passive scattering or pencil beam scanning.

Baseline demographics, tumor characteristics, treatment details, adverse events, tumor control, and survival were assessed. Acute and late toxicities were graded using Common Terminology Criteria for Adverse Events version 4.0. Acute toxicities were defined as occurring during or within 3 months after PBT completion. Acute toxicities during treatment were graded prospectively weekly by the treating physician and were retrospectively reviewed. Late toxicities were obtained through detailed retrospective electronic medical record review.

Statistical analysis

Distant metastasis-free survival (DMFS), local control (LC), and OS were calculated from start of PBT reRT until

the date of progression or death. Patients who remained alive were censored at last follow-up. Kaplan-Meier methodology was used to estimate time-to-event endpoints. Statistical analyses were conducted in R software, version 1.1.383.

Results

Thirty-one patients treated with PBT reRT from 2012 to 2020 were analyzed. The majority were male (71%, n = 22) and White (77.4%, n = 24). Most patients had initial primary disease that was T3 (77.4%, n = 24), node positive disease (N1 38.7%, N2 29.0%), and moderately (41.9%) or poorly (32.3%) differentiated disease. Patients most commonly had adenocarcinoma (54.8%, n = 17) of the lower esophagus (54.8%, n = 17) (Table 1). Three patients presented with M1 disease, with metastases to the lung, lung and adrenal gland, and bone, respectively. The patient with metastasis to the lung received 50.4 Gy in 28 fractions to the primary disease and 50 Gy in 3 fractions to the lung metastasis. The patient with metastases to lung and adrenal gland received 37.5 Gy in 15 fractions to the primary disease with concurrent chemotherapy, and the patient with bone metastasis received 50.4 Gy in 28 fractions to the primary disease with concurrent chemotherapy. All patients were treated with photons for their initial course of RT, and the majority received 50.4 Gy (range, 37.5-110.4) in 28 daily fractions (range, 15-33) with concurrent chemotherapy (67.7%, n = 21). The most common concurrent chemotherapy regimen was carboplatin/paclitaxel (57.1%, n = 12/21), 5-fluorouracil (5-FU) or capecitabine (9.5%, n = 2/21), and folinic acid, fluorouracil, and oxaliplatin (9.5%, n = 2/21). Four patients received an additional course of RT with photons targeting the esophagus or chest area (ie, to esophageal anastomosis, supraclavicular nodes, axilla, and internal mammary nodes) before PBT reRT for locoregionally recurrent disease, thereby receiving a cumulative dose of up to 110.4 Gy. One patient received hypofractionated RT to a dose of 37.5 Gy in 15 daily fractions. A total of 9 (29%) patients had undergone surgical resection: 7 patients underwent surgery post initial RT treatment, and 2 patients underwent surgery before initial RT treatment (Table 2).

The median time to recurrence from the end of initial RT was 11.4 months (range, 3.7-134.1), with a median interval of 21.3 months (range, 6.2-136.6) between the end of photon RT and the start of PBT re-RT. The majority of recurrences were local only (71%, n = 22), followed by local and regional (16.1%, n = 5) and regional only (12.9%, n = 4). PBT reRT was primarily delivered using uniform scanning/passive scattering (61.3%, n = 19), followed by pencil beam scanning (38.7%, n = 12). One patient received photon RT using intensity modulated RT (IMRT) for the first 4 fractions of the treatment, followed

Table 1 Patient and tumor characteristics (N = 31)

Characteristic	#
Age in years at time of reRT, median (range)	67 (53-87)
Sex, n (%)	
Male	22 (71.0%)
Female	9 (29.0%)
Race, n (%)	
White	24 (77.4%)
Black	2 (6.5%)
Asian	2 (6.5%)
Hispanic	2 (6.5%)
Other/unknown	1 (3.2%)
ECOG performance status at reRT, n (%)	
0	12 (38.7%)
1	13 (41.9%)
2	5 (16.1%)
Unknown	1 (3.2%)
Clinical stage at initial diagnosis, n (%)	
T stage	
T1	3 (9.7%)
T2	3 (9.7%)
T3	24 (77.4%)
Unknown	1 (3.2%)
N stage	
N0	9 (29.0%)
N1	12 (38.7%)
N2	9 (29.0%)
N3	0 (0.0%)
Unknown	1 (3.2%)
M stage	
M0	26 (83.9%)
M1	3 (9.7%)
Unknown	2 (6.5%)
Grade, n (%)	
Well differentiated	2 (6.5%)
Moderately differentiated	13 (41.9%)
Poorly differentiated	10 (32.3%)
Unknown	6 (19.4%)
Clinical group stage,* n (%)	
II	1 (3.2%)
IIA	1 (3.2%)
IIB	6 (19.4%)
IIIA	4 (12.9%)

(*continued on next page*)

Table 1 (*Continued*)

Characteristic	#
IIIB	13 (41.9%)
IV	3 (9.7%)
IVA	1 (3.2%)
Unknown	2 (6.5%)
Histology, n (%)	
Adenocarcinoma	17 (54.8%)
Squamous cell carcinoma	14 (45.2%)
Tumor location, n (%)	
Upper esophagus	2 (6.5%)
Middle esophagus	6 (19.4%)
Lower esophagus†	17 (54.8%)
Overlapping sites or NOS	6 (19.4%)

Abbreviations: AJCC = American Joint Committee on Cancer; ECOG = Eastern Cooperative Oncology Group; NOS = not otherwise specified; reRT = reirradiation.
*AJCC 7th ed. was used for cancers diagnosed until December 31, 2017 (n = 18) and AJCC 8th ed. thereafter (n = 4).
†Lower esophagus location including gastroesophageal junction

by PBT for the remainder of reRT treatment. Patients were treated with PBT to a median dose of 48.6 Gy relative biologic effectiveness (RBE) (range, 25.2-72.1). The majority of patients received fractionated daily radiation (n = 29) with a median of 25 daily fractions (range, 12-28). Two patients received twice-daily (bid) radiation, 59.95 Gy in 50 bid fractions and 72.14 Gy in 60 bid fractions, respectively. The majority of patients received concurrent chemotherapy (67.7%, n = 21), most commonly using carboplatin/paclitaxel (38.1%, n = 8/21), followed by 5-FU or capecitabine (23.8%, 5/21) and cisplatin/5-FU or capecitabine (14.3%, n = 3/21) (Table 2). Regarding the 22.6% (n = 7) who did not receive concurrent chemotherapy during the initial RT course, 1 patient had metastatic (M1) disease, and 2 patients had an Eastern Cooperative Oncology Group of 2, potentially influencing the decision against concurrent chemotherapy. For the remaining 4 patients, detailed information was not available to explain the omission of chemotherapy in their initial treatment.

At a median follow-up of 7.2 months (range, 0.9-64.7), 7 of 31 (22.6%) patients remained alive. Three patients died because of causes determined by the treating physician as not related to their malignancy, including 1 patient who succumbed to bacterial pneumonia, another to respiratory failure, and a third because of COVID-19. One patient died because of esophageal hemorrhage. Ten patients died because of the progression of their cancer. Additionally, there were 10 cases where the cause of death was unknown. We did not have information regarding local or distal failure for 13 patients. For 13 patients, detailed data on local or distal failure was incomplete because of death (11 patients) or loss to follow-up post-PBT (1 patient was lost to follow-up at 1 month, and another patient was lost to follow-up at 5 months). These 13 patients were initially included in the number at risk for local or distant recurrence; however, they were censored at the last known point of follow-up or at death. Out of the remaining 18 patients, 3 (16.7%) had locoregional-only recurrence, of whom 1 was surgically salvaged, 1 received chemotherapy, and 1 patient did not receive any further treatment. Distant-only failure was reported in 2 of 18 (11.1%) patients, and none of these patients received any further treatment. Both locoregional and distant failures occurred in 3 of 18 (16.7%) patients, of which 2 received chemotherapy and the remaining patient received salvaged surgery followed by chemotherapy. Six-month and 1-year LC were 80.5% and 67.1%, respectively (Fig. 1a). Six-month and 1-year DMFS were both 83.4% (Fig. 1b). Six-month and 1-year OS were 69.1% and 27%, respectively (Fig. 1c).

All but 2 patients completed PBT treatment as prescribed. One patient receiving concurrent chemotherapy and PBT reRT developed generalized weakness and stopped treatment at 37.78 Gy (RBE) in 23 fractions, and 2 months later the patient died because of esophageal hemorrhage. It was unclear if hemorrhage was related to PBT reRT or cancer progression. The second patient had symptomatic COVID-19 infection during treatment and stopped treatment at 25.2 Gy(RBE) in 14 fractions. The patient died 7 days later because of COVID-19 complications.

Grade 2 acute toxicities occurred in 94% of patients, with the most common being fatigue (n = 7), esophagitis (n = 4), dermatitis (n = 4), pain (n = 3), pain of the skin (n = 2), esophageal stenosis (n = 1), dysphagia (n = 1), dyspepsia (n = 1), constipation (n = 1), laryngitis (n = 1), pharyngitis (n = 1), cough (n = 1), nasal congestion (n = 1), and anorexia/weight loss (n = 1). Grade 3 acute toxicities occurred in 23% of patients, with the most common being esophagitis (n = 3), dysphagia (n = 1), dyspnea (n = 1), hoarseness (n = 1), and anorexia/weight loss (n = 1). No grade 4 acute events occurred. There was 1 acute grade 5 esophageal hemorrhage leading to death in the aforementioned patient who did not complete the entire PBT and concurrent carboplatin/paclitaxel treatment course as noted earlier. It is unclear whether the esophageal hemorrhage was related to treatment effect or due to tumor as no further information surrounding the death was available (Table 3). There were no grade ≥2 acute pericarditis or pneumonitis events.

Six patients either died or were lost to follow-up before 90 days post-PBT. Late toxicity was, therefore, assessed in the remaining 25 patients. Within this group, assessments were made for 13 patients at the 6-month and for 7 patients at the 12-month timepoint. Grade 2 late toxicities occurred in 24% of patients, including fatigue (n = 2),

Table 2 Treatment characteristics

Initial treatment	
Total dose − previous RT, median (range)	50.4 Gy (37.5-110.4*)
Concurrent chemotherapy	
Yes, n (%)	21/31 (67.7%)
No, n (%)	7/31 (22.6%)
Unknown, n (%)	3/31 (9.7%)
Type of concurrent systemic therapy	
Carboplatin + paclitaxel, n (%)	12/21 (57.1%)
5-FU or capecitabine, n (%)	2/21 (9.5%)
FOLFOX, n (%)	2/21 (9.5%)
5-FU + paclitaxel, n (%)	1/21 (4.8%)
5-FU + cisplatin, n (%)	1/21 (4.8%)
Cetuximab, n (%)	1/21 (4.8%)
Nivolumab, n (%)	1/21 (4.8%)
Unknown, n (%)	1/21 (4.8%)
Surgical resection of esophageal cancer	
Yes, n (%)	9 (29%)
No, n (%)	20 (64.5%)
Unknown, n (%)	2 (6.5%)
Timing of surgical resection	
Pre-RT, n (%)	2/9 (2.2%)
Post-RT, n (%)	7/9 (7.8%)
Recurrence treatment	
Time to recurrence from end of initial RT, median (range) months	11.4 (3.7-134.1)
Interval between initial RT and first reRT, median (range) months	17.4 (6.2-136.6)
Interval between last photon RT and PBT reRT, median (range) months	21.3 (6.2-136.6)
Site of recurrence	
Local	22 (71%)
Regional LNs	4 (12.9%)
Local + regional LNs	5 (16.1%)
ReRT modality†, n (%)	
Uniform scanning/passive scattering	19 (61.3%)
Pencil beam scanning	12 (38.7%)
ReRT dose, RBE, median (range)	48.6 Gy (25.2-72.1)
ReRT bid, n (%)	2 (6.5%)
Cumulative radiation dose, median (range)	99.9 Gy (79.1-182.5)
Concurrent chemotherapy, n (%)	
Yes	21 (67.7%)
No	10 (32.3%)
Concurrent systemic therapy agent(s)	
Carboplatin + paclitaxel	8/21 (38.1%)
5-FU or capecitabine	5/21 (23.8%)

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Table 2 (*Continued*)

Initial treatment	
Cisplatin and 5-FU or capecitabine	3/21 (14.3%)
Paclitaxel	2/21 (9.5%)
Cetuximab	1/21 (4.8%)
Docetaxel	1/21 (4.8%)
Pembrolizumab	1/21 (4.8%)

Abbreviations: 5-FU = 5-fluorouracil; bid = twice daily; FOLFOX = folinic acid, fluorouracil, and oxaliplatin; IMRT = intensity modulated RT; LN = lymph node; PBT = proton beam therapy; RBE = relative biologic effectiveness; reRT = reirradiation; RT = radiation therapy.
*Indicates instance in which 4 out of 31 patients received 1 additional course of reRT (2 total courses) before reRT with PBT for locoregional recurrent disease. Outlier represents cumulative dose of first 2 RT plans.
†One patient underwent photon RT (IMRT) for the first 4 fractions of his treatment and then he was switched to proton beam therapy using uniform scanning.

dysphagia (n = 1), pleural effusion (n = 1), and atrial fibrillation (n = 1). No grade ≥3 late toxicities were reported (Table 3).

Discussion

Currently, there are no standard treatment guidelines for locoregionally recurrent EC. Although outcomes of local therapies using salvage surgery or reRT with photons are similar, photon reRT can lead to serious complications, such as esophageal fistulas or perforation.[18] Furthermore, few patients are amenable to salvage surgery because of a history of prior surgery, the difficulty of operating in a previously irradiated field, or comorbidities. Thus, a considerable need remains for an improved local salvage therapy for recurrent EC. PBT is promising in the setting of reRT and has been used to treat head and neck cancers,[19-21] thoracic cancers,[22,23] breast cancers,[24,25] gynecologic cancers,[26] and gastrointestinal cancers.[27] The present study is one of few in the literature to report on outcomes in patients who received PBT reRT for locoregionally recurrent EC.

In our study, we found that re-RT PBT was overall well-tolerated. Although 23% of patients developed acute grade 3 toxicities and 1 patient developed acute grade 5 esophageal hemorrhage (the cause of which, treatment effect or tumor progression, was unclear), there were no late grade 3 or higher toxicities in our cohort. Our acute toxicity findings are comparable to the results of a prospective feasibility study of 14 patients with recurrent or de novo EC in a previously irradiated field treated with re-RT PBT.[16] In that study, Fernandes et al report nonhematologic acute grade 3 toxicities in 29% of patients and 1 acute grade 5 esophagopleural fistula, which was thought to be more likely secondary to tumor progression than RT. Additionally, a more recent retrospective study of 17 patients described a lower rate of acute grade 3 toxicity (12%) and no acute grade 4 or 5 toxicities.[17] This lower rate of acute toxicities may be because of the use of pencil beam scanning in the latter report versus passive scattering in the former report. However, in that latter study, DeCesaris et al did report higher rates of late toxicities similar to that in Fernandes et al, with 11.1% grade 3, 12.2% grade 4, and 6.6% grade 5 late toxicities. It is possible that the lower rate of late toxicities in our cohort could be attributed to a somewhat shorter median follow-up of 7.2 months (range, 0.9-64.7), compared with those in the Fernandes et al and DeCesaris et al studies of 10 months (range, 2-25) and 11.6 months (range, 2-36.6), respectively. Furthermore, most patients in these studies, including our own, received concurrent chemotherapy with PBT, which may have increased toxicity rates. The combination of these factors, including the use of heterogeneous systemic agents and the differences in the time intervals between the initial RT and re-RT with PBT, make it difficult to directly compare outcomes across these studies. Overall, however, the relatively low rates of acute and late toxicities in these studies highlight the benefits of using PBT in the setting of reRT for locoregionally recurrent or second primary EC compared with photons,[28] in which acute grade 5 toxicity rates have been reported to be as high as 30% despite the use of more modern techniques like IMRT.[9] PBT may be especially advantageous for EC given its central location and proximity to the heart and the lungs. Several studies on the use of PBT in the de novo EC setting reported proton therapy can achieve reduced rates of pulmonary toxicities, cardiac events, wound complications, and hospitalization duration,[29] improved survival,[30] and reduced total toxicity burden[31] relative to photon therapy, the latter of which was demonstrated in a recently reported randomized trial, the first proton versus photon randomized trial to support the use of proton over photon therapy.[32] These studies and those in the reRT setting for EC[15] demonstrate the toxicity reduction potential of proton therapy. In our study, for instance, only 1 case of pneumonitis (3.2%) was noted among patients who received PBT, compared with up to 12.8% rates of pneumonitis with conventional photon RT

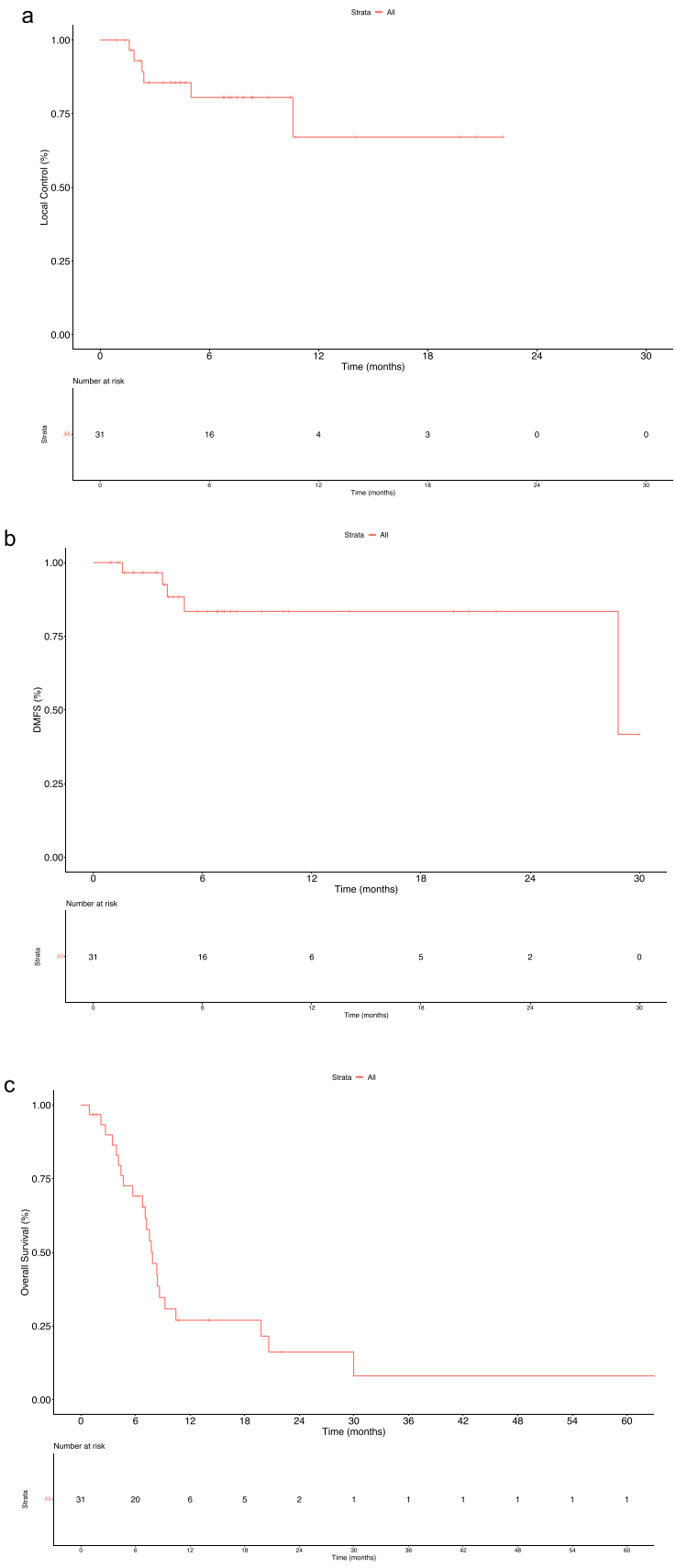

Figure 1 (a) Kaplan-Meier curve for local control (N = 31). (b) Kaplan-Meier curve for distant metastasis-free survival (N = 31). (c) Kaplan-Meier curve for overall survival (N = 31).

Table 3 Acute and late toxicity

Category	Toxicity	Total number of events	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Acute toxicity		130	93	29	7	0	1
Dermatologic		18	12	6	0	0	0
	Dermatitis	12	8	4	0	0	0
	Pain of skin	4	2	2	0	0	0
	Hand-foot syndrome	1	1	0	0	0	0
	Hyperpigmentation	1	1	0	0	0	0
Gastrointestinal		50	37	8	4	0	1
	Abdominal pain	1	1	0	0	0	0
	Constipation	5	4	1	0	0	0
	Diarrhea	3	3	0	0	0	0
	Dyspepsia	4	3	1	0	0	0
	Dysphagia	7	5	1	1	0	0
	Esophagitis	14	7	4	3	0	0
	Esophageal hemorrhage	1	0	0	0	0	1
	Esophageal stenosis	1	0	1	0	0	0
	Nausea/vomiting	12	12	0	0	0	0
	Oral pain	1	1	0	0	0	0
	Xerostomia	1	1	0	0	0	0
Nervous system		1	1	0	0	0	0
	Peripheral sensory neuropathy	1	1	0	0	0	0
Respiratory and thoracic		23	17	4	2	0	0
	Cough	8	6	1	1	0	0
	Dyspnea	6	5	0	1	0	0
	Hoarseness	2	2	0	0	0	0
	Laryngeal hemorrhage	1	1	0	0	0	0
	Laryngitis	1	0	1	0	0	0
	Nasal congestion	2	1	1	0	0	0
	Pharyngitis	1	0	1	0	0	0
	Pleuritic pain	1	1	0	0	0	0
	Pneumonitis	1	1	0	0	0	0
Systemic		38	26	11	1	0	0
	Anorexia/weight loss	15	13	1	1	0	0
	Fatigue	16	9	7	0	0	0
	Headache	1	1	0	0	0	0
	Pain	6	3	3	0	0	0
Late toxicity*	24	13	6	5	0	0	0
Cardiovascular		1	0	1	0	0	0
	Atrial fibrillation	1	0	1	0	0	0
Gastrointestinal		4	3	1	0	0	0
	Abdominal pain	1	1	0	0	0	0
	Diarrhea	2	2	0	0	0	0
	Dysphagia	1	0	1	0	0	0

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Table 3 (*Continued*)

Category	Toxicity	Total number of events	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Nervous system		2	0	0	0	0	0
	Peripheral sensory neuropathy	2	0	0	0	0	0
Respiratory		3	2	1	0	0	0
	Cough	1	1	0	0	0	0
	Pleural effusion	1	0	1	0	0	0
	Sore throat	1	1	0	0	0	0
Systemic		3	1	2	0	0	0
	Fatigue	3	1	2	0	0	0

*Twenty-five patients had follow-up data ≥90 days.

in the reRT setting.[10] Although PBT typically limits the dose to normal tissues more effectively compared with conformal photon-based therapies such as IMRT, in the setting of reRT, PBT still delivers a high cumulative dose to areas of overlap with the prior RT field. Both PBT and IMRT are advanced radiation techniques aimed at precisely targeting tumors while striving to minimize exposure to surrounding healthy tissues. However, despite these technological advances, some toxicities will be commonly observed using both modalities, including those affecting tissues within overlapping target volume that will receive comparable dose coverage and thus high cumulative doses with associated risks that are unavoidable regardless of the radiation modality used. Similar toxicities between PBT and IMRT may include skin reactions such as dermatitis and mucosal inflammation, particularly in areas like the esophagus that have previously received radiation.

Achieving locoregional control is crucial for patients with recurrent EC, as durable control can greatly enhance their quality of life, whereas achieving distant control can increase their overall survival rate. Nonetheless, to date, the outcomes for this group of patients continue to be extremely poor.[33] In our study, while effective LC and DMFS were achieved, the 1-year OS rate was only 27%. This low rate highlights the complex factors influencing patient outcomes. Our patient cohort is predominantly elderly, with a median age of 67 years (range, 53-87), and 71% being 65 years or older. This older age group inherently has a higher competing risk of death, which critically affects OS. Elderly patients often have multiple comorbidities, including pulmonary and cardiovascular disease, which are known to significantly affect survival. Research suggests that a large proportion of patients with EC may have undiagnosed or inadequately managed cardiovascular disease.[34] This issue is compounded by the increased risk of cardiotoxicity from oncologic treatments, particularly photon therapy.[35] Elderly patients with EC undergoing trimodality treatment are particularly susceptible to cardiotoxicity.[36] Furthermore, a comprehensive study from the Surveillance, Epidemiology, and End Results (SEER) database involving 5630 patients with EC revealed a higher risk of cardiac death in those receiving RT.[37] The advanced age of our patient population, along with the high competing risk of death and prevalent comorbidities, underlines the complexity of managing EC, especially in an elderly cohort. Although LC and DMFS are promising, the OS outcome is profoundly influenced by a combination of age, health status, and treatment effects, accentuating the challenges in treating EC in older patients.

Currently, there are limited data on the use of salvage treatments for recurrent or de novo EC. Only a handful of studies have investigated the effectiveness of PBT in this patient group. However, the reported disease control and survival outcomes vary among these studies. The difference in outcomes is likely due to a multitude of factors, such as initial staging, reRT dose, use of concurrent systemic therapy, and performance status at the time of reRT.[15-17] In addition, follow-up times were short in all of these studies (all under a median of 12 months), and thus caution should be taken when interpreting outcomes and toxicity results, especially late toxicities. Ultimately, the variability in patient characteristics and treatments in these studies prevents any meaningful comparison with our study.

Limitations of this study include its retrospective nature, limited follow-up duration, and heterogeneity of treatments at initial diagnosis and at recurrence, all of which limit its generalizability. Additionally, an important limitation to note is the absence of dosimetric data from the primary radiation course in our study. This restricts our ability to offer further details regarding the extent of overlap with prior RT fields or cumulative dose to organs at risk. Despite this limitation, our study is primarily focused on clinical outcomes, and we believe our findings still offer valuable insights within the clinical context. Future studies incorporating detailed dosimetric data will be beneficial to enhance the clinical applicability and broader understanding of clinical endpoints. Nonetheless,

one of the strengths of the study is that despite its retrospective nature, patient toxicities were monitored prospectively, which enhances the accuracy of the data compared with conventional retrospective studies. Furthermore, this report is the largest report to date and the first multi-institutional study to report clinical outcomes and toxicities in this patient population. As a result, our findings offer a greater degree of generalizability compared with previous reports from single institutions, providing a more precise reflection of real-world outcomes for patients undergoing reRT for recurrent EC using PBT.

Conclusion

This study suggests that PBT reRT for locoregionally recurrent esophageal/GEJ cancers is feasible, with encouraging rates of disease control and acceptable toxicity in the acute period. Although the rates of disease control appear promising, it is important to note that these findings are limited by a high competing risk of death because of poor prognosis of this patient population, and they are further constrained by challenges such as incomplete assessments and loss to follow-up. Future studies with larger sample sizes and longer follow-up, preferably in the setting of a prospective trial, are needed to understand further the long-term disease control and late toxicities associated with salvage PBT reRT in this patient population.

Disclosures

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References

1. Uhlenhopp DJ, Then EO, Sunkara T, Gaduputi V. Epidemiology of esophageal cancer: Update in global trends, etiology and risk factors. *Clin J Gastroenterol*. 2020;13:1010-1021.
2. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin*. 2023;73:17-48.
3. Eyck BM, van Lanschot JJB, Hulshof MCCM, et al. Ten-year outcome of neoadjuvant chemoradiotherapy plus surgery for esophageal cancer: The randomized controlled CROSS trial. *J Clin Oncol*. 2021;39:1995-2004.
4. Lee PC, Mirza FM, Port JL, et al. Predictors of recurrence and disease-free survival in patients with completely resected esophageal carcinoma. *J Thorac Cardiovasc Surg*. 2011;141:1196-1206.
5. Khan M, Urooj N, Syed AA, et al. Prognostic factors for recurrence in esophageal cancer patients treated with neoadjuvant therapy and surgery: A single-institution analysis. *Cureus*. 2020;12:e8108.
6. Gresham G, Hendifar AE, Spiegel B, et al. Wearable activity monitors to assess performance status and predict clinical outcomes in advanced cancer patients. *NPJ Digit Med*. 2018;1:27.
7. Oppedijk V, Van Der Gaast A, Van Lanschot JJB, et al. Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials. *J Clin Oncol*. 2014;32:385-391.
8. Robb WB, Messager M, Dahan L, et al. Patterns of recurrence in early-stage oesophageal cancer after chemoradiotherapy and surgery compared with surgery alone. *Br J Surg*. 2016;103:117-125.
9. Kim YS, Lee CG, Kim KH, et al. Re-irradiation of recurrent esophageal cancer after primary definitive radiotherapy. *Radiat Oncol J*. 2012;30:182-188.
10. Zhao K, Si Y, Sun L, Meng X, Yu J. Efficacy and toxicity of re-irradiation for esophageal cancer patients with locoregional recurrence: A retrospective analysis. *Radiat Oncol*. 2020;15:243.
11. Suit H, Goldberg S, Niemierko A, et al. Proton beams to replace photon beams in radical dose treatments. *Acta Oncol*. 2003;42:800-808.
12. Simone CB, Kramer K, O'Meara WP, et al. Predicted rates of secondary malignancies from proton versus photon radiation therapy for stage I seminoma. *Int J Radiat Oncol Biol Phys*. 2012;82:242-249.
13. Verma V, Rwigema J-CM, Malyapa RS, Regine WF, Simone 2nd CB. Systematic assessment of clinical outcomes and toxicities of proton radiotherapy for reirradiation. *Radiother Oncol*. 2017;125:21-30.
14. Simone CB, Plastaras JP, Jabbour SK, et al. Proton reirradiation: Expert recommendations for reducing toxicities and offering new chances of cure in patients with challenging recurrence malignancies. *Semin Radiat Oncol*. 2020;30:253-261.
15. Patel SA, Edgington SK, Adams J, Morse C, Ryan DP, Hong TS. Novel use of proton beam therapy for neoadjuvant treatment of radiation-associated squamous cell carcinoma of the esophagus. *J Gastrointest Oncol*. 2019;10:155-160.
16. Fernandes A, Berman AT, Mick R, et al. A prospective study of proton beam reirradiation for esophageal cancer. *Int J Radiat Oncol Biol Phys*. 2016;95:483-487.
17. DeCesaris CM, McCarroll R, Mishra MV, et al. Assessing outcomes of patients treated with re-irradiation utilizing proton pencil-beam scanning for primary or recurrent malignancies of the esophagus and gastroesophageal junction. *J Thorac Oncol*. 2020;15:1054-1064.
18. Chen Y, Lu Y, Wang Y, et al. Comparison of salvage chemoradiation versus salvage surgery for recurrent esophageal squamous cell carcinoma after definitive radiochemotherapy or radiotherapy alone. *Dis Esophagus*. 2014;27:134-140.
19. Romesser PB, Cahlon O, Scher ED, et al. Proton beam reirradiation for recurrent head and neck cancer: Multi-institutional report on feasibility and early outcomes. *Int J Radiat Oncol Biol Phys*. 2016;95:386-395.
20. McDonald MW, Zolali-Meybodi O, Lehnert SJ, et al. Reirradiation of recurrent and second primary head and neck cancer with proton therapy. *Int J Radiat Oncol Biol Phys*. 2016;96:808-819.
21. Lee A, Woods R, Mahfouz A, et al. Evaluation of proton therapy reirradiation for patients with recurrent head and neck squamous cell carcinoma. *JAMA Netw Open*. 2023;6. e2250607-e2250607.
22. Chao HH, Berman AT, Simone CB, et al. Multi-institutional prospective study of reirradiation with proton beam radiotherapy for locoregionally recurrent non−small cell lung cancer. *J Thorac Oncol*. 2017;12:281-292.
23. Badiyan SN, Rutenberg MS, Hoppe BS, et al. Clinical outcomes of patients with recurrent lung cancer reirradiated with proton therapy on the proton collaborative group and University of Florida Proton Therapy Institute prospective registry studies. *Pract Radiat Oncol*. 2019;9:280-288.

24. Thorpe CS, Niska JR, Girardo ME, et al. Proton beam therapy reirradiation for breast cancer: Multi-institutional prospective PCG registry analysis. *Breast J*. 2019;25:1160-1170.
25. Choi JI, Khan AJ, Powell SN, et al. Proton reirradiation for recurrent or new primary breast cancer in the setting of prior breast irradiation. *Radiother Oncol*. 2021;165:142-151.
26. Li YR, Kirk M, Lin L. Proton therapy for vaginal reirradiation. *Int J Part Ther*. 2016;3:320-326.
27. Berman AT, Both S, Sharkoski T, et al. Proton reirradiation of recurrent rectal cancer: Dosimetric comparison, toxicities, and preliminary outcomes. *Int J Part Ther*. 2014;1.
28. Xu X, Wang Z, Jiang S, Shang Y, Wu Y. Evaluating the optimal re-irradiation dose for locally recurrent esophageal squamous cell carcinoma after definitive radiotherapy. *Radiat Oncol*. 2019;14:191.
29. Lin SH, Merrell KW, Shen J, et al. Multi-institutional analysis of radiation modality use and postoperative outcomes of neoadjuvant chemoradiation for esophageal cancer. *Radiother Oncol*. 2017;123: 376-381.
30. Xi M, Xu C, Liao Z, et al. Comparative outcomes after definitive chemoradiotherapy using proton beam therapy versus intensity modulated radiation therapy for esophageal cancer: A retrospective, single-institutional analysis. *Int J Radiat Oncol Biol Phys*. 2017;99: 667-676.
31. Lin SH, Hobbs BP, Verma V, et al. Randomized phase IIB trial of proton beam therapy versus intensity-modulated radiation therapy for locally advanced esophageal cancer. *J Clin Oncol*. 2020;38:1569-1579.
32. Simone 2nd CB. First randomized trial supporting the use of proton over photon chemoradiotherapy in esophageal cancer. *J Clin Oncol*. 2020;38:2952-2955.
33. Butter R, Lagarde SM, van Oijen MGH, et al. Treatment strategies in recurrent esophageal or junctional cancer. *Dis Esophagus*. 2017;30:1-9.
34. Søndergaard MMA, Nordsmark M, Nielsen KM, Poulsen SH. Cardiovascular burden and adverse events in patients with esophageal cancer treated with chemoradiation for curative intent. *JACC CardioOncol*. 2021;3:711-721.
35. Beukema JC, van Luijk P, Widder J, Langendijk JA, Muijs CT. Is cardiac toxicity a relevant issue in the radiation treatment of esophageal cancer? *Radiother Oncol*. 2015;114:85-90.
36. Lester SC, Lin SH, Chuong M, et al. A multi-institutional analysis of trimodality therapy for esophageal cancer in elderly patients. *Int J Radiat Oncol Biol Phys*. 2017;98:820-828.
37. Gharzai L, Verma V, Denniston KA, Bhirud AR, Bennion NR, Lin C. Radiation therapy and cardiac death in long-term survivors of esophageal cancer: An analysis of the surveillance, epidemiology, and end result database. *PLoS One*. 2016;11: e0158916.