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Review Article

Current status and application of proton therapy for esophageal cancer

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ABSTRACT

Esophageal cancer remains one of the leading causes of death from cancer across the world despite advances in multimodality therapy. Although early-stage disease can often be treated surgically, the current state of the art for locally advanced disease is concurrent chemoradiation, followed by surgery whenever possible. The uniform midline tumor location puts a strong importance on the need for precise delivery of radiation that would minimize dose to the heart and lungs, and the biophysical properties of proton beam makes this modality potential ideal for esophageal cancer treatment. This review covers the current state of knowledge of proton therapy for esophageal cancer, focusing on published retrospective single- and multi-institutional clinical studies, and emerging data from prospective clinical trials, that support the benefit of protons vs photon-based radiation in reducing postoperative complications, cardiac toxicity, and severe radiation induced immune suppression, which may improve survival outcomes for patients. In addition, we discuss the incorporation of immunotherapy to the curative management of esophageal cancers in the not-too-distant future. However, there is still a lack of high-level evidence to support proton therapy in the treatment of esophageal cancer, and proton therapy has its limitations in clinical application. It is expected to see the results of future large-scale randomized clinical trials and the continuous improvement of proton radiotherapy technology.

Esophageal cancer remains one of the leading causes of death from cancer in the world despite recent advances in multimodality therapy [1]. Because both effective screening strategies and symptoms are lacking in early-stage esophageal cancer, disease is often diagnosed at advanced stages, with 5-year overall survival (OS) rates of only about 15%–20% [2]. The histologic subtype of esophageal cancer varies considerably with geographic location, with squamous cell carcinoma being the most common in East Asia and in South and East Africa and adenocarcinomas being the most common in Western countries [3–5].

For early-stage disease (pTis, pT1a, selected superficial pT1b without LVI), endoscopic resection can prolong clinical outcomes without the need for extensive esophageal resectionc [6]. For cases that are not suitable for endoscopic treatment, esophagectomy would be recommended. Esophagectomy alone is inadequate, however, for patients presenting with higher risk of lymph node metastases, such as lymphovascular stromal invasion. For high-risk patients with early stage disease, and locally advanced tumors, neoadjuvant chemoradiation therapy followed by surgical resection is the most commonly recommended therapy, although preoperative chemotherapy can also be used for adenocarcinomas. Definitive chemoradiation without surgery is curative in about a quarter of inoperable patients [7].

Owing to the location of esophageal tumors in the midline and central mediastinal, curative radiotherapy delivers substantial dose to the heart and lungs, either pre-operatively or definitively. Advances in photon (X-ray) radiation such as intensity modulated radiation therapy (IMRT) can reduce the dose intensity to the cardiopulmonary critical organs but still imposes low to intermediate dose exposure throughout the mediastinal and intrathoracic structures. Charged particles like protons deposit dose over a characteristic depth-dose curve, with the highest dose at the Bragg peak with rapid dose fall off beyond that point [8]. This dose characteristic gives proton beam therapy (PBT) a critical advantage over photon radiotherapy to substantially reduce low dose scatter to adjacent normal organs at risk which presumably should also reduce normal organ toxicity and improve patient outcomes. While PBT dosimetric advantage is seen in nearly all sites in the

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body, esophageal cancer is one of the few malignancies, such as pediatric cancer [9,10], chondrosarcoma and chordoma [11], ocular melanomas [12,13], brain tumors [14,15], head and neck cancer [16] and lung cancer [17], where clinical benefit is becoming more apparent with the use of PBT. We will survey the reported experiences on the use of PBT for esophageal cancer, review results from clinical trials, discuss patient selection and challenges, and explore some future directions.

Search strategy

In the process of writing this review, the following keywords: "proton therapy" OR "proton beam therapy" AND "esophageal cancer" were used to search in National Center for Biotechnology Information (PubMed). Relevant articles written in English from Jan 1999 to Oct 2020 were evaluated. Articles were included if they were about esophageal irradiation and protons. Data presented in abstract form were included if they added valuable information. Reviews, fundamental research or series with less than 10 patients were excluded. The literature search flow diagram is shown in the Supplement Figure. Additionally, bibliographic references and citations of the included studies were evaluated for additional eligible studies in order to avoid omission of relevant studies and reduce the chance of publication bias. Clinicaltrials.gov was used to identify the ongoing trials, using "esophageal cancer" as the disease specific term and "proton" for the other terms.

Dosimetric evaluations of proton therapy for esophageal cancer

Small planning studies of the last decade have demonstrated that for the most part, proton plan comparisons to photon-based plans for a given patient show substantial reduction in heart and lung doses with PBT without compromising tumor coverage [18–24]. In one dosimetric study of 21 patients with esophageal cancer [25], the use of single-field optimization spot scanning proton therapy was found to reduce the mean lung dose by 51.4% (range 35.1%–76.1%) and the mean heart dose by 40.9% (range 15.0%–57.4%) relative to photon-based volumetric modulated arc therapy. Since previous researches have shown that some dosimetric indicators of thoracic bone such as mean vertebral dose (MVD), thoracic vertebrae V5-30, mean rib dose and rib V5-20 were significantly associated with hematologic toxicity [26,27]. Another study by the same group involved patients with mid-esophagus cancer who had undergone 3-dimensional conformal (photon) radiation therapy (3DCRT) [28] investigating the possibility of reducing the bone dose in order to reduce hematological toxicity; three different kinds of volumetric modulated arc therapy plans and a proton therapy plan were created for each patient. Dosimetric comparisons of these plans revealed that only the proton plan showed significantly less exposure of bone, with smaller bone V10 and lower mean dose to the bone, especially for patients with large planning target volumes.

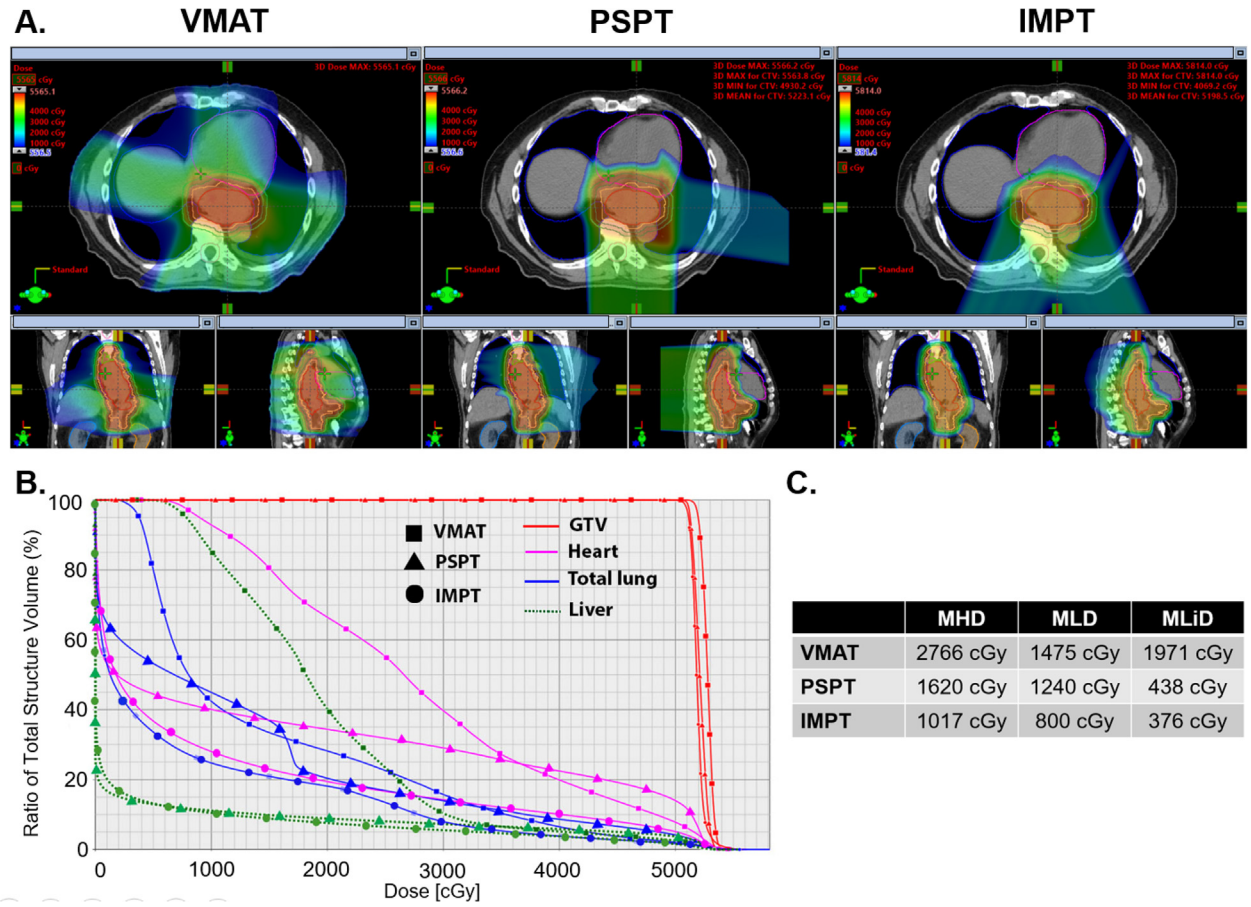
Despite heterogeneity between patients, the uniform midline positions of esophageal tumors relative to cardiopulmonary structures allow for appropriate dosimetric comparison between patients with tumors in similar locations. A large retrospective analysis of 477 esophageal cancer patients who had received IMRT and 250 who had received PBT, demonstrated that PBT significantly reduced the mean heart dose and heart V5-40 as well as the radiation exposure of all four heart chambers and four coronary arteries [29]. In the phase 2 randomized trial comparing PBT to IMRT, PBT had significantly lower doses to the lung, heart, and liver in all dosimetric parameters [30]. Fig. 1 illustrates an example in one patient the dosimetric comparison of pencil beam scanning proton therapy (which will be called heretofore intensity modulated proton therapy, or IMPT) compared with IMRT for treatment of distal esophageal cancer.

Intensity modulated proton therapy (IMPT), also known as "pencil beam proton therapy," is a recent technologic advance in PBT delivery. IMPT relies on electromagnetic control of the pencil beam to achieve comparable target coverage, which is superior to conventional passive-scattered proton therapy (PSPT) as it eliminates the need for compensators. And IMPT plans can further improve dose distributions over PSPT. In one analysis of 250 patients treated with protons, IMPT plans (N = 13) significantly reduced heart volume receiving doses in the range of 20–40 Gy as well as the radiation dose to the left atrium, right atrium, left main coronary artery, and left circumflex artery [29]. Nevertheless, it must be noted that due to the dosimetric distribution characteristics of PBT, the plan robustness of it becomes particularly critical when compared with IMRT, otherwise there will be a significant adverse impact on its ability for organ at risk (OAR) sparing and dose coverage of the target volume.

Clinical outcomes of proton therapy for esophageal cancer

Proton therapy without concurrent chemotherapy

Most studies of PBT given without concurrent chemotherapy for esophageal cancer were restricted to retrospective institutional analyses from Japan [31–35]. In one such study, Mizumoto et al. [33] reported 51 cases of esophageal squamous cell carcinomas treated with PBT with or without photons (X-rays). Of the 51 patients, 33 received combinations of photon therapy (median 46 Gy) and proton therapy (median 36 GyE) as a boost. And the other 18 patients received proton therapy alone (median 79 GyE, range 62–98 GyE). Treatment was well tolerated, and no patient required treatment interruptions from radiation-induced esophagitis or hematologic toxicity, only 6 cases developed grade 3 esophagitis. Postirradiation esophageal ulcers occurred in 9 of 27 patients (33%) who received <80 GyE and in 16 of 24 patients (67%) who received ≥80 GyE. Among those 51 patients, 40 (78%) had a complete response within 4 months after treatment and 7 (14%) had a partial response, for an overall response rate of 92%. The 5-year local control rate was 38.0% with the median local recurrence free survival of 25.5 months; the overall 5-year actuarial survival rate was 21.1% and the median survival time was 20.5 months. Another study evaluated the safety and efficacy of hyperfractionated photon therapy with a concomitant PBT boost dose for 19 patients with esophageal squamous cell cancer [34]. The median total dose in that study was 78 Gray-equivalents (GyE) (range 70–83 GyE), given over a median of 48 days (range 38–53 days). Of those 19 patients, 10 had clinical stage T3 or T4 disease. At 4 months after completion of treatment, 17 patients (89%) had a complete response and 2 (11%) had a partial response, for an overall response rate of 100%. Rates of local control were 93.8% at 1 year and 84.4% at 5 years, and the corresponding actuarial OS rates were 79.0% and 42.8%. In addition, only 1 patient developed late grade 3 esophageal toxicity at 6 months after therapy; no other severe (grade ≥3) non-hematologic toxicity (e.g., radiation pneumonia or heart failure) was observed thereafter. Another study from Japan confirmed the safety and effectiveness of high-dose (66–75.6 GyE) PBT without chemotherapy for 20 patients with esophageal cancer aged ≥65 [35]. The median patient age in that study was 78 years (range 65–89 years), and all patients were able to complete treatment. Episodes of grade 2–3 toxicity included esophageal ulcers (35%), pneumonitis (15%), esophageal stenosis (10%), and pleural effusion (10%); no grade 4–5 toxicity was observed. The local control and OS rates at 2 years were 89.4% and 81.8%, respectively.



	MHD	MLD	MLiD
VMAT	2766 cGy	1475 cGy	1971 cGy
PSPT	1620 cGy	1240 cGy	438 cGy
IMPT	1017 cGy	800 cGy	376 cGy

Fig. 1. Significant normal tissue sparing is achieved with Proton Beam Therapy (PBT, squares), which in this case is done with Intensity Modulated Proton Therapy, compared with intensity modulated radiation therapy (IMRT, triangles) for distal esophageal cancer. The PBT plan has a significantly lower mean heart (purple, 8.1 vs. 21.0 Gy) and lung (blue, 2.3 vs. 6.3 Gy) dose compared to IMRT.

Proton therapy with concurrent chemotherapy

The most commonly used curative management of esophageal cancer is concurrent chemoradiation, given as either neoadjuvant therapy (followed by surgery) or definitive therapy. As the use of proton therapy has increased over the past decade, several studies on the use of proton therapy for esophageal cancer with concurrent chemotherapy have been reported. One of the first series of 62 patients was reported from MD Anderson, consisting of 76% adenocarcinomas mostly located in the distal esophagus/gastroesophageal junction (78%). All were treated with PSPT to a median dose of 50.4 GyE [36]. Just under half (46.8%) of the patients were treated with preoperative chemoradiation, with (42%) or without (58%) induction chemotherapy before chemoradiation. The overall pathologic complete response (pCR) rate safter surgery was 28%, and near complete response (0–1% viable disease) was 50%. Grade 3 toxicities were <10%, with esophagitis, nausea, and fatigue being the most common, and one grade 2 and one grade 3 pneumonitis. There was one postoperative death and one patient who died from ventricular arrythmias. For IMPT with chemotherapy, a series of 19 patients treated at MD Anderson was reported (12 adenocarcinomas and 7 squamous cell carcinomas) [37]. Patients were treated to a median dose of 50.4 GyE in 28 fractions concurrently with chemotherapy, and 16 (84%) achieved clinical complete response of primary disease. Of the 4 patients who underwent esophagectomy, 2 achieved pathologic complete response of primary disease. The most common forms of acute grade 3 toxicity were esophagitis and fatigue (N = 3 (16%)). As for late toxicity, one patient experienced grade 3 esophageal stricture and one had grade 3 pleural effusion. At a median follow-up time of 17 months, the median OS time was 39.2 months, and at 2 years, the estimated OS, progression-free survival (PFS), local–regional recurrence–free survival (LRFS), and distant metastasis–free survival (DMFS) rates were 87.5%, 50.6%, 74%, and 72.9%.

While the aforementioned series were mostly done in esophageal adenocarcinomas, treatment outcomes after PBT with concurrent chemotherapy for mostly esophageal squamous cell carcinomas have been reported from Japan. In an earlier report, 40 patients were treated with definitive PBT and concurrent fluorouracil and nadaplatin at Tsukuba University, for a total dose of 60 GyE given in 30 fractions, with an additional boost of 4–10 GyE given when residual tumors were suspected [38]. At a median follow-up time of 24 months, no grade ≥3 cardiopulmonary toxic effects had been observed. Acute treatment-related hematologic toxicity was grade 3 in eight patients (20%) and grade 4 in two patients (5%). Grade 3 esophagitis was noted in nine patients (22%). At 2 years, the local control rate was 66.4% and the OS rate was 75.1%. Subsequent studies from Japan reported similar findings, confirming the feasibility and excellent outcomes of PBT for esophageal cancer [39–41]. One was in patients with early stage T1 esophageal squamous cell carcinoma treated at the National Cancer Center Hospital East, 44 of which received definitive concurrent chemotherapy and PBT to 60 GyE [41]. Only 5 patients developed local recurrence without nodal spread and were all salvaged with endoscopic resection or photodynamic therapy. The 3-year overall survival was 95%. Regarding adverse events, only grade 3 esophagitis (n = 1) was experienced, as for late toxicity, grade 3 or higher

cardio-pulmonary morbidities were not observed during the follow-up period. The second study was a retrospective combined analysis in 202 patients from four proton centers in Japan [40]. One-hundred twelve patients were treated with preoperative chemotherapy and PBT (97% squamous cell carcinoma). The 3-year and 5-year overall survival was 66.7% and 56.3%, respectively, and 5-year local control was 64.4%. The treatment was very well tolerated; only 3 patients developed grade 3 toxicity of pericardial effusion (N = 2) and pneumonia (N = 1).

Comparative outcomes of proton therapy versus photon therapy with concurrent chemotherapy

Retrospective single or multi-institutional studies

Cumulative reports have been done to compare clinical outcomes after chemoradiation with PBT versus photon therapy for patients with esophageal cancer (Table 1). In a recent series of 64 patients treated with IMPT (N = 32) or IMRT (N = 32) at the Mayo Clinic, radiation was given at a median dose of 45 GyE in 25 fractions with simultaneous integrated boot to 50 GyE [42]. There was some imbalances in histology, with two-thirds being adenocarcinomas in the IMPT group, and over 90% in the IMRT. Majority (72% IMPT vs 81% IMRT) of cases were treated with neoadjuvant therapy, with a pathologic complete response of 33% for IMPT and 39% for IMRT. There were no differences in acute treatment related toxicities between the two modalities, and postoperative complications were also similar, except for being numerically higher in IMRT for some complications (pneumonia and acute respiratory distress syndrome) but less so for others (tracheoesophageal fistula, cardiac arrhythmias). A combined analysis of multi-institutional data investigated how radiation modality influenced acute chemoradiation toxicities and postoperative outcomes after neoadjuvant chemoradiation in a series of 582 patients with esophageal cancer treated with 3DCRT (37%), IMRT (44%), or PBT (19%, all PSPT) [43]. No significant differences in baseline characteristics were found between the group of PBT and photon therapy, except for a higher incidence of hypertension (P = 0.025) and smoking pack-years (P = 0.041) in the PBT cohort. On multivariate analysis, PBT was found to significantly lower rates of acute grade $\geq$2 nausea (odds ratio [OR] = 0.41, P < 0.001) and hematologic toxicity (OR = 0.07, P < 0.001) when compared with photon therapy. Further study on the same group of patients confirmed the advantage of PBT in terms of three categories of postoperative complications plus length of (inpatient) stay (LOS) [44]. Significant differences were found in rates of pulmonary complications (16.2% PBT vs 24.2% IMRT vs 39.5% 3DCRT, P = 0.001), cardiac complications (11.7% PBT vs 11.7% IMRT vs 27.4% 3DCRT, P < 0.001) and wound complications (4.5% PBT vs 14.1% IMRT vs 15.3% 3DCRT, P = 0.014). Mean LOS was also associated with treatment modality (9.3 days PBT vs 11.6 days IMRT vs 13.2 days 3DCRT, P < 0.0001).

For patients who underwent definitive chemoradiation, a report from MD Anderson Cancer Center retrospectively analyzed 343 patients with esophageal cancer who had received either PBT (n = 132) or IMRT (n = 211) [45]. Most baseline and treatment variables were balanced between the two treatment groups, except for the elderly Caucasian patients were more likely to receive PBT. Compared with the IMRT group, patients given PBT had significantly better 5-year rates of OS (41.6% vs 31.6%, P = 0.011), PFS (34.9% vs 20.4%, P = 0.001), and DMFS (64.9% vs 49.6%, P = 0.031). A slight (although non-significant) difference in favor of PBT was also noted in 5-year LRFS rates (59.9% vs 49.9%, P = 0.075). Subgroup analysis according to clinical disease stage indicated improved 5-year rates of OS (34.6% vs 25.0%, P = 0.038) and PFS (33.5% vs 13.2%, P = 0.005) for patients with stage III disease receiving PBT when compared to IMRT patients. These authors concluded that PBT could lead to better OS, PFS, and LRFS than IMRT, especially for patients with locally advanced esophageal cancer. According to the authors, better dose distribution, lower cardiopulmonary toxicity, plausible greater biological efficacy, lymphocyte sparing and the effect of increasing sensitivity of tumor cells to cytotoxic T-lymphocyte killing are the possible reasons for better prognosis of the PBT group. A study in 44 patients focused on late cardiopulmonary toxicity after definitive concurrent chemoradiation with either 3DCRT (n = 19) or PBT (n = 25) for esophageal cancer confirmed that the rates of grade $\geq$2 pulmonary and cardiac toxic events were lower in the PBT group (0% vs 18.2% for pulmonary and 4.0% vs 52.6% for cardiac) [46]. Also, the two incidents of grade 5 toxicity (1 pharmacologic pneumonia and 1 pulmonary infection) were both in the 3DCRT group.

Lymphocytes are highly sensitive to ionizing radiation, and grade 4 lymphopenia nadir during radiation therapy for esophageal cancer is common and linked with poor outcomes [47]. It was found that the incidence of grade 4 lymphopenia is significantly reduced in patients treated with PBT (mostly PSPT) when compared to IMRT (15.5% vs 33.1%, P < 0.001) [47]. In a separate analysis in patients who received definitive CRT, patients treated with PBT were matched by propensity score with those treated with IMRT based on patient and disease characteristics. IMRT patients were at higher risk of grade 4 lymphopenia than those who received PBT for tumors in the lower esophagus (P = 0.005) but not necessarily for those with tumors in the upper or middle esophagus (P = 0.32), presumably due to the proximity to the heart and areas of greatest blood flow that could be better spared with PBT [48]. This is similarly seen in patients treated with neoadjuvant CRT in a study of 480 patients, with propensity-score-matching 136 patients given IMRT with 136 patients given PBT [49]. The incidence of grade 4 lymphopenia was 40% for IMRT and 18% for PBT (P = 0.0001), with the use of PBT associated with a lower risk of grade 4 lymphopenia (OR = 0.29, P < 0.0001) on multivariable analysis. These findings corroborate with findings from the Mayo Clinic, reporting the incidence of grade 4 lymphopenia nadir of 55.7% with IMRT and 21.5% with IMPT (OR = 0.19, P < 0.001) [50].

Cardiotoxicity has long been regarded as a late side effect of thoracic radiation. Recent studies have shown that severe cardiac events were relatively common with early onset in lung cancer patients after chemoradiation therapy, with the radiation dose to the left anterior descending coronary artery being a strong predictor of severe cardiac events [51–53]. One would presume that cardiac events should be reduced in esophageal cancer patients treated with PBT. In a 59 patient esophageal cancer study with only 16 PBT cases showed that the cardiac dosimetric advantage of PBT over IMRT or 3D-photon radiation did not reveal a significant advantage in survival outcomes [54]. However, Wang et al. [55] conducted a larger retrospective analysis in 479 patients with biopsy-confirmed esophageal cancer, treated with IMRT (N = 320) or PBT (N = 159). Grade 3 or higher (G3+) cardiac events occurred in 18% of patients at a median of 7 months. Cardiac dose parameters were much lower in patients treated with PBT in heart $V5_{Gy}$ (P < 0.001), $V30_{Gy}$ (P < 0.001) and mean heart dose (MHD) (Gy) (P < 0.001). A significantly higher cumulative time-to-G3+ cardiac events was found in patients who received IMRT compared to patients who received PBT (IMRT vs. PBT, HR = 1.746; 95%CI, 1.065–2.862, P = 0.027). Moreover, in subgroup analysis of patients with pre-existing heart disease, PBT showed a greater advantage in reducing high-grade cardiac events (2-y rates 30% vs. 11%; 5-y rates 32% vs. 14%; P = 0.018) compared with the group of patients without pre-existing heart disease (2-y rates 14% vs. 11%; 5-y rates 18% vs. 13%; P = 0.345). Furthermore, G3+ cardiac events were associated with worse overall survival (P = 0.041).

Table 1
Selected studies of clinical outcomes after different radiotherapy modalities for esophageal cancer.

Study and reference	No. of patients	Chemotherapy	Follow-up time	Survival	Lung toxicity	Heart Toxicity	Other toxicities
Bhangoo et al. (2020) [42]	64 (32 IMRT, 32 IMPT)	Carboplatin and paclitaxel (91%)	10 months (IMPT), 14 months IMRT	1-y OS: 71% IMRT, 74% IMPT (P = 0.62); PFS: IMRT 45%, IMPT 71% (P = 0.15); LRC: IMRT 80%, IMPT 92% (P = 0.76); DMFS: 65% IMRT, 87% IMPT (P = 0.08)	Pneumonia: 28% IMRT, 13% IMPT; ARDS: 17% IMRT, 0% IMPT	Cardiac arrhythmia: 17% IMRT, 53% IMPT	Esophageal stricture: 11% IMRT, 7% IMPT; Anastomotic leak: 22% IMRT, 20% IMPT; Anastomotic stricture: 39% IMRT, 27% IMPT; TEF: 0% IMRT, 13% IMPT
Chuong et al. (2015) [43]	582 (37% 3DCRT, 44% IMRT, 19% PBT)	Various	NR	N/A			Grade $\geq$2 acute nausea: PBT vs. RT, OR = 0.41, (P < 0.001); Grade $\geq$2 hematologic: PBT vs. RT, OR = 0.07, (P < 0.001)
Makishima et al. (2015) [46]	44 (19 XRT, 25 PBT)	Fluorouracil and cisplatin	NR	N/A	Grade $\geq$2 pulmonary toxicity: XRT 18.2%, PBT 0%	Grade $\geq$2 cardiac toxicity: XRT 52.6%, PBT 4.0%	
Xi et al. (2017) [45]	343 (211 IMRT, 132 PBT)	Platinum or taxane with fluorouracil	65.1 months	5-y OS: IMRT 31.6% vs. PBT 41.4% (P = 0.011); 5-y PFS: IMRT 20.4% vs. PBT 34.9% (P = 0.001);5-y DMFS: IMRT 48.6% vs. PBT 64.9% (P = 0.031)	Grade $\geq$3: Pneumonitis 2.9% IMRT, 1.6% PBT; Pleural effusion 1.9% IMRT, 0.8% PBT	Grade $\geq$3: Pericardial effusion 2.4% IMRT, 0.8% PBT	Grade $\geq$3: Fatigue 4.3% IMRT, 3.8% PBT; Weight loss 1.4% IMRT, 0.8% PBT; Nausea 7.1% IMRT, 6.8% PBT; Anorexia 1.9% IMRT, 1.5% PBT; Esophagitis 14.7% IMRT, 11.4% PBT; Skin reaction 0.9% IMRT, 1.5% PBT; Esophageal fistula 1.4% IMRT, 0.0% PBT; Esophageal stricture 8.1% IMRT, 9.8% PBT
Lin et al. (2017) [44]	580 (214 3DCRT, 255 IMRT, 111 PBT)	Various	NR	N/A	Pulmonary complications: 3DCRT 39.5% vs. IMRT 24.3% vs. PBT 16.2% (P < 0.001)	Cardiac complications: 3DCRT 27.4% vs. IMRT 11.7% vs. PBT 11.7% (P < 0.001)	Wound complications: 3DCRT 15.3% vs. IMRT 14.1% vs. PBT 4.5% (P = 0.014); Mean LOS: 3DCRT 13.2d vs. IMRT 11.6d vs. PBT 9.3d (P < 0.0001)
Routman et al. (2019) [50]	144 (65 RT, 79 PBT)	Carboplatin and paclitaxel	NR	N/A			G4L: RT 56% vs. PBT 22% (P < 0.01)
Fang et al. (2018) [48]	448 (283 IMRT, 165 PBT)	NR	55 months	N/A			G4L: IMRT vs. PBT OD = 2.13 (P = 0.01)
Shiraishi et al. (2018) [49]	480 (344 IMRT, 146 PBT)	Various	NR	N/A			G4L: IMRT 40.4% vs. PBT 17.6% (P < 0.0001)
Lin et al. (2019) [30]	107 (61 IMRT, 46 PBT)	Various	44.1 months	3-y OS: IMRT 50.8% vs. PBT 51.2% (P = 0.60); 5-y PFS: IMRT 44.5% vs. PBT 44.5% (P = 0.70)			Mean TTB: IMRT (39.9; 95% highest posterior density interval, 26.2–54.9) vs. PBT (17.4; 10.5–25.0); Mean POC score: IMRT (19.1; 7.3–32.3) vs. PBT (2.5; 0.3–5.2)

Abbreviations: 3DCRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; PBT, proton beam therapy; NR, not reported; OR, odds ratio; XRT, X-ray (photon) radiation therapy; LOS, length of [inpatient] stay; OS, overall survival; PFS, progression-free survival; DMFS, distant metastatic-free survival; G4L, grade 4 lymphopenia; TTB, total toxicity burden; POC, postoperative complication; TEF, tracheoesophageal fistula; ARDS, Acute Respiratory Distress Syndrome.

Table 2
Clinical trials of proton therapy for esophageal cancer.

NCT ID	Title	Phase	No. of Patients	Status	Primary Objective(s)	Institution
02213497	Dose Escalation of Neoadjuvant Proton Beam Radiotherapy With Concurrent Chemotherapy in Locally Advanced Esophageal Cancer	I	30	Recruiting	Adverse events	University of Pennsylvania, Abramson Cancer Center
02452021	Pencil Beam Scanning Proton Radiotherapy for Esophageal Cancer	Obs	30	Active, not recruiting	Rate of CTCAE acute grade 3 or higher adverse effects	Mayo Clinic
03482791	Proton Beam Therapy in the Treatment of Esophageal Cancer	II	40	Recruiting	Patient-reported outcomes	Washington University School of Medicine
01512589	Proton Beam Therapy Vs Intensity-Modulated Radiation Therapy	II	180	Active, not recruiting	PFS, TTB	The University of Texas MD Anderson Cancer Center
01684904	Proton Therapy for Esophageal Cancer	II	38	Recruiting	OS, adverse events	Loma Linda University Medical Center
03801876	Comparing Proton Therapy to Photon Radiation Therapy for Esophageal Cancer	III	300	Recruiting	OS, Incidence of grade 3+ cardiopulmonary adverse events	NRG Oncology Multicenter

Abbreviations: NCT, National Clinical Trials; Obs, Observational study; CTCAE, Common Terminology Criteria of Adverse Events; OS, overall survival; TTB, total toxicity burden.

Prospective clinical trials

Most of the prospective studies that are currently accruing patients are single institutional, single arm studies (Table 2). The only reported randomized trial was a phase 2b study at MD Anderson (NCT01512589) [30]. This trial used the novel primary endpoint of total toxicity burden (TTB), a composite score of 11 distinct adverse events (AEs). TTB was devised to quantify the extent of cumulative AE severity experienced by a patient undergoing trimodality therapy (CRT with the possibility of surgery) over the duration of 1 year from the start of treatment. The endpoint synthesized common toxicities with postoperative complications (POCs) in operated patients. Altogether, 145 patients were randomly assigned (72 IMRT, 73 PBT), and 107 patients (61 IMRT, 46 PBT (80% PSPT)) were evaluable. Most unevaluable patients randomized to PBT were denied insurance (81%), while patients randomized to IMRT often withdrew consent due to the request to be treated with PBT (64%). Among all baseline clinical characteristics, the only difference across the treatment modality subgroups was Zubrod performance status (worse in patients undergoing PBT, P = 0.02). Median follow-up was 44.1 months. Fifty-one patients (30 IMRT, 21 PBT) underwent esophagectomy. Patients receiving IMRT experienced an average TTB score that was 2.3 times higher than (TTB = 39.9; 95% highest posterior density interval, 26.2–54.9) than PBT (TTB = 17.4; 10.5–25.0). The mean POC score was 7.6 times higher for IMRT (TTB = 19.1; 7.3–32.3) versus PBT (TTB = 2.5; 0.3–5.2). The posterior probability that mean TTB was lower for PBT compared with IMRT was 0.9989, which exceeded the trial's stopping boundary of 0.9942 at the 67% interim analysis. The trial failed to demonstrate statistically significant differences in PFS, OS, or quality of life measures based on EQ5D, although it was not powered to show those differences. This is the first randomized evidence to support the treatment toxicity benefit of PBT compared to IMRT. Further validation of these results will occur on the currently accruing phase 3 randomized trial, NRG-GI006 (NCT03801876). The primary endpoint is to determine if OS is improved with the use of PBT vs IMRT; however, if OS of PBT is considered non-inferior to IMRT as part of planned protocol treatment, the co-primary endpoint is to determine if there will be less grade 3+ cardiopulmonary toxicity with the use of PBT than with IMRT. There are also a number of secondary objectives, which include patient reported outcomes comparison between modalities, quality-adjusted life years evaluation, pathologic response rate, cost-benefit economic analysis, length of hospitalization, incidence of grade 4 lymphopenia, comparison of lymphocyte nadir, disease specific outcomes such as locoregional failure free survival, distant metastatic failure free survival, and progression free survival, and comparison of TTB between modalities.

Health-related quality of life is another important aspect that warrants consideration. Garant et al. [56] reported on 125 patients enrolled in a prospective registry study at Mayo Clinic who received preoperative or definitive CRT for esophageal cancer. The baseline characteristics between PRT and XRT cohort are roughly equivalent, except that the PRT cohort had an older mean age, a smaller mean CTV, and a higher prescription dose. Patients completed the Functional Assessment of Cancer Therapy-Esophagus (FACT-E) questionnaire before CRT and during the last week of CRT. They found that the use of PBT was associated with significantly less decline in FACT-E scores during treatment compared with XRT (−12.7 vs −20.6, P = 0.026).

Role of proton therapy in re-irradiation

Minimized scatter dose to surrounding normal tissues enables the consideration of using PBT for repeat irradiation in patients with esophageal cancer with prior radiation exposure (Table 3). As part of a prospective proton reirradiation protocol at University of Pennsylvania, 14 patients with a history of thoracic radiation and newly diagnosed or locally recurrent esophageal cancer were reported [57]. The median interval between radiation courses was 32 months (range 10–307 months). The median prescribed dose for the re-irradiation was 54.0 GyE (range 50.4–61.2 GyE); median cumulative RT dose of 109.8 Gy (range 76–129.4 Gy); and 11 of the 14 patients (79%) received concurrent chemotherapy. At a median follow-up time of 10 months from the start of re-irradiation (range 2–25 months), four patients (14%) had grade 3 non-hematologic acute toxicity (dysphagia [14%], dehydration [14%], and pneumonia [7%]). One patient died of acute esophagopleural fistula, which was probably related to tumor progression rather than adverse effect of the radiation. The four late grade 3 toxic events were heart failure (7%), esophageal stenosis (7%), esophageal ulceration (7%), and dysphagia (7%). Another patient died with a late esophageal ulcer, again more likely related to tumor progression than to the reirradiation.

Table 3
Treatment and outcome details for proton-beam therapy re-irradiation in patients with recurrent or second primary esophageal cancer.

Reference	No. of Patients	Median Prior Dose (range)	Median Re-irradiation Prescription Dose (range)	Median Time to Re-irradiation (range)	Median Follow-up (range)	Disease Specific Outcomes	Survival Outcomes	Lung Toxicity	Heart Toxicity	Other Toxicities
Fernandes et al. (2016) [57]	14	54 Gy (25.5–70)	54GyE (50.4–61.2)	32 months (10–307 months)	10 months (2–25 months)	9 of 14 with LRR, 6 of 14 with DM, 8 of 10 with dysphagia improved/ stabilized	Median OS 14 months (95% CI, 7–21 months), 1-year OS 71%.	Acute: grade 3: pneumonia (n = 1)	Late: grade 3: heart failure (n = 1)	Acute: grade 3: dehydration (n = 2), dysphagia (n = 2), GI bleed (n = 1), hyponatremia (n = 1), weight loss (n = 1); grade 5: esophagopleural fistula (n = 1) Late: dysphagia (n = 1), esophageal stenosis (n = 1), esophageal ulcer (n = 1); grade 5: esophageal ulcer (n = 1)
Patel et al. (2019) [59]	3	36.0 Gy (15–36)	50.4GyE (45–50.4)	30 years (5–41 years)	26 months (22–72 months)	0/3 (0%) with LRR or DM	All alive at 22, 26, and 72 months post-op.		Late: intra-op cardiac arrest (n = 1)	Acute: mild/moderate odynophagia (n = 2), esophageal stricture (n = 1), hematemesis (n = 1), moderate/ severe esophagitis (n = 1).
DeCesaris et al. (2020) [58]	17	50.4 Gy (40–108)	53.4GyE (40.0–108.0)	37.6 months (11.6–584 months)	11.6 months (2.0–36.6 months)	1-year LC 75.3%; 1-year DC 83.4%	Median OS 19.5 months (95% CI, 5.7–33.3 months)			Acute: grade 3: dysphagia (n = 1), esophagitis (n = 1) Late: grade 3: esophageal stenosis (n = 2); grade 4: esophageal stenosis (n = 1), TEF (n = 1); grade 5: TEF (n = 1).

Gy, Gray; GyE, Gray-equivalent; LRR, locoregional recurrence; DM, distant metastasis; OS, overall survival; CI, confidence interval; GI, gastrointestinal; LC, local control; DC, distant control; TEF, tracheoesophageal fistula.

DeCesaris et al. [58] have published a first series using IMPT for reirradiation of esophageal and gastroesophageal junction (GEJ) malignant tumors locally recurrent from the primary treatment or from previous radiation exposure for another indication. A total of 17 patients were included for analysis. The median prescribed dose is 53.4 GyE; the cumulative RT dose with prior radiation is estimated to be at the median of 104.7 Gy (range 94–156 Gy); 15 of 17 (88%) had concurrent chemotherapy. At a median follow-up of 11.6 months, 1-year local control was 75.3% and overall survival was 68.9%. There were five (27.8%) grade 3 or higher late toxicities. When matched for clinical target volume coverage, IMPT plans delivered significantly lower doses to the spinal cord, lungs, liver, and heart (all $P < 0.05$); five volumetric-modulated arc therapy plans would have been undeliverable on the basis of physician-specified OAR constraints. In a small case series, three patients with primary esophageal cancer diagnosis with prior chest radiation were radiated with PBT and concurrent chemotherapy followed by an esophagectomy. All are alive with excellent clinical outcomes [59]. These results suggest that use of PBT for re-irradiation is not only feasible, but in many cases medically necessary, with modest radiation-related toxicity and favorable survival even for high-risk patients. However, since the data on re-irradiation are limited, we should still take a cautious attitude towards the use of PBT for re-irradiation before more high-level evidence appears.

Patient selection for proton therapy

As compared to photons, protons have a clear dosimetric benefit in esophageal cancer particularly regarding the dose to the heart, lung and spleen. However, the extent to which dose reductions in critical organs translate into a clinically meaningful benefit, in terms of reduced complications, does not only depend on the dosimetric advantages. First, not every dose reduction in normal tissues is expected to result in a clinical benefit, e.g. when the dose with photons is already below the threshold dose for a given side effect. Second, other independent risk factors for radiation-induced side effects, like the elderly [60,61], baseline (cardiovascular) risk profiles [55], and/or BMI, together with the range of dose volume histogram (DVH) parameters, like the mean lung dose, affect the patients estimated clinical benefit [62–64].

In the Netherlands, patients are selected for proton therapy using a model-based approach. Multivariable normal tissue complication probability (NTCP) models, containing at least one or more DVH parameter and non-DVH predictors, are used to select patients that are expected to benefit most of proton radiotherapy by translating the dosimetric advantage (Δdose) into an estimated clinical advantage (ΔNCTP) for each individual patient. A national protocol for selection of patients with esophageal cancer for proton therapy is currently under development and might be based on an NTCP-model for the Total Toxicity Burden (TTB) [65]. In such an approach, patients only qualify for proton therapy if the TTB is expected to drop with a certain minimal threshold based on a prediction model for the TTB. In fact, model-based selection is stricter then patient selection based on the outcome of a positive randomized trial as only patients with a predefined difference in the risk of the TTB above a certain threshold will be selected instead of all patients that meet the inclusion criteria of a positive RCT [30].

The next step in the model-based approach is model-based clinical evaluation [66] which can be considered an evidence-based alternative for RCT's. To this purpose, all patients are embedded in a prospective observational cohort study in order to validate the clinical benefit estimates and optimize the NTCP models even further, resulting in a continuous loop of improved and effective

patient selection. In a model-based clinical evaluation study, the observed toxicity rates with IMPT are compared to the expected toxicity rates based on the photon plans of the same patients, made for the plan comparison [52].

Current limitations and challenges in proton therapy

Although the physical properties of protons confer certain advantages over photons, those properties also introduce certain challenges. Their scattering properties mean that protons have a larger penumbra than photons; as a consequence, large volumes of tissues away from the target may receive relatively low doses, but the doses to normal tissues near the target volume may be higher with PBT [67]. Also, the assumption that the relative biological effectiveness (RBE) of protons is a constant 1.1 relative to photons is common in clinical practice, but RBE in fact varies depending on linear energy transfer (LET), tissue type, and other factors [68]. If RBE is arbitrarily set to 1.1 without consideration of these other effects, that assumption may lead to unexpected tumor recurrence or toxicity. Current RBE prediction models are somewhat simplistic and are based on limited measured data, and as such more research is needed to improve the understanding of RBE in living organisms [69].

Further, differences in tissue density along the path of the protons during delivery affect the dose distribution, especially for tumors in complex heterogeneous environments like the thorax. Tumor movement with cardiorespiratory motion also poses substantial problems requiring that such movement be accounted for. Although some related uncertainties can be reduced by technical means, such as four-dimensional computed tomography (4DCT)-based motion management, robust optimization and evaluation, active motion management (e.g., breath hold), beam gating, rescanning, tracking and adaptive planning [70], residual uncertainty still exists. These uncertainties are incorporated into treatment planning and evaluation, with safety margins built in to accommodate for these uncertainties. Nevertheless, proton therapy may not be appropriate for all patients due to these issues, especially for tumors located at the GE junction with complex movement.

Unlike megavoltage photons, proton beam is particularly sensitive to anatomic changes that would alter the electron density in the beam path. And the target area of esophageal cancer is mostly located in the chest and upper abdomen, where the density distribution of tissues is complex. Any reductions in tumor volume over the course of treatment also pose challenges, as the different densities of replacement tissues can lead to uneven proton dose distributions and unnecessary radiation transfer to the lung, heart, and other normal tissues. Thus, it is often necessary to perform frequent in-room volumetric imaging with cone-beam CT to monitor these anatomic or tumor changes or perform periodic verification 4DCT re-simulations and re-create treatment plans during the course of PBT.

Typically, dose-volume histograms are used as the basis for evaluating radiotherapy plans and making treatment decisions. The general assumption is that the dose distribution seen in the treatment plan is what is actually delivered to the patients. However, in reality uncertainty is introduced as a consequence of both anatomic complexities of the chest and upper abdomen and the approximations and assumptions in the algorithms and formulas used to calculate the dose distribution. A more sophisticated Monte Carlo dose algorithm to overcome the limitations of existing algorithms and models used in PBT was recently verified and implemented [71]. Moreover, DVH based toxicity prediction models disregard organ's regional dose response as demonstrated in the recent literatures on image based data mining on both heart [72] and lungs [73]. In particular, the analysis of the MD Anderson randomized trial of IMRT versus PSPT for non-small cell lung cancer [73], showed that the regions significantly spared by protons were those apparently not strongly sensitive for radiation-induced lung damage. Therefore, the normal tissue sparing that protons indeed provided actually occurred in a region that was not involved in the development of radiation pneumonitis. This issue should be discussed as a further step towards a more effective model-based patient selection. Meanwhile, improving the accuracy and efficiency of PBT also requires overcoming some technical limitations in the commercially available devices at a given center, such as spot size, energy switching capabilities, image guidance, respiratory gating, dynamic collimation, and others [67].

Future directions

Previous studies have shown that PBT has certain dosimetric advantages over photon therapy, however most of the aforementioned studies were done with PSPT. Most of the newer centers coming online nowadays are all strictly IMPT capable, so the potential for clinical outcomes to continue to improve with the improved dosimetry of IMPT [74].

Recent interest has heightened in the possibility of combining radiation therapy (with photons or protons) with immunotherapies for the treatment of esophageal cancer. The interim results of the Checkmate 577 trial [75], demonstrated that nivolumab (Opdivo), given as adjuvant therapy for patients with resected EC/GEJC, reduced the risk of recurrence or death by 31% and doubled median DFS versus placebo. As of May 20, 2021, adjuvant nivolumab is FDA approved in high-risk patients after trimodality therapy.

As it is known, lymphocytes play an important role in immunotherapy through a variety of mechanisms [76], with lymphopenia having a negative impact on the clinical outcome of immunotherapy [77–79]. Cho et al. [77] retrospectively analyzed 268 patients with advanced NSCLC undergoing immunotherapy. Lymphopenia was identified as an independent predictor for poor prognosis. Another study by Ho et al. [78] indicated that in patients with head and neck squamous cell carcinomas, the lower pretreatment ALC is significantly associated with the poorer response to anti-PD1 therapy. Besides, patients with pretreatment ALC <600 cells/μl were found to have significant worse PFS than those with pretreatment ALC ≥600 cells/μl. Recent study by Chen et al. [79] analyzed 153 patients with solid tumors treated with immuno-radiotherapy. Low post-RT ALC was associated with low rates of abscopal effects (3.9% vs. 34.2%), and resulted in significantly worse PFS and OS. Therefore, the lymphocyte-sparing effect of proton therapy maybe pivotal to augmenting immunotherapy response. In addition, a molecular-level study demonstrated that PBT has comparable or even enhanced ability to stimulate immunogenic response as compared with photon therapy [80]. Taken together, the combination of PBT with immunotherapy is an important and promising research direction in the future.

Conclusions

The consistent midline location and relative distribution of tumors in the thoracic esophageal locations relative to adjacent critical organs makes esophageal cancer almost an ideal candidate for the use of PBT. The dosimetric superiority of PBT relative to the best photon-based approaches in sparing heart, lung, and arguably also the liver and spleen, is translating to emerging clinical benefits seen in retrospective and prospective studies. Definitive large randomized trials will be needed to prove the benefits seen, and these are currently ongoing in the US or being planned in Europe. However, instead of randomizing all patients, since not all patients may

benefit from PBT, model-based selected based on NTCP models could be another way to select patients for the use of PBT. However, PBT still has some limitations that must be addressed. With further improvements in the technology of PBT planning and delivery, and with relevant basic and clinical research on the use of particle therapy for cancer treatment, we expect the potential of PBT to be fully realized, particularly in combination with immunotherapy in future studies.

Declaration of Competing Interest

SHL receives grant funding from Beyond Spring Pharmaceuticals, STCube Pharmaceuticals, Nektar Therapeutics, is on the advisory board for STCube Pharmaceuticals, Creatv Microtech, and AstraZeneca, and is a consultant for XRAD Therapeutics.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2021.09.004.

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