



The Role of Modern Radiotherapy Technology in the Treatment of Esophageal Cancer

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Radiation therapy (RT) has improved patient outcomes, but treatment-related complication rates remain high. In the conventional 2-dimensional and 3-dimensional conformal RT (3D-CRT) era, there was little room for toxicity reduction because of the need to balance the estimated toxicity to organs at risk (OARs), derived from dose-volume histogram data for organs including the lung, heart, spinal cord, and liver, with the planning target volume (PTV) dose. Intensity-modulated RT (IMRT) is an advanced form of conformal RT that utilizes computer-controlled linear accelerators to deliver precise radiation doses to the PTV. The dosimetric advantages of IMRT enable better sparing of normal tissues and OARs than is possible with 3D-CRT. A major breakthrough in the treatment of esophageal cancer (EC), whether early or locally advanced, is the use of proton beam therapy (PBT). Protons deposit their highest dose of radiation at the tumor, while leaving none behind; the resulting effective dose reduction to healthy tissues and OARs considerably reduces acute and delayed RT-related toxicity. In recent studies, PBT has been found to alleviate severe lymphopenia resulting from combined chemo-radiation, opening up the possibility of reducing immune suppression, which might be associated with a poor prognosis in cases of locally advanced EC.

Keywords: Esophageal neoplasms, Radiotherapy, Intensity-modulated radiotherapy, Proton therapy

Introduction

The treatment of esophageal cancer (EC) entails a multi-disciplinary approach, in which specialists in thoracic surgery, radiation oncology, medical oncology, diagnostic radiology, and upper gastrointestinal (GI) endoscopy share their expertise. Although the indications of radiation therapy (RT) for EC have expanded to include earlier-stage disease in recent years, RT has mainly played a role in the treatment of locally advanced (LA) cases. The details of RT in the treatment of LA-EC have been fairly stable, and still depend upon the results of definitive chemoradiation reported by the Radiation Therapy Oncology Group (RTOG) 85-01 and Intergroup (INT) 0123 randomized trials of 2-dimensional (2D) RT [1,2]. In the meantime, RT technology has evolved to become more precise, conformal, and innovative, as exemplified by intensity-modulated RT (IMRT), stereotactic radiosurgery, and proton beam therapy (PBT).

In this article, we review how modern RT technologies, focusing on IMRT and PBT, have brought about potential improvements in the outcomes of RT for EC, in terms of both toxicity and efficacy.

Technical advancement of modern radiotherapy

Intensity-modulated radiation therapy

Because optimizing a treatment plan for EC is challenging due to the location of the esophagus, which is surrounded by critical organs such as the spinal cord, lung, and heart, traditional techniques such as 2D-RT and 3-dimensional conformal RT (3D-CRT) have failed to deliver homogeneous and adequate doses to the tumor, limiting exposure to critical organs. IMRT is an advanced mode of external-beam RT that uses computer-controlled multi-leaf



collimators to deliver precise radiation doses to the tumor. IMRT allows the radiation dose to be focused on the tumor, while minimizing the dose to surrounding normal critical structures. Since IMRT became commercially available in the early 2000s, its use has become more common, and it has now prevailed over 3D-CRT, particularly for tumors in troublesome locations. IMRT has shown better performance, in terms of higher conformality and avoidance of critical organs, than 3D-CRT in treatment planning comparison studies for EC [3,4]. Additionally, some investigators have reported favorable clinical outcomes and acceptable toxicity profiles in EC patients treated with IMRT [5,6]. Nicolini et al. [4] reported that the 3-year overall survival (OS) and progression-free survival (PFS) rates were 42.2% and 40.7%, respectively, at a median follow-up interval of 20.3 months, with only 13% of patients experiencing grade 3 esophagitis, in a retrospective study of 45 EC patients who received 63 Gy over 28 fractions to the gross tumor volume (GTV). In another retrospective study of 676 patients with EC by Lin et al. [6], IMRT showed better OS than 3D-CRT (hazard ratio, 0.72; $p < 0.001$). In their report, a higher cumulative incidence of cardiac death was seen in the 3D-CRT group (5-year estimate, 11.7% in the 3D-CRT group versus 5.4% in the IMRT group), although no significant difference was found in terms of cancer-specific mortality or distant metastasis [6].

Proton beam therapy

Particle therapy, as a next-generation RT technique, has been drawing steady interest since the mid-2000s. PBT, the most common type of particle therapy, is advantageous over other types of external beam RT that the dose is deposited over a narrow range of depth, with no exit dose and a minimal scattered dose. Early adopters of PBT reported favorable results for EC [7-13]. In a small Japanese series, combinations of X-rays and proton therapy for EC were effective, but the details of treatment-related toxicity were not reported [7-10]. PBT provided better sparing of the lung than did IMRT in a comparative planning study at M. D. Anderson Cancer Center (MDACC) [11]. Pencil beam scanning and intensity-modulated PBT for distal EC further lowered the dose to the heart, lung, and liver. It was also suggested that the dosimetric benefits of PBT should be tailored to each patient according to their specific cardiac and pulmonary risks [12,13]. In another recent comparative planning study from MDACC, PBT resulted in a significantly lower mean heart dose and volume of the heart receiving a dose of 5–40 Gy, as well as lower radiation ex-

posure to the 4 chambers of the heart and 4 coronary arteries, compared with IMRT [14]. Several retrospective studies demonstrated the dosimetric superiority of PBT to 3D-CRT and IMRT, demonstrating actual reductions in cardiopulmonary toxicity with PBT [15-17].

Application of modern radiation therapy techniques in esophageal cancer

Superficial esophageal cancer

The detection rate of superficial esophageal cancer (SEC), which is defined as a tumor limited to the mucosa or submucosa, has been increasing as a result of widespread endoscopic screening and the development of new endoscopic techniques [18-20]. As the esophagus has abundant lymphatic channels that originate in the submucosal layer and extend intramurally as well as extramurally, the lymph node (LN) metastasis rate is very high even in clinically LN negative SEC, occurring in up to 25.7% of pT1b cases after surgery [21]. Local procedures such as endoscopic mucosal resection or submucosal dissection (ESD) can be offered to patients with SEC, because surgery for EC is an extensive procedure with a postoperative mortality rate of 0%–7% [22-24] and a high frequency of serious complications [25,26]. However, these local procedures alone are not considered sufficient for SEC in terms of oncologic safety in cases of extensive T1a, positive (close) margin, T1b, or lymphatic invasion. Therefore, external-beam RT with or without concurrent chemotherapy is often adopted for the definitive treatment of SEC. There is controversy regarding whether SEC should be treated using involved-field RT (IFRT) or extended field-RT (EFRT), as LN metastasis after IFRT even with chemotherapy is substantial and difficult to salvage, while most cases of primary local recurrence or metachronous primary EC are successfully salvaged with endoscopic resection or surgery [27-29]. IFRT involves delivering radiation to the GTV without elective nodal irradiation (ENI), with the initial clinical target volume (CTV2) extending 5 cm cranio-caudally from the GTV and 1–2 cm radially from the GTV. In contrast, for EFRT, the CTV2 encompasses the entire esophagus and mediastinum including the pretracheal, retrotracheal, and paratracheal, subcarinal, and peri-esophageal LNs, with or without the supraclavicular LN, and part of the abdomen including the left gastric, para-aortic, and celiac LNs (Fig. 1). The final clinical target volume (CTV1) covers the GTV with a margin of at least 2 cm cranio-caudally and 1 cm

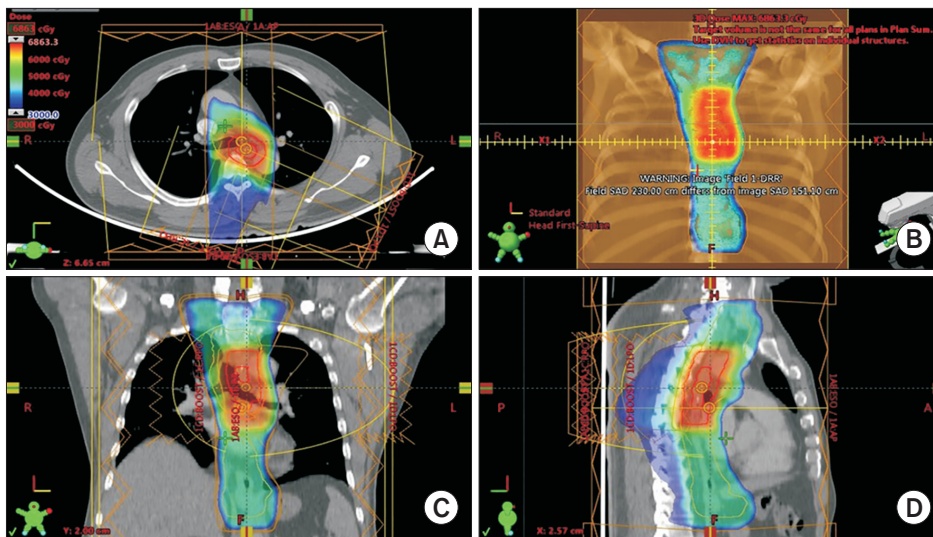


Fig. 1. (A–D) A typical extended-field radiotherapy plan using proton beam therapy for a patient with intrathoracic superficial esophageal cancer. The isodose distribution is shown as a color-wash pattern, from red (high dose) to blue (low dose). The final PTV and initial PTV are designated as red and green areas, respectively. PTV, planning target volume.

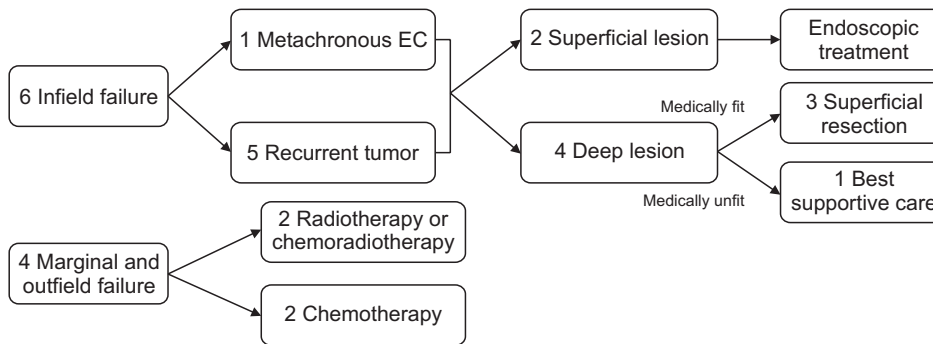


Fig. 2. Salvage treatment for patients with superficial EC who experience infield, marginal, and outfield regional failure. EC, esophageal cancer.

radially in both IFRT and EFRT. Then, the planning target volume (PTV) is defined as the CTV plus 0.5–1 cm. A total dose of 44 Gy and 60–66 Gy are delivered once daily to the initial PTV (PTV2) and the final PTV (PTV1), respectively.

EFRT is a unique RT field definition for SEC that we developed, and the efficacy and safety of EFRT without chemotherapy were previously reported in 24 patients [30]. We updated the results of LN-negative T1–T3 EC patients, including 41 with SEC, to explore the role of ENI. Most of these patients received EFRT (92.6%) without chemotherapy (90.2%) using modern techniques including 3D-CRT (43.9%), IMRT (0.98%), and PBT (46.3%). The median follow-up duration was 40 months (range, 14–92 months). Nineteen of the 41 SEC patients underwent ESD followed by RT owing to submucosal invasion (n=15) and a close or involved resection, with margins less than 1 mm (n=4).

In patients with SEC, local recurrence was the most common pattern of failure (n=6, 18%), followed by LN metastasis (n=5, 11%) and distant metastasis (n=4, 8%).

Among the 6 patients with local recurrence, 1 had a metachronous primary tumor and the other 5 had recurrence of the initial primary tumors. Isolated distant metastasis without local recurrence or LN metastasis was not observed in any patients with SEC. Fig. 2 shows the salvage treatment for patients with SEC who presented with loco-regional recurrence. Among the 6 patients who experienced infield recurrence, 2 and 3 patients were successfully salvaged by ESD and esophagectomy, respectively. Four patients who presented with marginal or outfield failures were treated with chemotherapy with or without RT. The 3-year OS, PFS, and local control rates for SEC were 86%, 78% and 87%, respectively.

Among all LN-negative T1–T3 EC patients who underwent concurrent chemoradiotherapy, 9 patients (60%) developed grade ≥2 acute esophagitis, while among the patients who received RT alone, 8 patients (21%) developed grade ≥2 acute esophagitis (p=0.005). EFRT did not increase the risk of grade ≥2 acute esophagitis compared with IFRT (28% after EFRT versus 63% after IFRT,

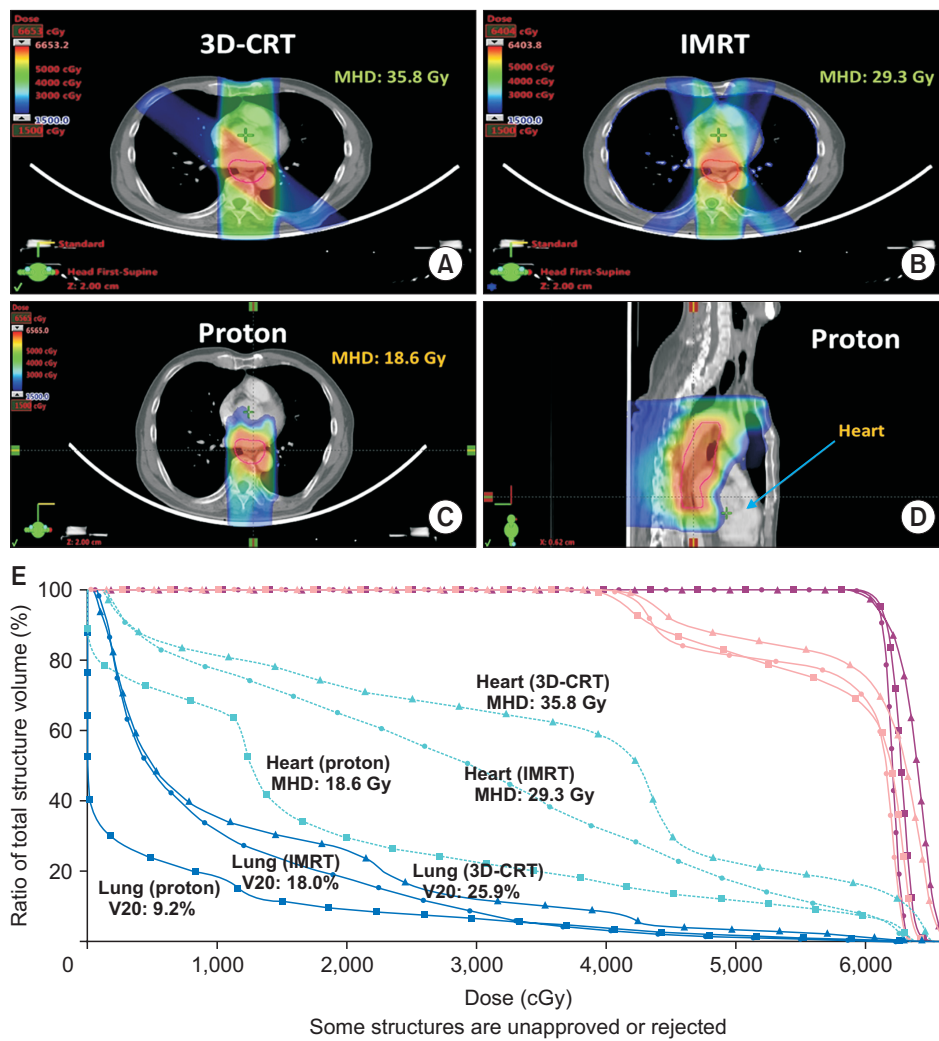


Fig. 3. Neoadjuvant proton beam therapy plan for a patient with locally advanced esophageal cancer. (A–D) The isodose distribution is shown as a color-wash pattern, from red (high dose) to blue (low dose). (E) A cumulative dose-volume histogram of a critical organ receiving at least 20 Gy; MHD, mean heart dose. 3D-CRT, 3-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy.

$p=0.092$).

In summary, long-term survival is expected for SEC patients with EFRT, and there might be little role for chemotherapy based on our study. The administration of an elective RT dose to clinically undetectable LN metastasis showed promising results, supporting the justification for EFRT for SEC. However, no long-term toxicity reports of EFRT have yet been published. Advanced technologies such as IMRT or PBT may reduce long-term complications by considerably decreasing the unnecessary lung dose, heart dose, and integral dose in EFRT for SEC. As depicted in Fig. 3A–D, PBT can effectively reduce the unnecessary and potentially harmful dose delivered to the lung and heart compared to X-ray treatment. A phase II trial of EFRT with PBT in SEC patients to evaluate the efficacy and toxicity that we initiated in 2018 will answer these questions.

Locally advanced esophageal cancer

Decades ago, the clinical outcome of definitive CRT for EC was very poor, with a 5-year OS rate of 26% reported in RTOG 85-01 [1]. The following INT trial evaluated radiation dose escalation (RDE) to overcome the high observed local recurrence rate of about 40%, but failed to demonstrate a survival benefit despite RDE ranging from 50.4 Gy in 28 fractions to 64.8 Gy in 36 fractions, both with 4 cycles of 5-fluorouracil and cisplatin [2]. However, RDE for LA-EC remains controversial, since in the INT trial, patients in the high-dose arm had worse OS and 7 of 11 deaths occurred during the RT period before reaching 50.4 Gy, meaning that RDE might not have been the cause of the higher mortality rate. Since then, several other trials have investigated RDE using pure RDE or hypofractionated RT with modern techniques [5,6,31]. In a phase I/II trial

testing more than >2 Gy to GTV with IMRT, the maximum tolerated dose was 63 Gy over 28 fractions, and 70% of cases were locally controlled with a similar rate of acute esophagitis to a historical control group [32]. Promising results have also been reported by RDE studies using PBT [7-10], and several prospective trials testing RDE for EC using positron emission tomography-computed tomography-based IMRT (NCT03113214 and NCT02741856) and PBT (NCT03234842 and NCT02213497) are ongoing.

Neoadjuvant chemoradiation (nCRT), which has been regarded as the standard of care since the CROSS (Chemo-Radiotherapy for Oesophageal cancer followed by Surgery Study) trial series [33,34], offers an appealing option to use PBT for EC. In a retrospective study, advanced RT technologies using either IMRT or PBT significantly reduced postoperative pulmonary and gastro-intestinal complication rates compared to 3D-CRT in EC patients. After adjusting for confounding factors, pulmonary and GI complications were significantly more common in patients treated with 3D-CRT than in those treated with IMRT (odds ratio [OR], 2.018; 95% confidence interval [CI], 1.104–3.688; OR, 1.704; 95% CI, 1.03–2.82, respectively) or PBT (OR, 3.154; 95% CI, 1.365–7.289; OR, 1.55; 95% CI, 0.78–3.08, respectively) [15]. A pooled analysis of PBT versus X-ray RT included 580 lower esophageal/gastroesophageal junction cancer patients. Both IMRT and PBT were associated with a significantly reduced rate of postoperative complications and length of stay compared to 3D-CRT, and PBT displayed the greatest benefit, with pulmonary toxicity of 16% (PBT) versus 40% (3D-CRT) [17].

PBT has a comparative advantage in reducing hematological or immunological toxicity over X-ray RT in treating EC. Treatment-induced lymphopenia has been associated with worse clinical outcomes in patients with various cancers [35-38], and RT is a factor related with lymphopenia because lymphocytes and their precursors are very sensitive to ionizing radiation. One proposed mechanism is that lymphopenia occurs via RT exposure of the circulating blood pool, as lymphopenia is found after RT even in tissues such as the breast and brain, which contain little bone marrow or lymphatic tissue [39,40]. As shown in Fig. 3E, PBT can effectively reduce the lung dose (V20-lung: 3D-CRT versus IMRT versus PBT, 25.9% versus 18.0% versus 9.2%), heart dose (mean heart dose, MHD: 3D-CRT versus IMRT versus PBT, 35.8 Gy versus 29.3 Gy versus 18.6 Gy), as well as the integral dose (data not shown) compared to 3D-CRT and IMRT for LA-EC. Because lymphocytes are exquisitely radiosensitive at low doses, PBT is more beneficial than 3D-CRT and IMRT in terms of both

immunological and cardiopulmonary toxicity. Shiraishi et al. [41] compared the risk of radiation-induced grade IV lymphopenia between PBT and IMRT patients with EC (n=136 in each group) in a propensity score-matched analysis. PBT patients had grade 4 neutropenia markedly less frequently than IMRT patients (17.6% versus 40.34%, $p < 0.0001$). In a multivariate analysis, PBT was found to be an independent predictor of grade 4 lymphopenia (OR, 0.29; 95% CI, 0.16–0.52; $p < 0.0001$). However, grade 4 lymphopenia was not found to be an independent predictor of poorer OS [41].

In summary, advanced RT techniques such as IMRT or PBT not only enable RDE to improve local control in the definitive CRT for LA-EC, but significantly reduce postoperative complications in nCRT compared to 3D-CRT. In particular, PBT has the additional advantage of causing less severe lymphopenia compared to X-ray RT, which is promising for the treatment of LA-EC.

Conclusion

Modern RT technologies have changed the old concept of a 50.4 Gy total dose with concurrent chemotherapy for EC, but the associations of RDE with a reduced toxicity profile and clinical outcomes in the context of new RT techniques such as IMRT or PBT should be proven in well-designed prospective trials. PBT has been steadily drawing attention as an ideal RT technology for both SEC and LA-EC due to its dramatic reduction of cardiopulmonary and hematological toxicity, but more evidence is also needed from clinical trials.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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