Esophagus Cancer

13

Steven H. Lin, Heng Li, and Daniel Gomez

Contents

13.1 Introduction

Worldwide, esophageal cancer (EC) is the sixth leading cause of death and is responsible for over 400,000 cases (4.9%) [1]. It is notable that the incidence differs greatly, depending on the region of the world. The highest incidence is in the Asian and Middle Eastern countries [2]. In most Western countries, such as in the United States, adenocarcinoma has eclipsed squamous cell carcinoma as the predominant histologic type and usually afflicts white males. In contrast, squamous cell carcinoma is mostly related to smoking and alcoholism in Asia and Middle Eastern countries. In addition, adenocarcinoma is largely related to the growing epidemic of obesity in the western and other developed countries and the associated reflux esophagitis and Barrett's pre-neoplasia that result [3].

Since surgical resection with or without adjuvant therapy is the standard approach, with cure rates that are approximately 20%, preoperative chemoradiation

S.H. Lin • H. Li • D. Gomez (✉)
MD Anderson Cancer Center, Houston, TX, USA
e-mail: dgomez@mdanderson.org

N. Lee et al. (eds.), *Target Volume Delineation and Treatment Planning for Particle Therapy*, Practical Guides in Radiation Oncology,
https://doi.org/10.1007/978-3-319-42478-1_13

is now increasingly being adopted due to the evidence showing an improvement in overall survival compared to surgery alone. The largest of the published randomized trials performed in the modern era was the phase III randomized study from the Dutch group, in which 366 evaluable patients were randomized to surgery vs. preoperative chemoradiation to 41.4 Gy with carboplatin and paclitaxel [4]. Notably, there was a significantly improved median OS in the preoperative group of 49.4 months vs. 24.0 months in the surgery alone group. The pathologic complete response (pCR) in the preoperative chemoradiation group was overall 29%. The pCR rate of squamous cell carcinoma was higher compared to adenocarcinoma (49% vs. 23%, $p = 0.008$), which also translated to an improved overall survival difference of chemoradiation relative to surgery alone in squamous tumors relative to adenocarcinomas (adjusted HR 0.42 (0.23–0.79) vs. HR 0.74 (0.54–1.02)).

Due to the location of the disease in the central mediastinum, proton beam therapy (PBT) is ideal for the treatment of EC. That is, mid- and distal esophageal tumors span posteriorly across the heart and are very close proximity to the left atrium and anteriorly to the thoracic vertebrae. Dose comparisons with 3D conformal therapy and IMRT will be described further below.

13.2 Simulation, Target Delineation, and Radiation Dose/Fractionation

Simulation—respiratory motion should be assessed using a four-dimensional (4D) scan. Note that the esophagus and surrounding structures can move substantially with respiratory motion, particularly at the GE junction. Patients should ideally be simulated with their arms above their head, to maximize the number of beam arrangements that can be used. To improve reproducibility, patients should be advised to be NPO for at least 3 h prior to the simulation and each daily treatment.

Target delineation—target delineation differs depending on the location of the tumor within the esophagus. Upper esophagus tumors are defined as those within the cervical and upper thoracic regions, and lower esophagus tumors are in the mid- and distal esophagus, including at the GE junction. Siewert type III GE junction tumors should be managed like gastric cancers, including target delineation.

Upper esophagus tumors—the GTV consists of the gross tumor. The CTV consists of a 3.5 cm margin superiorly-inferiorly and a 1 cm margin laterally, but not crossing anatomic boundaries (modified for boundaries such as vessels or the bone). However, for cervical esophagus lesions, the upper margin should be the inferior border of the cricoid cartilage. The CTV should also include elective treatment of the supraclavicular fossa bilaterally, even if not involved.

Lower esophagus tumors—the GTV consists of the gross tumor. The CTV consists of a 3.5 cm margin superiorly-inferiorly and a 1 cm margin laterally, but not crossing anatomic boundaries (modified for boundaries such as vessels or the bone). The CTV should also include the left gastric lymph nodes for patients with distal esophagus/GEJ tumors (Siewert type I/II disease). For patients with node-positive disease, the celiac axis should also be electively covered if not involved.

With particle therapy, The PTV is only used for recording and reporting purposes (ICRU 78). The PTV is generated by expanding the CTV with a patient setup margin, which is 0.5–1.0 cm, based on the image guidance that is available. At our institution, we utilize daily kV imaging and thus a 0.5 cm PTV margin.

In addition to the PTV, a dosimetric margin is also needed for particle therapy due to range uncertainties and modulation of beams, which will be described in more detail in the planning techniques below.

Radiation dose (upper esophagus tumors)—patients with upper esophagus tumors are less likely to undergo surgery. Therefore, dose escalation above 50.4 Gy can be considered (50.4–60 Gy in 1.8–2.0 Gy fractions).

Lower esophagus tumors—the standard dose remains 40–50.4 Gy in 1.8–2.0 Gy fractions. Dose escalation can be considered in the context of a clinical trial.

	Upper esophagus tumors	Lower esophagus tumors
GTV (with internal motion)	Gross tumor	Gross tumor
CTV	*Cervical*—superior to cricoid cartilage, inferior 3.5 cm, lateral 1 cm (respecting anatomic boundaries), bilateral SCV fossa *Upper thoracic*—superior-inferior 3.5 cm, lateral 1 cm (respecting anatomical boundaries)	*Middle esophagus*—superior-inferior 3.5 cm, lateral 1 cm (respecting anatomical boundaries), left gastric and celiac lymph nodes not considered unless involved *Distal esophagus/GEJ (Siewert I/II)*—superior-inferior 3.5 cm, lateral 1 cm (respecting anatomical boundaries), routinely electively cover left gastric lymph nodes, celiac nodes in node-positive disease *Siewert type III*—treat like gastric cancer
Patient setup margin	0.5–1.0 cm—0.5 cm if daily kV IGRT used	0.5–1.0 cm—0.5 cm if daily kV IGRT used
Prescription dose	50.4–60 Gy RBE in 1.8–2.0 Gy fractions	40–50.4 Gy RBE in 1.8–2.0 Gy fractions

13.3 Patient Positioning, Immobilization, and Treatment Verification

Patients should be placed supine and immobilized in a 5-point mask with indexed head, neck, and shoulder stabilization in patients with cervical tumors.

For patients with thoracic and GEJ tumors, immobilization involves the use of indexed upper vac-lok/alpha cradle, with bilateral arms up. Vac-lok deflation has to be monitored.

Isocenter is placed at the carina.

Daily kV imaging should be used for all patients. If available, weekly in-room volumetric imaging (e.g., cone-beam CT scan or CT on rails) can be obtained weekly.

Breath-holding and gating techniques are not typically done in esophagus cancer tumors; however, they have the potential to be used for target motion management.

Substantial changes in anatomy and/or tumor size during the course of treatment are rare, and thus adaptive simulations are not routinely scheduled. However, if daily or weekly imaging shows changes in normal tissue or tumor or if the patient undergoes a prolonged treatment break, then we do recommend that a verification CT study be performed as soon as possible.

13.3.1 Passive Scattering PBT Planning

Typically for patients with distal tumors, the beam arrangement is most commonly posteroanterior (PA) and left lateral oblique (LAO) (Fig. 13.1). However, optimal beam arrangements are determined on a case-by-case basis, and alternative beam arrangements can be used. For proximal to mid-esophagus tumors, an anteroposterior (AP) and PA beam arrangement could be considered, exercising caution in the AP direction because of the range uncertainty into the spinal cord.

For free-breathing treatment, in order to ensure target coverage in all breathing phases, a planning diaphragm structure is created from the T0 to T50 phases of the 4DCT. The density of the diaphragm is then overridden using the average Hounsfield unit (HU) of the maximum intensity projection (MIP) scan generated from the 4DCT. The treatment plan is then designed with the overridden average CT. This technique ensures adequate coverage to the distal end of target even with respiratory motion as shown in Fig. 13.1.

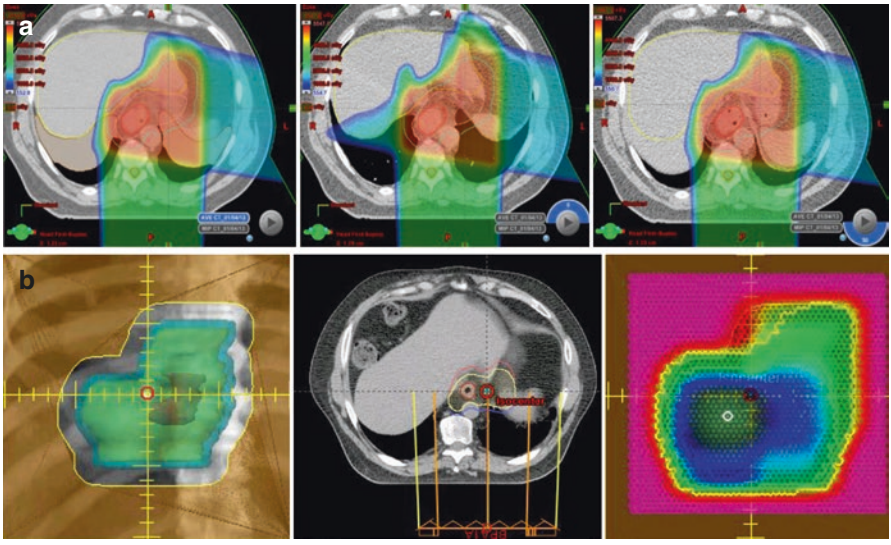
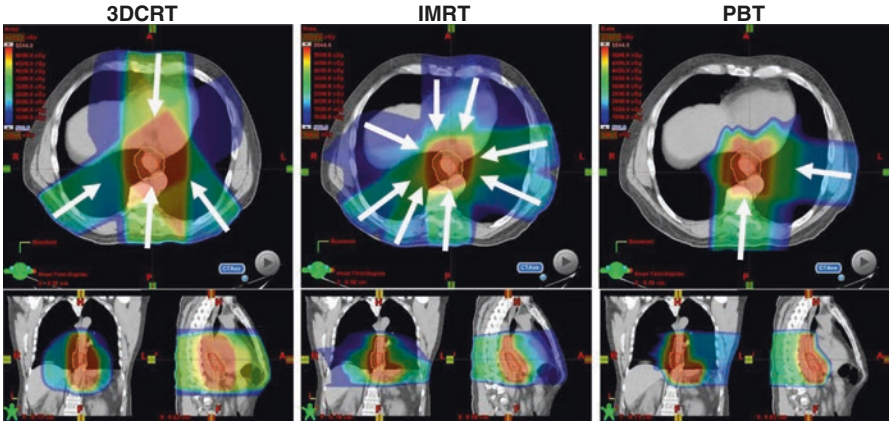


Fig. 13.1 Overriding diaphragm in treatment for esophagus cancer. (**a**) *Left*: plan dose calculated on average CT with diaphragm override. *Middle*: dose calculated on T0. *Right*: dose calculated on T50. (**b**) *Left*: aperture design with lateral margin consists of setup margin and dosimetric margin to account for beam penumbra. *Middle*: distal (*red*) and proximal (*blue*) margins. *Right*: compensator design with smearing



3DCRT: 4-field static photons; IMRT: 5-field modulated photons; PBT: 2-field passive scatter protons (PA/LPO)

Fig. 13.2 Beam arrangement and dosimetric comparisons of photon (3D or IMRT) and PBT plans for a distal esophageal tumor

Typical margins for passive proton beam treatment planning were used [5]: aperture design with setup margin and dosimetric margin, beamline design that includes distal and proximal margins based on beam range to account for range uncertainties, and compensator design with smear margin to ensure distal target coverage (Fig. 13.2).

13.3.2 IMPT Treatment Planning

IMPT offers superior dose conformity compared to PSPT, and it delivers less integral dose than IMRT. However, IMPT is more sensitive to respiratory motion than PSPT and therefore poses an even larger challenge in implementation of the technique. This is particularly relevant for distal esophageal tumors.

One way to assess the impact of respiratory motion is to assess the changes of water equivalent thickness (WET) of the proton beam. A study has shown that the change in WET is correlated with respiratory motion which generates dose uncertainty for distal esophageal treatment plans [6].

The same study also established that for distal esophagus, the optimal beam angles range between 150 and 210 degrees, to avoid the diaphragm motion in the beam path. Typically two to three beams could be used for the plan in this range.

Both single-field optimization (SFO), where each field is optimized to deliver the prescribed dose to target dose to target volume [7], and IMPT, where all spots from all fields are optimized simultaneously (Chap. 3), could be used for PBS planning. In general, IMPT offers more flexibility with more degrees of freedom and could result in more conformal dose distribution, but IMPT plans are also less robust compared to SFO plans due to the complex dose distribution in each fields. For esophageal tumors, SFO and IMPT plans could achieve similar quality for current dose

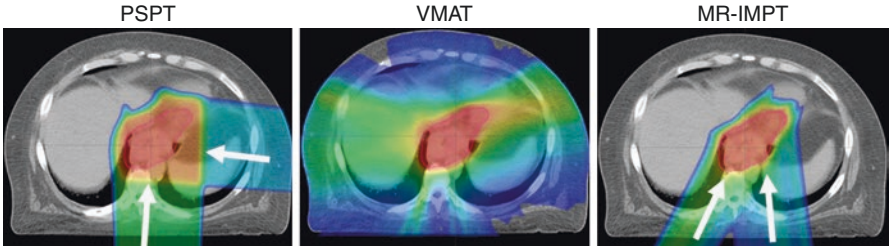


Fig. 13.3 Demonstration of benefit of IMPT compared to PSPT and VMAT in distal esophagus cancer. Note that there are improved conformality and sparing of the surrounding liver, stomach, heart, and soft tissue

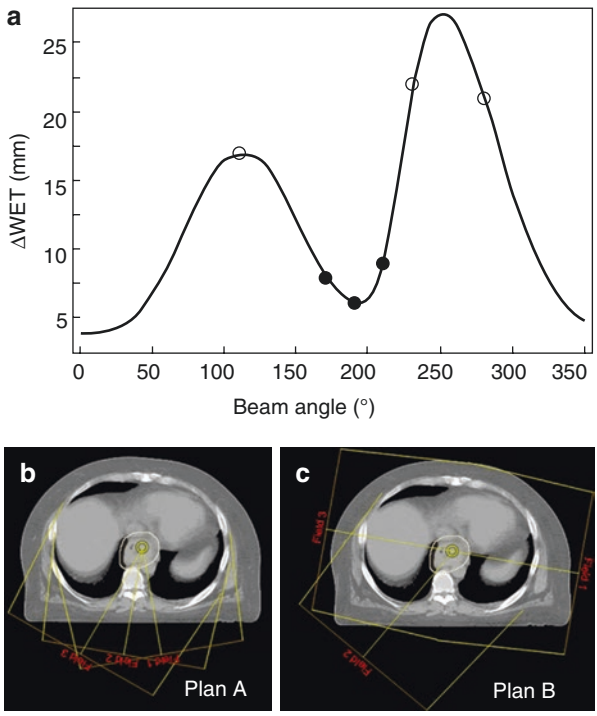


Fig. 13.4 (**a**) An example of a ΔWET curve created by plotting ΔWET value against beam angle. The solid circles indicate the three beam angles that are in the approximate range of the minimum ΔWET. These are the beam angles used in plan A. The open circles correspond to the three beam angles around the maximum ΔWET, which are the beam angles used in plan B. (**b**) Beam arrangement for plan A. (**c**) Beam arrangement for plan B. The contour is ICTV (From reference [6])

prescription levels, with the exception of slightly elevated spinal cord dose in the SFO plans but still within 45–50 GY(RBE).

4D treatment planning and robustness optimization could further reduce the impact of respiratory motion to the dose distribution, but these techniques may not be readily available [6]. However, active target motion management techniques such as breath holding could be employed (Figs. 13.3 and 13.4).

13.4 Dosimetric and Toxicity Comparison

A 3D conformal approach for esophagus cancer introduces relatively higher radiation dose to the heart, especially with an AP beam. IMRT is able to reduce the high-dose scatter across the heart by placing the entrance dose posteriorly, thereby subjecting the heart and lung dose to low exit radiation dose. Proton beam further improves the dosimetric parameters since with the Bragg peak, there is virtually no exit dose. Therefore, even with only two beams used in passive scattering proton, there is a substantial reduction in dose to the lung and heart. A number of dosimetric planning studies have been conducted that have compared proton beam with photon modalities. In a study comparing photons vs. protons using 3D planning (3DCRT vs. PSPT) in five patients, improved dosing to the spinal cord, lung, heart, and kidneys was found, with better tumor control probability by 2–23% units (mean 20%) [8].

The dosimetric benefit described above is also observed when compared to IMRT plans. This proton vs. photon comparison was done in a study comparing IMRT to two-field AP/PA or three-field AP/two posterior oblique PSPT field arrangements in 15 patients [9]. While PSBT substantially reduced the V5–V20, mean lung dose, and spinal cord dose, the dose-sparing effect was not observed in the heart. This discrepancy is likely due to the suboptimal beam arrangement that these earlier experiences reflected, as we recently demonstrated in a planning study comparing passive scattering proton therapy (PSPT) with IMRT in 55 patients with mid- to distal ECs to determine the dosimetric or anatomic factors that led to suboptimal proton dose distribution [10]. Specifically, we identified patients with "suboptimal" dosimetry compared to IMRT and then attempted to determine whether the dosimetric characteristics could be improved with alternative approaches. We found that the primary reasons for suboptimal dosimetry were (1) nonstandard beam arrangements such as AP/PA or AP/PA/left lateral approach, (2) 1:1 beam weighting of the left lateral/PA beam, and/or (3) unique patient anatomy such as the CTV wrapping around the heart.

Clinically, our institution has also compared toxicity in PBT vs. photon techniques, both from a dosimetric and clinical outcome standpoint [11]. During this period, 208, 164, and 72 patients were treated with 3D, IMRT, or PSBT, respectively. With regard to comparative dosimetry, significant differences were appreciated between each of the modalities, particularly for PBT as compared to the other modalities.

We also evaluated the incidence of postoperative pulmonary, cardiac, wound, and gastrointestinal (GI) complications in 444 patients treated with neoadjuvant chemoradiation from 1998 to 2011. On univariate analysis, a number of factors predicted for adverse events, but the radiation modality used was only associated with pulmonary and GI complications. On multivariate analysis, only radiation modality and pre-radiation diffusion capacity of the lung for carbon monoxide (D_{LCO}) were independently associated with pulmonary complications. With regard to GI complications, radiation modality trended toward statistical significance between the two techniques, with protons having a slightly improved incidence of

these adverse events. When the three radiation modalities were compared, there was a significant increase in pulmonary complications of 3D vs. IMRT (odds ratio [OR], 4.10; 95% confidence interval [CI] 1.37–12.29) or 3D vs. PBT (OR 9.13; 95% CI, 1.83–45.42), but there was no difference in IMRT vs. PBT after adjusting for the pre-radiation D_{LCO} level (OR 2.23; 95% CI, 0.86–5.76) [11].

Investigators from the University of Pennsylvania recently published a prospective study of 14 patients who received PSPT for recurrent esophagus cancer over a 15-year period at their institution, to assess the outcomes and toxicity of this approach. The authors reported one grade 5 toxicity, an esophagopleural fistula that may have been related to tumor progression, as well as four grade 3 toxicities: heart failure, esophageal stricture, esophageal ulceration, and percutaneous endoscopic gastrostomy tube dependence. The median OS time was 14 months, leading the authors to conclude that this approach has an "encouraging" symptom control rate and "favorable" survival [12].

The utility of PBT (passive scattering or IMPT) vs. photon (IMRT) techniques should be further evaluated in prospective, randomized trials. MD Anderson Cancer Center is currently leading a phase IIB randomized study comparing these approaches (NCT01512589), with the co-primary endpoints being total toxicity burden and disease-free survival. Anticipated accrual is 180 patients, with approximately 50% accrual at the time of this publication.

13.5 Future Developments

Substantial progress has been made with regard to proton therapy in esophagus cancer over the past decade. Dosimetry has been compared to IMRT and 3DCRT, optimal beam arrangements have been defined, planning techniques have been refined, IMPT has been implemented, and comparative effectiveness studies have been initiated. The next 10–20 years will likely involve further refinement of IMPT in this setting, along with the standardization of planning approaches. The identification of appropriate patients for this approach will also be critical, and one substantial benefit from the completion of ongoing randomized studies will be to determine the subsets of patients that derive the greatest clinical benefit from the utilization of proton therapy. Ideally, this approach will be possible in an increasing number of patients with limited treatment options, such as those with in-field local failures. Finally, imaging studies will enhance our understanding of the differences between proton and photon techniques in the context of both tumor response and toxicity. Fields such as radiomics in combination with sensitive imaging modalities (MRI, PET) will improve our comprehension of the early effects of protons and whether these can be predictive and prognostic of ultimate outcomes.

References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin. 2010;60(5):277–300.
2. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61(2):69–90.
3. Enzinger PC, Mayer RJ. Esophageal cancer. N Engl J Med. 2003;349(23):2241–52.
4. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074–84.
5. Li H, Giebeler A, Dong L, et al. Treatment planning for passive scattering proton therapy. In: Das IJ, Paganetti H, editors. Principles and practice of proton beam therapy; 2015.
6. Yu J, Zhang X, Liao L, et al. Motion-robust intensity-modulated proton therapy for distal esophageal cancer. Med Phys. 2016;43(3):1111.
7. Zhu XR, Sahoo N, Zhang X, et al. Intensity modulated proton therapy treatment planning using single-field optimization: the impact of monitor unit constraints on plan quality. Med Phys. 2010;37(3):1210–9.
8. Isacsson U, LennernÃs B, Grusell E, Jung B, Montelius A, Glimelius B. Comparative treatment planning between proton and x-ray therapy in esophageal cancer. Int J Radiat Oncol Biol Phy. 1998;41(2):441–50.
9. Zhang X, Kl Z, Guerrero TM, et al. Four-dimensional computed tomography-based treatment planning for intensity-modulated radiation therapy and proton therapy for distal esophageal cancer. Int J Radiat Oncol Biol Phys. 2008;72(1):278–87.
10. Wang J, Palmer M, Bilton SD, et al. Comparing proton beam to intensity modulated radiation therapy planning in esophageal cancer. Int J Particle Ther. 2015;1(4):866–77.
11. Wang J, Wei C, Tucker SL, et al. Predictors of postoperative complications after trimodality therapy for esophageal cancer. Int J Radiat Oncol Biol Phys. 2013;86(5):885–91.
12. 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(1):483–7.