International Journal of Radiation Oncology biology • physics

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Critical Review

Improving Outcomes for Esophageal Cancer using Proton Beam Therapy

Michael D. Chuong, MD,[*] Christopher L. Hallemeier, MD,[†] Salma K. Jabbour, MD,[‡] Jen Yu, PhD,[*] Shahed Badiyan, MD,[*] Kenneth W. Merrell, MD,[†] Mark V. Mishra, MD,[*] Heng Li, PhD,[||] Vivek Verma, MD,[§] and Steven H. Lin, MD, PhD[||]

Department of Radiation Oncology, University of Maryland Medical Center, Baltimore, Maryland; †Department of Radiation Oncology, Mayo Clinic, Rochester, Minnesota; ‡Department of Radiation Oncology, Rutgers Cancer Institute of New Jersey, New Brunswick, New Jersey; §Department of Radiation Oncology, University of Nebraska Medical Center, Omaha, Nebraska; and ||Department of Radiation Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas

Received Sep 30, 2015, and in revised form Nov 25, 2015. Accepted for publication Nov 30, 2015.

Radiation therapy (RT) plays an essential role in the management of esophageal cancer. Because the esophagus is a centrally located thoracic structure there is a need to balance the delivery of appropriately high dose to the target while minimizing dose to nearby critical structures. Radiation dose received by these critical structures, especially the heart and lungs, may lead to clinically significant toxicities, including pneumonitis, pericarditis, and myocardial infarction. Although technological advancements in photon RT delivery like intensity modulated RT have decreased the risk of such toxicities, a growing body of evidence indicates that further risk reductions are achieved with proton beam therapy (PBT). Herein we review the published dosimetric and clinical PBT literature for esophageal cancer, including motion management considerations, the potential for reirradiation, radiation dose escalation, and ongoing esophageal PBT clinical trials. We also consider the potential cost-effectiveness of PBT relative to photon RT.

Introduction

Esophageal cancer remains one of the deadliest cancers despite progress in the treatment of this disease over the past several decades. Worldwide there are an estimated 456,000 new esophageal cancer cases and 400,000 deaths annually (1). Although the incidence of esophageal cancer in the United States is lower than in many Asian and African countries, the annual number of expected American deaths from esophageal cancer (approximately 16,000) still rivals the predicted number of new diagnoses (approximately 18,000) (2).

For patients with locally advanced esophageal cancer deemed suitable for surgery, the standard treatment recommendation is neoadjuvant chemoradiation (CRT) followed by esophagectomy. This is based on prospective data showing

Reprint requests to: Steven H. Lin, MD, PhD, Department of Radiation Oncology, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Unit 097, Houston, TX 77030. Tel: (713) 563-8490; E-mail: shlin@mdanderson.org

Conflict of interest: none.

Int J Radiation Oncol Biol Phys, Vol. 95, No. 1, pp. 488–497, 2016
0360-3016/$ - see front matter
http://dx.doi.org/10.1016/j.ijrobp.2015.11.043

superior local control (LC) and overall survival (OS) compared with esophagectomy alone (3). For those who are not surgical candidates definitive CRT is recommended, which results in a significantly greater likelihood of survival at 5 years compared with radiation therapy (RT) alone (4). Thus, RT plays a central role in the treatment of locally advanced esophageal cancer regardless of surgical appropriateness.

Radiation therapy for esophageal cancer is challenging because of the central location of the esophagus within the thorax, resulting in a need to delicately balance minimizing radiation dose to nearby critical structures (ie, heart, lung, and spinal cord) while maintaining an effectively high dose to the target. Lung and heart doses in particular have been shown to increase the likelihood of pneumonitis, post-operative pulmonary complications (5, 6), heart wall motion abnormalities, coronary artery disease, pericarditis, and myocardial infarction (7-9).

Technological advances in RT delivery have led to an evolution in the treatment of esophageal cancer over the last half century by achieving increasingly better normal tissue sparing while maintaining accurate dose delivery to the target. In the era of 2-dimensional (2D) planning, generous treatment ports were used to ensure adequate target coverage, but 2D RT also exposed significant volumes of normal tissues to high doses and led to serious complications. Increasing conformity around the target resulting in superior normal tissue sparing was later achieved using 3-dimensional conformal RT (3D-CRT), and this was subsequently improved upon even further with the advent of intensity modulated radiation therapy (IMRT) (10-12). For example, Chandra et al (10) found that 7-field IMRT compared with 3D-CRT significantly reduced the percentage of lung receiving at least 10 Gy (V10) from 40.4% to 29.2% ($P=.01$), V20 from 19.3% to 13.5% ($P=.01$), and mean lung dose (MLD) from 14.8 Gy to 11.8 Gy ($P=.01$). This decrease in normal tissue dose achieved with IMRT has been suggested to result in clinically meaningful outcomes (13, 14). A study from MD Anderson Cancer Center reported a propensity score–adjusted comparison of long-term clinical outcomes between 3D-CRT and IMRT. Intensity modulated RT was associated with significantly higher OS, but there was no difference in cancer-related deaths or pulmonary-related deaths. The key difference was seen in the patients who received 3D-CRT, who had a significantly higher risk of cardiac-related deaths ($P=.049$) and other-cause deaths (72.6% vs 52.9%, $P<.0001$) (13). These data highlight that treatment outcomes are not only dependent on the ability to deliver adequate radiation dose to esophageal cancers, but that the overall health of the patient is directly affected by treatment-related toxicity. These toxicities could be further reduced using advanced treatment delivery technologies, such as IMRT and proton beam therapy (PBT). In fact, the physics of PBT is ideally suited for tumors of the esophagus as compared with photon RT because of the significantly reduced exit dose through the heart and lungs.

Proton beam therapy has historically been used to treat select cancers; however, a growing collection of studies suggest that PBT is not only safe and effective in treating esophageal cancer, but that the side-effect profile may also be improved over traditional photon-based techniques. Herein we review published dosimetric and clinical PBT literature for esophageal cancer, including some of the exciting potential applications of PBT that capitalizes on the toxicity sparing effects of PBT. We also consider the potential cost-effectiveness of PBT relative to photon-based techniques.

Dosimetric Comparison of Proton Versus Photon Therapy

Proton beam therapy has traditionally been delivered using a passive scattering technique, in which placing scattering material in the path of the proton beam spreads out a proton beam while compensators and collimators are used to conform dose to the target. The potential benefits of passive scattering proton therapy (PSPT) over 3D-CRT for esophageal cancer were suggested by a comparative treatment planning study published in 1998 (15). Both radiation modalities provided excellent target coverage, although sparing of the heart, lungs, spinal cord, and kidneys favored PSPT for all patients. The mean tumor control probability increased by a mean 20%-units (2%- to 23%-units) using the best proton plan, assuming a 5% normal tissue complication probability. On the basis of these data the authors predicted that radiation dose escalation above 40-50 Gy(RBE [relative biological effectiveness]) would be more feasible using protons. Passive scattering proton therapy was shown in a recently published dosimetric comparison with 3D-CRT to also be advantageous when prescribing a total dose of 60 Gy(RBE) in 30 fractions (16). Passive scattering proton therapy was delivered using an anterior–posterior/posterior–anterior (AP/PA) beam arrangement for most patients, whereas 3D-CRT was given using AP/PA and oblique beams to limit the spinal cord dose. Significant normal tissue sparing was achieved using PSPT, including lung V5-V20, mean lung dose, and heart V30-V50 ($P<.001$), and this translated into reduced cardiac and pulmonary morbidity based on normal tissue complication probability calculations. Dose escalation using PBT is more thoroughly discussed below.

Passive scattering proton therapy has been shown to reduce normal tissue dose compared with IMRT. Zhang et al performed a comparative planning study of 2-beam PSPT (AP/PA), 3-beam PSPT (AP/posterior obliques), and IMRT for distal esophageal or gastroesophageal junction (GEJ) cancer (17). The prescription dose was 50.4 Gy(RBE) in 28 fractions. Although target volume coverage was similar between all plans, PSPT delivered significantly less dose to the lung than IMRT. Not surprisingly, the ability to spare the lungs from doses less than