Review Article

Proton beam therapy for the treatment of esophageal cancer

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Abstract: Radiation therapy (RT) has become an important component in the curative management of esophageal cancer (EC) worldwide. Since most of the ECs seen in the Western hemisphere (i.e., Europe and the United States) are located in the mid- to distal-esophageal locations, heart and lungs invariably receive significant radiation doses. Much of the normal tissue exposure could be reduced with the utilization of advanced radiation technologies, notably intensity modulated radiation therapy (IMRT). Proton beam therapy (PBT) provides the ability to even further reduce normal tissue exposure because of its lack of exit dose, which is expected to provide clinically meaningful benefit for at least some EC patients. Herein, we provide an overview of the comparative effectiveness of proton versus photon therapy, summarize the published clinical experience, and describe the future outlook of PBT development in EC.

Keywords: Proton therapy; esophageal cancer (EC); trimodality therapy; intensity modulated radiation therapy (IMRT)

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Trimodality management as the standard treatment approach for esophageal cancers (ECs)

While around 450,000 new cases of EC are diagnosed worldwide each year, the number of annual deaths from EC is nearly as high (~400,000) (1). The incidence of EC varies worldwide by region, and is the highest in Asia and the Middle East where smoking and alcohol use are prevalent risk factors (2). In Western countries, adenocarcinoma (ACC) has surpassed squamous cell carcinoma (SCC) as the predominant EC histology, reflecting the high rates of obesity and gastroesophageal reflux disease (3).

Radiation therapy (RT) plays a critical role in the management of locally advanced EC. In surgically appropriate EC patients, neoadjuvant conformal radiation therapy (CRT) has increasingly become a standard of care in lieu of surgery alone. An Irish trial was the first to randomize patients to neoadjuvant CRT or surgery alone; 3-year overall survival (OS) significantly favored CRT (32% *vs.* 6%) (4). This trial has been criticized due to the poor survival in the surgery alone arm due in part to inadequate surgical resection and lymph node dissection, short median follow-up of 10 months, and suboptimal staging. Randomized trials from the University of Michigan (5) and Australia (6) reported no significant survival benefit with neoadjuvant CRT. In a United States cooperative group trial, 5-year OS was significantly higher with CRT followed by surgery compared to surgery alone (39% *vs.* 16%), despite the trial closing early due to poor accrual (7). The use of neoadjuvant CRT had not been widely adopted as a result of these mixed results; this was also despite support for CRT from a meta-analysis of ten randomized trials that concluded a significant survival benefit existed for CRT [HR 0.81; 95% confidence interval (CI), 0.70–0.93; P=0.002], and to

a lesser degree chemotherapy alone (HR 0.90; 95% CI, 0.81–1.00; P=0.05) (8). A larger meta-analysis for patients with esophageal ACC more recently arrived at a similar conclusion (9). The strongest evidence supporting the use of neoadjuvant CRT comes from a Dutch randomized trial, which is not only the largest of the randomized neoadjuvant CRT trials (n=366), but also importantly was performed in the modern era (10). Randomization was to surgery alone or neoadjuvant RT (41.4 Gy) and carboplatin/paclitaxel; median OS was significantly higher in the CRT arm (49.4 *vs.* 24 months). The long-term outcomes of this trial were recently published, and with median follow-up of 84.1 months in surviving patients, median OS was significantly better in the CRT arm (48.6 *vs.* 24 months; P=0.003) (11). In light of the CROSS trial results, CRT plays a critical role in the treatment of resectable EC.

Finally, CRT also plays a critical role in the management of non-metastatic EC patients who are not surgical candidates. Radiation Therapy Oncology Group (RTOG) 85-01 was a trial that randomized unresectable patients to receive either definitive CRT or RT alone and showed significantly higher 5-year OS in patients who received CRT (26% *vs.* 0%) (12,13).

The importance of radiation techniques on long-term morbidity/mortality in EC patients

Precision medicine mandates the proper selection of patients for specific therapies. Only with individualized approaches could the benefits outweigh the toxicities of such therapies. Since radiotherapy has become an integral component in the standardized management of EC, and given the fact that the majority of ECs in the Western hemisphere reside in the mid-to-distal locations, it is uniformly unavoidable that nearly all patients will have a significant dose exposure to the heart and lung structures. Radiotherapy delivery techniques become a critical factor in order to limit the radiation exposure to these vital organs. Thoracic radiotherapy, whether to the breast or lymphomas, has been long implicated in late onset of cardiovascular morbidity and mortality (14-16). A meta-analysis of randomized trials in women with breast cancer showed a 62% increase in cardiogenic mortality in patients treated with radiotherapy (17). In a population-based case-control study of 2,168 women treated with adjuvant radiotherapy for breast cancer, there was a 7% relative risk increase of developing cardiovascular events per 1 Gy mean dose to the heart (18). The risk was isolated to left sided breast cancer. An increased risk was observed as early as 4 years after exposure.

For EC, the evolution of 2-dimensional (2D) or 3-dimensional (3D) techniques to intensity modulated radiation therapy (IMRT) significantly reduces the exposure of the surrounding organs (19). There are no prospective randomized trials that are ongoing to assess the clinical importance of the observed dosimetric differences, so data are limited to single institutional observational datasets. A propensity matched analysis of single institutional dataset showed that IMRT *vs.* 3D conformal radiotherapy (3DCRT) significantly improved all-cause mortality and local control, but not in cancer specific, pulmonary, or distant metastatic disease (20). The notion that the difference in survival outcomes could be influenced by the radiation delivery techniques was not fully corroborated by another single institution data, which found no difference in OS except for reduced short-term toxicity (21). A recently published propensity score adjusted analysis was conducted using the Surveillance, Epidemiology, and End Results (SEER) and Texas Cancer Registry-Medicare linked databases for treatment outcomes of 2,553 non-metastatic EC patients treated with either 3DCRT (2,240 patients) or IMRT (313 patients) between 2002–2009 (22). The two cohorts were well balanced with regards to patient, tumor and treatment specific characteristics and variables. Using multivariate propensity score adjusted analysis, there was a significant improvement in OS, cardiac-specific survival, and "other" (non-cancer, pulmonary, or cardiac-specific) cause-survival in the IMRT group, but not for cancer-specific or pulmonary-related survival. The crude yearly rate of cardiac mortality remained constant over time at about 5% for the 3DCRT cohort, which was almost 5 times the rate seen in the IMRT cohort. While these analyses are only hypothesis-generating evidence at best, they do provide the best evidence to-date on the potential clinical impact that IMRT has on EC survival, possibly by the cardiac sparing effects of IMRT over 3D approaches.

Dosimetric comparison of protons and photons for EC

Except for cervical or proximal esophagus, proton beam therapy (PBT) may be the ideal beam delivery tool for mid and distal esophageal tumors since these tumors are surrounded by the heart anteriorly and the lungs bilaterally. This is simply because of the physics of charged particle

interaction with tissue, which results in the Bragg peak that is not seen for photon-based radiation. Whether 3DCRT or IMRT, photon radiation delivers exit dose through the vital organs in the thoracic cavity. PBT has excellent dosimetric parameters since it virtually has no exit dose, resulting in a substantial dose reduction to the lung and heart.

Dosimetric advantages of PBT compared to photon therapy for EC have been suggested by several studies. In 1998, Isacsson *et al.* suggested that PBT could better spare organs at risk (OARs) with potentially higher tumor control probability compared to 3DCRT; the authors also suggested that dose escalation may be more feasible using protons and there is mounting evidence that this is true (23). More recently, Makishima *et al.* found lung and heart doses to be lower in 44 EC patients using PBT compared to 3DCRT, which led to a reduction in normal tissue complication probability (24).

Advantages to using PBT have also been suggested when compared to IMRT. A study by Zhang and colleagues examined target volume coverage and OAR doses between 2-beam (AP/PA) PBT, 3-beam (AP/posterior obliques) PBT, and IMRT plans in 15 EC patients assuming a prescription dose of 50.4 Gy [relative biologic effectiveness (RBE)] in 1.8 Gy (RBE) fractions (25). While PBT and IMRT yielded similar target volume coverage, the lowest lung V5–V20 and mean lung dose (MLD) were achieved using PBT; this could reduce the risk of pulmonary complications, especially for the 2-beam PBT plans which delivered the lowest lung doses. The heart dose was higher in the 2-beam compared to the 3-beam PBT plan, however.

Investigators at Loma Linda University recently published a dosimetric comparison of 3DCRT, IMRT, and PBT for ten patients with distal esophageal or gastroesophageal junction (GEJ) cancers (26). In line with previous studies, PBT resulted in significantly lower dose to the lung, liver, heart, and spinal cord. Interestingly, the authors showed that PBT delivered lower dose not only to the entire heart but also the left anterior descending artery, left ventricle, pericardium; this may be clinically relevant based on data suggesting that cardiotoxicity risks are affected by dose delivered to particular regions of the heart (27). A large planning study was recently conducted comparing passively scattered proton therapy (PSPT) with IMRT in 55 patients with mid to distal EC (28). The cohort of patients all received PBT, along with optimized IMRT planning (29). Overall PBT was better than IMRT in lowering the mean lung and heart doses for nearly all cases.

Proton delivery techniques: PSPT versus pencil beam scanning (PBS) proton therapy

While the studies described above used PSPT, a more recently developed technique called PBS also has been shown to offer dosimetric benefits for EC patients compared to photon therapy, in large part due to greater proximal dose conformity (30,31). While dosimetric comparisons of PSPT and PBS are lacking for EC, a recent study found that PBS resulted in higher target volume conformity as well as reduced dose to the heart and liver compared to PSPT (32).

Only recently have PBS delivery systems become commercially available. PBS uses magnets to spatially steer the proton pencil beam in the x and y axis. Switching of the beam energy determines spatial position in the z axis. Compared to PSPT, PBS yields greater target conformity and lower integral dose proximal to the target volume. Additionally, PBS allows use of intensity modulated proton therapy (IMPT), in which each field delivers a non-uniform weighting of spots, based on specified optimization goals.

Several challenges exist in the implementation of PBS for EC. Because the scanning beam delivers dose to the target volume in spatially discrete "spots" over a treatment time of a few minutes, intrafractional motion of the target volume may result in significant heterogeneities in the dose delivered within the target volume (33,34). Additionally, changes in tissue density along the beam path can impact proton range, resulting in target volume dose deficiencies and/or excess dose in normal tissues (32,35). This is especially significant at the dome of the diaphragm, where, depending on the phase of the respiratory cycle, a beam in fixed position may traverse mostly air (lung) or soft tissue (diaphragm). These issues may be mitigated with careful planning (32,36).

Patient positioning and immobilization devices should be designed to minimize setup uncertainty. A 4-dimensional computed tomography scan should be performed to assess and address movement of the target volume and diaphragm (37,38). Respiratory gating may be utilized to minimize internal motion of the target, especially when the target volume extends into the stomach. Respiratory gating may also minimize variation in tissue density/proton stopping power along the beam path. Beam angles should be carefully selected to minimize respiratory cycle-related changes in water equivalent tissue; posterior/posterior oblique beams that pass through the spine and medial diaphragm are most robust against water equivalent thickness changes during

the respiratory cycle. Use of multiple beams and repainting techniques may also improve plan robustness by minimizing the overall impact of motion interplay effects on plan integrity (32,36,39,40).

Clinical experience of PBT for the management of ECs

The clinical experience PBT for EC has been limited to institutional studies. The initial experiences reported from the University of Tsukuba were with PBT alone without chemotherapy (41). The most recent update included 51 patients treated between 1985 to 2005, with hybrid photon therapy to 46 Gy and a proton therapy boost to 80 Gy (RBE) (42). Recently, this group reported their experience of proton beam with concurrent chemotherapy with cisplatin/5FU (43). Forty consecutive patients were treated to 60 Gy (RBE) after an initial 40–50 Gy (RBE) to a larger field using an AP/PA beam arrangement. All were treated with definitive therapy without surgery. No grade 3 or higher cardiopulmonary toxicities were reported. The 3-year OS was 70%, and the 2-year DFS was 77% and locoregional control was 66%.

Recently, investigators from the University of Texas MD Anderson Cancer Center reported initial experiences of PBT with chemotherapy for EC. The preliminary experience involving 62 patients was published in 2012 (44). Most had ACCs (76%) with stage II–III disease (84%). Nearly all patients were treated to 50.4 Gy (RBE) in 28 fractions. Preoperative therapy was given for 47% of the patients. Treatment was well tolerated with limited grade 3 toxicities. There was one case each of grade 2 and 3 radiation pneumonitis, respectively. The 3-year OS, relapse-free, distant metastatic, and local regional free survival were 51.7%, 40.5%, 66.7%, and 56.5%, respectively. In a second study confined to preoperatively treated patients, the incidence of postoperative pulmonary, cardiac, wound and gastrointestinal (GI) complications was evaluated in patients treated with neoadjuvant chemoradiation from 1998 to 2011 (45). During this period, 444 patients were treated with 3DCRT [208], IMRT [164] or PBT [72]. On univariate analysis, the radiation modality used was significantly associated with pulmonary and GI complications. In the multivariate analysis (MVA), only radiation modality and pre-radiation Diffuse Capacity of the Lung for carbon monoxide (D_{LCO}) were independently associated with pulmonary complications. Radiation modality was not significantly associated with risk of GI complications on MVA. The risk of postoperative pulmonary complications was seen when 3DCRT was compared to IMRT [odds ratio (OR), 4.10; 95% CI, 1.37–12.29] or 3DCRT was compared to PBT (OR 9.13; 95% CI, 1.83–45.42), but there was no statistically significant difference for IMRT *vs.* PBT (OR 2.23; 95% CI, 0.86–5.76). MLD was most predictive of pulmonary toxicities, and when MLD was added into the multivariable model, radiation modality no longer was significantly associated with pulmonary toxicities. It is hypothesized that advanced technologies like PBT or IMRT, as compared to 3DCRT, deliver a lower MLD that translated to lower risk of pulmonary complications.

Clinical trials of PBT for EC

To date, there have been no published prospective clinical trials evaluating the adverse events and efficacy of PBT for EC; however, there are several ongoing trials in the United States. Single arm prospective studies are assessing pre-operative PSPT (Loma Linda University, NCT01684904) or PBS PBT (Mayo Clinic, NCT02452021) with concurrent carboplatin and paclitaxel prior to esophagectomy. Investigators at the University of Pennsylvania are conducting a phase I trial of escalated dose PBT and carboplatin/paclitaxel prior to esophagectomy (NCT02213497). Investigators at MD Anderson Cancer Center are leading a phase IIb randomized trial comparing PBT and IMRT for patients with EC (NCT01512589). The primary endpoints are progression-free survival and total toxicity burden, which is a composite endpoint including serious adverse events and postoperative complications. Results from these prospective clinical trials will greatly improve our knowledge regarding the role of proton therapy for EC.

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Footnote

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