Helical Tomotherapy For Radiochemotherapy In Esophageal Cancer: A Preferred Plan?

Gary Y. Yang, MD

The addition of systemic chemotherapy to local radiation therapy in the non-surgical management of esophageal cancer has offered the opportunity for long-term survival (1). However, this survival benefit has come at the cost of increased side effects. The standard dose of radiation remains up to 50 Gy in the definitive or pre-operative setting despite previous attempts to dose escalate (2). Even at this modest dose, the majority of concurrent chemoradiation patients experience grade 3 or higher toxicities when utilizing conventional radiation techniques. When concurrent chemotherapy and radiation are delivered neoadjuvantly, the combination appears to increase resectability, produce tumor downstaging and may impact local control, disease-free survival, and overall survival (3-5). This tri-modality approach, while relatively effective, has been shown with peri-operative rates of toxicity of 11-12% (6). The esophagus is a centrally located structure, surrounded by the lungs, normal esophagus, heart and spinal cord. For the treating radiation oncologist, achieving adequate dose to the gross tumor volume and adjacent clinical targets while limiting dose to the surrounding critical normal tissues represents a therapeutic challenge.

Emerging radiation technologies are aimed at improving that therapeutic ratio in this disease where the results remain modest at best, and morbidity is significant. Intensity modulated radiation therapy (IMRT) offer the opportunity to "shape" radiation dose, optimally sparing normal tissue while allowing adequate coverage to tumor volumes. Dosimetrically, the use of IMRT could be of benefit in the treatment of esophageal cancer where the target is surrounded by radiosensitive tissues. Helical tomotherapy is a form of IMRT delivered on a continuous helix, with the source being collimated to a fan beam which is modulated with a binary multi-leaf collimator (7). During treatment, the patient is moved through a ring gantry resulting in a helical beam delivery. Image-guidance is in the form of daily pre-treatment megavoltage CT. In this issue of the Journal of Thoracic Disease, Chen et al. report their results utilizing helical tomotherapy in the definitive and pre-operative management of patient with locally advanced esophageal cancer (8). To date, there is very limited published data on the use of tomotherapy in esophageal cancer. On the basis of dosimetric analysis, one previous study by Chen et al. found that based on isodose distributions and dose-volume histograms (DVHs), tomotherapy allowed for sharper dose gradients, more conformal coverage, and better homogeneity when compared with step-and-shoot IMRT or 3D-Conformal Radiotherapy (3D-CRT) (9). In addition the volume of lung receiving at least 20 Gy (V20) and the volume of heart receiving V30 and V45 were significantly reduced with tomotherapy. It is notable; however, that tomotherapy resulted in larger lung volume receiving V10 when compared to 3D-CRT.

In the current study, 20 consecutive patients are treated with concurrent chemoradiation, with ten receiving definitive 10 patients receiving definitive therapy and 10 going on to surgery. The total dose to the gross disease was 50 Gy in standard fractionation, with 45 Gy delivered simultaneously to the regions of subclinical disease, while surrounding normal tissue limits were established prior to

Department of Radiation Medicine, Roswell Park Cancer Institute, Buffalo, NY

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Address for correspondence: Gary Y. Yang, MD, Associate Professor, Director, GI Radiation Oncology, Department of Radiation Medicine, Roswell Park Cancer Institute, Buffalo, NY 14263. USA.Tel: (716) 845-3296; Fax: (716) 845-7616 Email: gary.yang@roswellpark.org

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planning. All patients were able to complete the prescribed chemoradiation with 60% of patients receiving definitive treatment achieving radiographic complete response (cCR). In addition, 20% of patients undergoing esophagectomy had a pathologic CR, with another 40% (4/10) having only microscopic disease. The overall survival rates for the entire cohort, the definitive chemoradiation, and tri-modality group were 64.3%, 50.0%, and 78.8% respectively. The rate of acute grade 3 toxicity was 45%, while post-operative morbidity was seen in 60% of patients, including 5 anastomotic leaks and 2 cases of pneumonitis.

The outcomes from this single institution study compare favorably with published studies evaluating both definitive chemoradiation and tri-modality therapy. In addition, the rate of grade 3 acute toxicity is promising. It is also worth noting that of 8 patients planned from the start of therapy to undergo neoadjuvant chemoradiation follow by esophagectomy, 7 of those patients were able to complete that prescribed regimen. As the authors alluded to in the discussion, the location of the esophagus as a central structure in the thorax allows for maximal conformal benefit of the tomotherapy technology. In addition, normal tissue is further spared by field margin reduction on the target that is permitted by utilizing daily axial imaging.

Helical tomotherapy appears well-suited for the definitive non-surgical management of locally advanced esophageal cancer. Dosimetric analysis has shown tomotherapy's ability to reduce lung V20 and cardiac V30 and V45, dosimetric parameters used to predict treatment toxicity (9). Among patients receiving non-surgical management, this has translated to a favorable outcome and toxicity profile in the current study. There may be slightly more hesitation regarding its widespread use for neoadjuvant therapy. When chemoradiation is followed by esophagectomy, it appears that different dosimetric parameters may need to be considered. In particular, the dose and volume of lung irradiation need to be strongly considered. Pulmonary toxicity in the setting of esophagectomy is critical as evidenced by one study reporting a 15% rate of significant pulmonary complications that accounted for 55% of mortality following esophagectomy (10). As mentioned in the current study, Lee et al. found that with tri-modality therapy, the dose-threshold for lung volume may be less than expected for non-surgical treatment, with pulmonary complications noted more often (35% vs. 8%, $p = 0.014$) when the pulmonary V10 was at least 40% vs. less than 40% and when the V15 was at least 30% vs. less than 30% (33% vs. 10%, $p = 0.036$) (11). A follow-up study by Wang et al. found on multivariate analysis that the volume of the lung spared from doses of at least 5 Gy was the only independent dosimetric factor predictive of pulmonary complication (12). These data suggest that small doses of radiation, previously felt to be relatively meaningless, affect the rate of post-operative pulmonary complication and may negatively impact on peri-operative morbidity and mortality. By the helical nature of tomotherapy dose delivery small amounts of radiation are deposited in a relatively large portion of normal tissue depending on tumor location and size. The authors have identified this potential hazard and in found the 2 cases of post-operative pulmonary complications that the patients had a V10 of at least 40%.

Overall, the results of this study are promising and warrant further investigation. This technology may allow for dose escalation where previous studies have failed to demonstrate a benefit. Local failure continues to be a concern in these patients and perhaps further study of dose escalation with modern technology may improve upon those results. Additionally, its use in tri-modality therapy should be further investigated as meaningful dosimetric parameters of normal tissue toxicity continue to be developed and refined.

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