

Impact of neoadjuvant proton vs. photon chemoradiotherapy (CRT) on post-operative outcomes in patients with esophageal cancer treated with trimodality therapy – a multi-institutional analysis

Christopher L. Hallemeier, M.D.¹ Michael Chuong, M.D.² Kenneth W. Merrell, M.D.¹ Sarah E. James, M.D., Ph.D.¹
Michael G. Haddock, M.D.¹ Neha Bhooshan, M.D., Ph.D.² Minesh Mehta, M.D.² Arlene M. Correa, Ph.D.³ Zhongxing
Liao, M.D.³ Reza Mehran, M.D.³ Steven H. Lin, M.D., Ph.D.³

¹Mayo Clinic, Rochester, MN, USA

²University of Maryland, Baltimore, MD, USA

³The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Background: For esophageal cancer, proton radiotherapy (RT) delivers lower dose to organs at risk, compared to photon RT. The purpose of this analysis was to compare post-operative outcomes in esophageal cancer patients treated with neoadjuvant photon vs. proton CRT. We hypothesized that neoadjuvant proton (vs. photon) CRT would be associated with similar surgical oncologic outcomes, a lower rate of post-operative complications, and improved overall survival (OS).

Materials/Methods: This was a multi-institutional retrospective analysis of patients with locally advanced, non-metastatic esophageal cancer who underwent curative-intent esophagectomy following neoadjuvant CRT between 2007 and 2013. RT modality was classified as photon (3D conformal or intensity modulated RT) or proton. Chi-Square or Fisher's exact tests assessed associations between RT modality and margin negative resection (R0) rate, pathologic complete response (pCR) rate of the primary tumor, post-operative complications (pulmonary, gastrointestinal, cardiac, and wound healing), hospital length of stay (LOS), and 90 day postoperative mortality. OS was calculated from the date of surgery using the Kaplan-Meier technique. Univariable (UVA) and multivariable (MVA) Cox models assessed for association between patient/treatment covariates and OS.

Results: The analysis included 582 patients. RT modality was photon in 471 (81%, including 44% IMRT and 37% 3D) and proton in 111 (19%) patients. Median age was 61 years. Histology was adenocarcinoma in 92%. Median RT dose was 50.4 Gy. Surgical approach was open thoracotomy and/or laparotomy in 98%.

R0 resection was achieved in 95% for photon and 96% for proton (p=0.8). pCR rates were 32% for photon and 31% for proton (p=0.9). Post-operative complication rates are summarized in the table.

Outcome	Photon (n=471)	Proton (n=111)	p-value
Hospital LOS, mean, days	12	9	<0.0001
Post-operative complications, %			
Cardiac	19	12	0.10
Pulmonary	28	14	0.003
Gastrointestinal	22	19	0.5
Wound	15	5	0.002
Any	56	41	0.005

Median follow-up after surgery was 2.3 (range 0.1 – 7.4) years. Mortality rates at 90 days were 4.2% for photon and 0.9% for proton (p=0.15). On UVA, proton RT was associated with reduced risk of death (HR=0.67, 95% CI 0.46-0.97, p=0.03), compared to photon RT. OS at 3 years was 70% for proton vs. 58% for photon. On MVA, age (p=0.01), clinical stage (p=0.04), tumor grade (p<0.001), and pCR (p=0.001) were associated with risk of death, while RT modality (photon v. proton) was not.

Conclusions: Neoadjuvant proton RT was associated with a lower rate of post-operative complications and shorter hospital LOS, compared to photon RT. OS was superior with proton vs. photon RT, although this difference was not statistically significant in the MVA model.