Radiation Pneumonitis: Proton Therapy Local Dose Response and Clinical Symptoms

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Abstract

Radiation pneumonitis (RP), a major toxicity following thoracic radiotherapy (RT), is expected to diminish with proton therapy. RP due to MV x-ray RT appears on FDG PET imaging as metabolic enhancement within the lungs with a linear dose response**.** This study evaluates the relationship between local proton radiation dose and pulmonary toxicity in esophagus cancer patients. 96 patients treated with chemoradiotherapy were selected for this study. Their treatment planning CT was registered with the restaging PET/CT. The lung standard uptake values (SUV) were evaluated using a slope of the normalized SUV versus radiation dose which corresponded to the pulmonary metabolic radiation dose response (PMRR). CTCAEv4 clinical RP scores were and modeling was performed to determine correlations between PMRR, standard dosimetric parameters, and RP clinical outcomes. Regression modeling of the normalized SUV vs proton dose found adequate correlation between these two variables, with mean PMRR values of 0.020 and 0.011 for the symptomatic and asymptomatic respectively. Dosimetric parameters were also found to be significantly higher for the symptomatic group. The dose response reported in this study is similar to to that seen for MV x-ray RT and may be used to estimate the proton Relative Biological Effectiveness (RBE) for RP.

Introduction

The use of proton therapy to treat a variety of cancer locations, particularly those of the thorax, has increased in recent years. One of the downfalls of conventional X-ray therapy is that treatment often injures functional portions of the lung that are not involved in the disease volume which needs to be treated[1]. The presumed benefit of proton therapy comes from the fact that, unlike X-ray, the maximal dose can be concentrated to the desired region at the Bragg peak, with minimal exposure to the tissue beyond[2], several studies have reported improvement of local control and disease-free survival with the use of proton therapy[3]. However, most toxicity reports in the current literature are reliant on subjective data and treatment planning correlations[4]. To date, there has not been an effective method of objectively measuring pulmonary reaction to injury after radiation in proton therapy.

Radiation pneumonitis (RP) is among the most severe complications that can occur with thoracic radiation therapy[5]. RP is an inflammatory reaction that takes place within lung tissue in response to radiation damage[6]. This process can be observed using [^{18}F]-fluorodeoxyglucose positron emission tomography.

At the University of Texas M. D. Anderson Cancer Center, patients with esophageal cancer routinely undergo restaging FDG PET/CT 6 weeks after chemoradiation therapy to identify patients with interval metastases[7]. In this study, we want to evaluate the relationship between local proton radiation dose and pulmonary toxicity in esophagus cancer patients.

Materials and Methods

Ninety-six patients treated with chemoradiotherapy at The University of Texas MD Anderson Proton Therapy Center for esophageal cancer who received restaging FDG PET/CT imaging were selected. Each received between 45 and 60.6 Co-60 Gy equivalent (CGE, median 50.4) in 1.8 CGE fractions and FDG PET/CT imaging between 21 and 86 days after proton therapy.

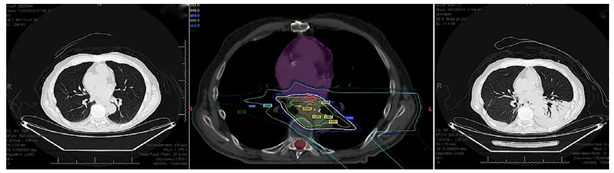

Figure 1: Left – Axial CT Planning image of esophageal cancer patient prior to undergoing Proton RT. Middle – Axial Proton RT dose map and plan. Right – Restaging CT shows consolidation and effusion in the dose field of the left lung.

CT Planning images and the restaging FDG PET/CT was imported into MatLab (MathWorks, Natick, MA) and manual segmentation of the lungs was performed on each CT volume. A pulmonary segmentation algorithm[8], based on an eight-point connectivity scheme and a set of three seed points, was applied to each treatment planning CT image set. A robust affine registration was used on the treatment planning CT and the PET/CT CT images. The registered images were visually verified, and minor adjustments of less than 1 cm along each axis were made to improve the registration of the lung regions. The standard uptake values (SUV) were calculated from the PET count rate by using the following equation:

$$Standard\ Uptake\ Value = \frac{^{18}F\text{-}FDG\ count\ rate\ per\ mL \times body\ weight\ (g)}{decay\text{-}corrected\ ^{18}F\text{-}FDG\ injected\ dose\ (Bq)}$$

The slope of the normalized SUV versus radiation dose, referred to as the pulmonary metabolic radiation dose response (PMRR), was evaluated for each case with regression modeling. Histograms were formed of the FDG PET count rate versus radiation dose in 2-Gy intervals by using the following equation:

$$Normalized\ ^{18}F\text{-}FDG\ Uptake = \frac{count\ rate\ irradiated\ lung\ per\ mL}{count\ rate\ non\text{-}irradiated\ lung\ per\ mL}$$

Deviation of the dose response from a linear model was tested for each case. CTCAEv4 clinical RP scores were obtained from the consensus of 6 clinicians. Modeling was performed to determine the interaction of the PMRR with standard dosimetric parameters (MLD, V_5, V_{10}, and V_{20}) and RP clinical outcomes.

Results

Hierarchical regression modeling of the normalized SUV versus proton dose per case found an adequate fit with linear models (Figure 2).

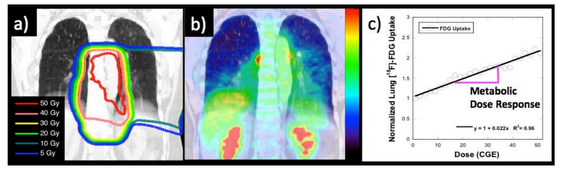

Figure 2. FDG PET proton therapy dose response. a) Coronal section through the treatment planning CT and proton therapy isodose distribution for an esophagus cancer patient. **b)** Corresponding section through the post-treatment restaging [^{18}F]-FDG PET/CT image, obtained approximately 6 weeks after completion of proton therapy. **c)** The normalized FDG uptake response versus proton therapy dose, given in cobalt-60 Gy equivalents (CGE), is shown for this case along with the linear regression result. The FDG uptake response is normalized to the unirradiated (0 – 2 CGE) lung response allowing each case acts as its own internal control. This individual's dose-response is best characterized by the slope, which we refer to as the pulmonary metabolic radiation dose response (PMRR).

The RP CTCAEv4 toxicity scores were: 0 grade 4/5, 7 grade 3, 20 grade 2, 35 grade 1, and 34 grade 0. Dosimetric, PMRR, and mean SUV per 10 Gy bin values are summarized by symptomatic (CTCAEv4 grade ≥ 2) and asymptomatic groups in the table.

	N	MLD	V5	V10	V20	PMRR	SUV_{0-10}	SUV_{10-20}	SUV_{20-30}	SUV_{30-40}	SUV_{40-50}
Asymptomatic	69	5.29	23.29	19.37	10.74	0.011	0.65	0.78	0.88	0.97	1.02
Symptomatic	27	7.80	34.89	27.38	15.96	0.020	0.69	0.85	0.98	1.13	1.24
p-value	-	0.0001	<0.0001	<0.0001	<0.0001	0.006	0.797	0.681	0.144	0.115	0.058

(All dose values are in CGE = 1.1 × Gy and the PMRR's in CGE^{-1}.)

Each dosimetric parameter was significantly higher for the symptomatic group. The mean PMRR was 0.020 for the symptomatic and 0.011 for the asymptomatic (p=0.006).

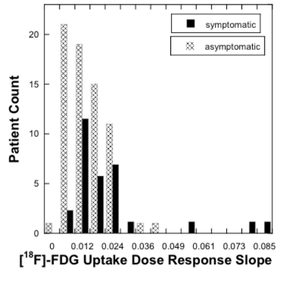

Figure 3. Distribution of the pulmonary metabolic radiation dose response (PMRR). A linear regression was applied to the normalized FDG uptake response versus proton therapy dose for each of the 96 esophagus cancer cases studied in this study. The patient records were reviewed and scored for symptomatic pneumonitis using CTCAEv4. Symptomatic (CTCAEv4 grade ≥ 2) and asymptomatic groups were formed and their distributions are shown in histogram plot. The symptomatic group was found to have significantly higher PMRR values (p = 0.006).

On cross-validation combining dosimetric parameters with the PMRR had a greater sensitivity and accuracy identifying RP symptomatic cases than either alone.

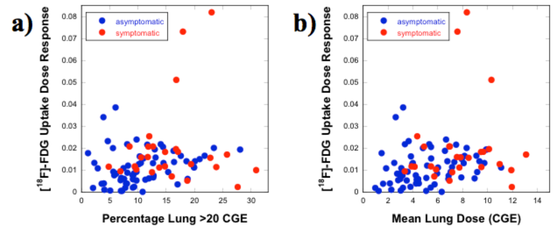

Figure 3. Combining dose-volume with metabolic dose response. Toxicity analysis based on pulmonary metabolic radiation response (PMRR) and mean lung dose (MLD). **a)** Plot of toxicity outcome by PMRR and MLD. The lines delineate regions for which there is an 80% probability of grade 2 or higher toxicity. **b)**. Plot of toxicity outcome by PMRR and V20. The lines delineate regions for which there is an 80% probability of grade 2 or higher toxicity.

Conclusion

The proton therapy RP dose response on FDG PET/CT imaging exhibited a linear relationship on statistical modeling. Symptomatic patients had a significantly (p=0.006) higher dose-response slope (or PMRR) than asymptomatic patients. This dose response is similar to that reported for MV x-ray RT[10] and together they may estimate the proton RBE for RP.

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Acknowledgements: This presentation is supported by the National Cancer Institute through the U54 CA096297/CA096300: UPR/MDACC Partnership for Excellence in Cancer Research Training Program. For further information, please contact Vincent Bernard at vbernar12@gmail.com.