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Original article

Pre-treatment non-target lung FDG-PET uptake predicts symptomatic radiation pneumonitis following Stereotactic Ablative Radiotherapy (SABR)

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ABSTRACT

Purpose: To determine if pre-treatment non-target lung FDG-PET uptake predicts for symptomatic radiation pneumonitis (RP) following lung stereotactic ablative radiotherapy (SABR).
Methods: We reviewed a 258 patient database from our institution to identify 28 patients who experienced symptomatic (grade $\geqslant$ 2) RP after SABR, and compared them to 57 controls who did not develop symptomatic RP. We compared clinical, dosimetric and functional imaging characteristics between the 2 cohorts including pre-treatment non-target lung FDG-PET uptake.
Results: Median follow-up time was 26.9 months. Patients who experienced symptomatic RP had significantly higher non-target lung FDG-PET uptake as measured by mean SUV ($p < 0.0001$) than controls. ROC analysis for symptomatic RP revealed area under the curve (AUC) of 0.74, with sensitivity 82.1% and specificity 57.9% with cutoff mean non-target lung SUV > 0.56. Predictive value increased (AUC of 0.82) when mean non-target lung SUV was combined with mean lung dose (MLD). We developed a 0–2 point model using these 2 variables, 1 point each for SUV > 0.56 or MLD > 5.88 Gy equivalent dose in 2 Gy per fraction (EQD2), predictive for symptomatic RP in our cohort with hazard ratio 10.01 for score 2 versus 0 ($p < 0.001$).
Conclusions: Patients with elevated pre-SABR non-target lung FDG-PET uptake are at increased risk of symptomatic RP after lung SABR. Our predictive model suggests patients with mean non-target lung SUV > 0.56 and MLD > 5.88 Gy EQD2 are at highest risk. Our predictive model should be validated in an external cohort before clinical implementation.
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Stereotactic ablative radiotherapy (SABR) has become an increasingly common definitive treatment for early stage non-small cell lung cancer (NSCLC) and lung oligometastases [1–7]. However, toxicity remains a concern, with radiation pneumonitis (RP) being a potentially serious treatment related toxicity in some patients [8–13]. Symptoms of RP include dyspnea, cough, decreased pulmonary function, and can lead to significant morbidity and mortality [14,15]. Retrospective studies have demonstrated that dosimetric factors including mean lung dose and V20 increase the risk of RP after SABR, but with relatively poor predictive ability [10,13,16–21]. Studies have been published which utilize

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pre-treatment or early-treatment functional imaging characteristics of non-target lung parenchyma to predict symptomatic RP after conventionally fractionated radiotherapy [15,22–25]. Other studies have shown that the pre-treatment finding of interstitial lung disease on computed tomography (CT) correlates with increased susceptibility to symptomatic RP [26–30]. To our knowledge, no study has yet utilized functional imaging characteristics of non-tumor lung to predict symptomatic radiation pneumonitis after SABR.

Here we retrospectively analyze clinical, dosimetric and fluorodeoxyglucose positron emission tomography (FDG-PET) characteristics of patients in our institution treated with SABR for lung tumors. We show that pre-SABR non-target lung FDG-PET uptake correlates with risk of symptomatic RP after SABR, and could be used for risk stratification. We develop a predictive model for symptomatic RP that incorporates both non-target lung FDG-PET uptake and SABR dosimetric parameters.

Methods and materials

Patients

We conducted a retrospective review of patients with lung tumors treated with SABR using intensity-modulated radiotherapy (IMRT) at the Stanford Cancer Center between May 2000 and August 2014, with institutional review board approval. All patients had biopsy-proven primary or metastatic lung tumors, and the majority had pre-treatment FDG-PET-computed tomography (PET-CT). Imaging was performed within 1 month of starting SABR.

PET-CT imaging

PET-CT imaging was performed within 1 month of starting SABR for the majority of patients as part of initial staging and/or radiation treatment planning. Our treatment planning PET-CT imaging protocol has previously been described [31]. Briefly, following an 8 h fast, patients were injected with 10–18 mCi of FDG, and imaged 45–60 min later on a GE Discovery PET-CT scanner (GE Medical Systems, Milwaukee, WI) or a Siemens Somatom Definition AS+ PET-CT scanner (Siemens Healthcare, Mountain View, CA). Reported blood glucose levels were between 80 and 160 mg/dl at time of injection. We performed helical CT scan for attenuation correction.

SABR and dosimetry

For a subset of patients, generally those with lower lobe tumor location, peri-tumoral metallic fiducial markers were implanted prior to treatment to facilitate image-guided tumor localization during treatment [32]. During radiotherapy simulation, customized immobilization devices were formed for each patient, and 4-dimensional CT (4-D CT) and PET-CT acquired in the treatment position. The treating physicians contoured the gross tumor volume (GTV) on axial CT slices using lung windows, with the aid of fused PET scan. Respiration-induced tumor motion was assessed by analyzing the 4-D CT, managed by respiratory gating or motion-inclusive technique, and used to design the internal target volume (ITV). A 0.5 cm margin was added to the ITV to form the planning target volume (PTV). Contouring of heart, lungs and other thoracic organs at risk was performed in accordance to RTOG guidelines [33].

Treatment was delivered as 15–60 Gy in 1–8 fractions using 6 or 10 MV photons on one of three image-guided SABR treatment systems: the CyberKnife (Accuray Inc., Sunnyvale, CA) using the Synchrony dynamic tumor tracking system, the Trilogy (Varian Medical Systems, Palo Alto, CA), or the TrueBeam STx (Varian Medical Systems, Palo Alto, CA). Daily kilovoltage (kV) X-ray portal imaging and cone-beam CT were performed just prior to treatment delivery for anatomy-based matching. Treatment planning goals included covering at least 95% of the PTV with the prescription dose, and centering the point of maximum dose (at least 120% of the prescription dose) inside the GTV. Heterogeneity corrections were used routinely for dose calculations.

Follow-up and outcomes assessment

Patients were followed by physical exam and diagnostic CT of the thorax and/or PET-CT every 2–3 months for the first year, every 4 months for the second year, every 6 months for the third year, and yearly thereafter. Overall Survival (OS) was assessed by review of patient records and the Social Security Death Index. We graded radiation pneumonitis using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. For the purpose of this analysis, symptomatic RP was defined as CTCAE grade $\geqslant 2$ at any point during the follow-up period, and no symptomatic RP was defined as CTCAE grade 0–1 throughout the follow-up period.

Dosimetric and PET-CT analysis

We compared 28 patients who experienced symptomatic radiation pneumonitis (RP) with 57 control patients who did not experience symptomatic RP. These 57 control patients were representative of the entire non-RP cohort of 226 patients, with no significant differences detected by Chi-Square and Fisher exact testing of multiple patient, tumor and treatment characteristics (Table S3). For the 28 symptomatic RP patients and 57 controls, we performed dosimetric and FDG-PET uptake analyses. Mean lung dose and lung V20 (percentage of lung parenchyma receiving at least 20 Gy) were calculated with appropriate dose heterogeneity corrections, and doses were converted to equivalent dose in 2 Gy per fraction assuming an α/β ratio of 3 for late effects (EQD2). Tumor maximum standardized uptake value (SUV) was measured and recorded from pre-treatment FDG-PET scan. PET-CT and treatment planning CT fusion and associated lung contours were confirmed; total lung minus PTV (non-target lung) and ipsilateral non-target lung were constructed using the Boolean contouring tool in MIM version 6.1 (MIM Software, Cleveland, OH) which allowed for volumetric subtraction of clinician-generated contours [34]. FDG-PET uptake of the non-target lung was measured, and the following values were recorded—SUV85 (85th percentile SUV), SUV90 (90th percentile SUV), SUV95 (95th percentile SUV), and mean SUV. All contouring and dosimetric analysis was performed using MIM version 6.1.

Statistical analyses

Univariate and multivariate hazard ratios (HR) were calculated via Cox regression analysis with corresponding Wald 95% confidence intervals and p-values, adjusted for the competing risk of death. Hazard ratios for our PET uptake variables are expressed per 0.1 unit increase. Differences between treatment groups were assessed with student's *t*-test when comparing continuous variables, or Fisher's exact test or Chi-square test when comparing discrete variables. We also performed logistic regression with receiver operating characteristic (ROC) analyses and calculated area under the curve (AUC). We used Youden's J statistic to identify the optimal cut-off point for our ROC analyses. Our scoring model was applied to a weighted version of our experimental cohort with each control represented four times in order to estimate incidence in the entire treated population, using the cumulative incidence function adjusted for the competing risk of death with comparison of arms using Gray's test for equality. A linear Cox model adjusted for the

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