Changes in post-treatment cardiac PET avidity predict overall survival in lung cancer patients treated with chemoradiation: Secondary analysis of the ACRIN 6668/RTOG 0235 clinical trial

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Abstract

The purpose of this work was to use data from a large co-operative group trial to evaluate whether metabolic FDG-PET changes in the heart for lung cancer patients can predict for clinical outcomes. The study found that cardiac SUV changes following definitive chemoradiation are significantly (HR 0.811, 95% CI 0.68–0.96, \( p = 0.017 \)) associated with overall survival in locally advanced NSCLC patients. If validated in a prospective cohort, our data show the potential for cardiac metabolic changes to be an early predictor for clinical outcomes.

Keywords

Lung cancer; Functional imaging; Cardiac toxicity

The clinical impact of higher radiation doses to the heart has been demonstrated in previous studies, namely decreased overall survival (OS), cardiac toxicity, and lung toxicity [1-4]. The Radiation Therapy Oncology Group (RTOG) 0617 dose escalation study for patients with locally advanced non-small cell lung carcinoma (NSCLC) found that increased heart dose was significantly associated with a decrease in OS based on multivariate analysis [1].

Positron emission tomography (PET), which utilizes a fluorodeoxyglucose (FDG) radioactive tracer for measurement via standard uptake values (SUV), is a standard imaging modality in lung cancer management used for detection of disease, staging, and assessment of response to treatment [5]. Although typically used to evaluate primary tumors and
affected lymph node basins, SUV measurements can be used to evaluate the response of normal tissues to treatment [6-9]. FDG-PET imaging is an accepted diagnostic tool to evaluate cardiac inflammation [8,10,11]. In addition, FDG-PET has been used to evaluate the response of normal tissue to treatment, including normal lung in lung cancer patients, the heart in esophageal cancer patients, and the parotid glands in head and neck cancer patients [6,7,9,12-15].

ACRIN 6668/RTOG 0235 was a multicenter clinical trial that assessed the prognostic value of tumor-based functional imaging, in particular FDG-PET, in patients with inoperable locally advanced NSCLC following definitive chemoradiation [17]. The purpose of this work was to use the ACRIN 6668/RTOG 0235 FDG-PET imaging data to evaluate the ability of cardiac functional imaging to predict for clinical outcomes using a large patient cohort of NSCLC patients.

Materials and methods

The study design of ACRIN 6668/RTOG 0235 has been described previously [17]. In brief, 239 patients were enrolled on the study which included adults >18 years with stage IIB to III (using 1997 AJCC staging criteria) NSCLC treated with definitive chemoradiation. Patients had a Zubrod performance status of 0–1. Patients with small-cell lung carcinoma and bronchoalveolar subtype were excluded from the study. Patients received radiation with >60 Gy and concurrent platinum-based doublet chemotherapy without surgery. Maintenance chemotherapy was allowed on the trial. All patients had pre-treatment FDG-PET or FDG-PET/CT on a scanner qualified by the American College of Radiology Imaging Core Laboratory. Conventional modern equipment and time correction for FDG-PET were used in the study. Patients had to fast for >4 h and have a blood glucose level less than 200 mg/dL before FDG injection. Emission scanning began 50–70 min after injection. Post-treatment imaging was performed approximately 12–16 weeks after radiotherapy on the same scanner as was used to acquire pre-treatment images. The primary objective of the study was to determine the relationship of survival to post-treatment peak SUV in the tumor. All available pre-treatment and post-treatment imaging were collected via Digital Imaging and Communications in Medicine (DICOM) files on The Cancer Imaging Archive (TCIA) Public Access website [18]. Of the evaluable ACRIN 6668/RTOG 0235 patients, eligibility for the current analysis included patients for whom pre- and post-treatment PET/CT data was acquired and for whom OS data was available.

For each eligible patient, the heart was contoured on both the pre- and post-treatment PET/CT scans based on RTOG contouring guidelines and the mean and max Standard Uptake Value (SUV-mean and SUVmax) were calculated for each heart contour using MIM software. One investigator contoured the heart for the 77 patients included and one radiation oncologist reviewed all heart contours for accuracy. The cardiac change was calculated as the post-treatment SUV minus the pre-treatment SUV. Both relative and absolute SUV changes were calculated. The ability of the SUV cardiac changes to predict for overall survival was assessed using multivariable Cox modeling, while controlling for covariates including age and stage. OS for patients with positive SUV changes (a post-treatment
increase in cardiac SUV) or negative SUV changes (a post-treatment decrease in cardiac SUV) was statistically compared in our analysis using t-tests.

**Results**

Of the evaluable 239 ACRIN 6668/RTOG 0235 patients, 77 were eligible for the current analysis. The median age for patients included in the analysis was 64 years (range 43–82 years). 35 patients had stage II disease while 42 had stage III disease. A total of 41 patients had a Zubrod performance status of 1 and 36 had a Zubrod performance status of 0. The median OS for the entire cohort included in this analysis was 469 days (range 144–1640 days).

The median pre-treatment SUVmean for the heart was 1.9 (range 0.9–5.6) and the median post-treatment SUVmean for the heart was 2.0 (range 1.0–6.1). On multivariate analysis, relative SUVmean cardiac change from pre- to post-treatment was predictive of OS with a HR of 0.811 (95% CI 0.68–0.96, p = 0.017). Absolute SUVmean cardiac change demonstrated a HR of 0.954 (95% CI 0.92–0.99, p = 0.007). Absolute SUVmax change from pre- to post-treatment demonstrated a HR of 0.811 (95% CI 0.68–0.96, p = 0.017). Relative SUVmax cardiac change showed a HR of 0.996 (95% CI 0.99–1.00, p = 0.006). Kaplan-Meier analysis demonstrated significant separation between patients with positive versus negative SUVmean change (p < 0.01), favoring the positive subset with regards to OS (Fig. 1). The median OS for patients with a negative SUVmean cardiac change was 413 days and the median OS for patients with a positive SUVmean cardiac change was 585 days (p = 0.016) (Fig. 2).

**Discussion**

Our data demonstrate that cardiac SUV changes are significantly (p = 0.017) associated with OS in NSCLC patients. Specifically, the median OS for patients with a negative SUVmean change between pre- and post-treatment PET-CT was less than those patients with a positive SUVmean difference (413 days versus 585 days). SUVmean cardiac change was predictive of OS with a HR of 0.811 (95% CI 0.68–0.96, p = 0.017). These findings are in line with previously reported literature evaluating functional imaging in the heart [14-16]. Specifically, previous studies have shown that functional imaging in the heart exhibits a dose–response and that the imaging findings can be predictive of clinical outcomes.

There are two significant advantages of using the ACRIN 6668/RTOG 0235 data: (1) the increased number of patient data available for analysis and (2) the fact that PET-CT images were acquired on the same scanner. The presented 77 patient study provides one of the largest functional imaging studies presented, and we hypothesize the significant findings of the survival curves (p < 0.01, Fig. 1) can be attributed to both the large patient dataset and the fact that the pre- and post-treatment PET-CT scans were acquired on the same scanner.

Previous work has shown that cardiac irradiation leads to microvascular damage, and as a result, cardiac perfusion is reduced proportional to the received dose [15,19-21]. This reduction in cardiac perfusion can ultimately lead to changes in FDG uptake [15]. In regard to a potential mechanistic explanation for the cardiac SUV findings, radiation causes cardiac
microvascular injury in proportion to dose leading to local ischemia [21]. As a result of this ischemia, the heart responds via an inflammatory response with metabolic remodeling or enhanced glucose uptake (measured by an increase in SUV) [22]. If the tissue is unable to adapt, it is lost and a reduction in SUV is detected. Additional prospective work with a robust cardiac information dataset will be necessary to draw further conclusions in regard to the mechanism behind the aforementioned results.

There were several shortcomings to our study. Follow-up post-treatment PET and/or survival data was not available for 162 patients from ACRIN 6668/RTOG 0235 which may have impacted the results. Our data showed that pre- to post-treatment SUV changes were predictive of OS, however data were not available to assess whether death was due to cardiac-related events or pre-existing cardiac comorbidities. Although cardiac-specific mortality and morbidity would have been ideal to evaluate, studies show a correlation between cardiac-related treatment parameters and overall survival [1]. Furthermore, complete radiotherapy plans and dose data were not available for evaluation. Therefore, direct cardiac dose–response relationships could not be derived from this work. Nonetheless, this data provides compelling evidence that distinct phenotypes with divergent outcomes can be identified with FDG-PET imaging. Specifically, patients who are at increased risk of death based on their post-treatment imaging can be identified. Future work will aim to further clarify the functional imaging findings in a prospective setting with relevant clinical survival data to draw additional conclusions. If validated in a prospective cohort, our data show the potential for cardiac metabolic changes to be an early predictor for clinical outcomes.

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Fig. 1.
Kaplan-Meier Analysis. Patients with a positive cardiac SUVmean change (light grey) demonstrate a significantly higher surviving fraction in comparison to those patients with a negative cardiac SUVmean change (black). The cardiac SUVmean change was calculated as the post-treatment SUVmean minus the pre-treatment SUVmean.
Fig. 2.
Comparison of Overall Survival Data by SUVmean Change. The median OS for patients with a negative SUVmean cardiac change (dark grey) was 413 days and the median OS for patients with a positive SUVmean cardiac change was 585 days (light grey). SUVmean cardiac change was predictive of OS with a HR of 0.811 (95% CI 0.68–0.96, \( p = 0.017 \)).