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Pre-treatment FDG-PET predicts the site of in-field progression following concurrent chemoradiotherapy for stage III non-small cell lung cancer

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ABSTRACT

Purpose: Locoregional progression following definitive chemoradiotherapy (CRT) for locally advanced non-small cell lung cancer (NSCLC) is common. In this study, we explore the utility of pre-treatment PET for predicting sites of disease progression following CRT.

Methods: We identified patients treated at our institution with definitive, concurrent CRT for stage III NSCLC in the years 2007–2010 who underwent staging FDG-PET/CT. Using a semiautomatic gradient-based tool, visible thoracic hypermetabolic lesions were contoured on each patient's pre-treatment PET. Post-treatment imaging was reviewed to identify specific locations of disease progression.

Patients' maximum SUV (SUVmax_pat) and metabolic tumor volume (MTV_pat) were evaluated as predictors of clinical outcomes using logrank testing. Competing risks analysis was performed to examine the relationship between lesion (tumor or lymph node) MTV (MTV_les) and the risk of local disease progression. Patient death and progression in other sites were treated as competing risks.

Results: 28 patients with 82 hypermetabolic lesions (27 pulmonary tumors, 55 lymph nodes) met inclusion criteria. Median follow-up was 39.0 months for living patients. Median progression-free survival (PFS) was 12.4 months, and median overall survival (OS) was 31.8 months. Low MTV_pat was associated with improved PFS (median 14.3 months for MTV < 60 cc vs. 9.7 months for MTV > 60 cc, $p = 0.039$).

MTV_les was strongly associated with the risk of local disease progression. The 2-year cumulative incidence rate (CIR) for progression in lesions larger than 25 cc was 45%, compared to 5% for lesions under 25 cc ($p < 0.001$).

Conclusion: Pre-treatment PET can be used to identify specific lesions at high risk for treatment failure following definitive CRT for locally advanced NSCLC. Selective treatment intensification to high-risk lesions should be studied as a strategy to improve clinical outcomes in this patient population.

1. Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of cancer mortality in the United States and worldwide [1]. For most of the approximately 30% of NSCLC patients who are diagnosed with locally advanced disease, standard treatment consists of fractionated (1.8–2.0 Gy/day) external beam radiotherapy (RT) to a dose of 60–66 Gy with concurrent platinum-based chemotherapy. This treatment approach yields median survival times of only approximately 20 months and locoregional control rates of approximately 50% [2–5].

Attempts to improve outcomes for locally advanced NSCLC patients by intensifying therapy have thus far been unsuccessful

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[6–8]. In RTOG 0617, dose escalation from 60 Gy to 74 Gy unexpectedly led to a decrease in overall survival (OS) and did not improve local disease control [9]. In that study, the RT prescription dose was delivered to the entire target volume, which included the primary tumor and involved lymph nodes.

Several groups have shown in retrospective reports that pre-treatment disease burden, measured as metabolic tumor volume (MTV) on FDG-PET, is a powerful prognostic factor for NSCLC patients [10,11]. ACRIN 6668/RTOG 0235 demonstrated that high post-treatment maximum SUV (SUVmax) correlated with inferior survival after treatment with definitive chemoradiotherapy (CRT) for stage III NSCLC [12]. In a secondary analysis of that trial, we found that high post-treatment SUV is also a risk factor for locoregional disease progression. Additionally, the probability that a particular tumor or lymph node had a high SUVmax on post-treatment imaging was directly related to that lesion's MTV on pre-treatment imaging. We therefore hypothesize that a lesion's pre-treatment MTV can be used to predict the risk of disease progression in that particular region. To our knowledge, this has not been studied previously.

2. Methods

2.1. Patient selection

We searched an institutional database for patients treated with definitive concurrent CRT for stage III NSCLC in the years 2007–2010 who underwent FDG-PET/CT within 90 days prior to the start of CRT. Patients treated with induction chemotherapy prior to CRT or with surgical resection before or after RT were excluded. Patients with less than 6 months of follow-up at our institution (due to missing data or death within 6 months) after initiation of therapy were also omitted from this analysis.

2.2. PET analysis

PET images were transferred to a commercially-available software package (MIMvista Corp., Cleveland, OH). Using a semi-automatic gradient-based contouring algorithm ("PET Edge"), all visible thoracic hypermetabolic lesions were contoured for each patient by a single observer (NO). Lesions were coded as pulmonary tumor or by lymph node station. Maximum SUV (SUVmax) and metabolic tumor volume (MTV) for each lesion were tabulated. Composite metrics (e.g. total MTV) were recorded for each patient.

2.3. RT plan analysis

RT plans were reviewed in our department's treatment planning software (Varian Medical Systems, Palo Alto, CA). Individual gross tumor volumes (GTVs) for each pulmonary tumor and nodal lesion visualized on PET were generated on planning CTs using lung and/or soft tissue window levels, as appropriate. Approximate planning target volumes (PTVs) for each pulmonary, hilar, and mediastinal lesion were generated by expanding each GTV by 10 mm radially and 15 mm superiorly and inferiorly. For supraclavicular lymph nodes and apical lung tumors, uniform expansions of 10 mm were utilized. In some cases, these volumes differed slightly from the target volumes used for the actual treatment planning process. The dose received by 90% of each PTV (D90) was recorded.

2.4. Follow-up imaging

We reviewed post-treatment imaging studies for each patient included in this analysis. Imaging with CT or PET/CT was generally performed every three months during the first year of follow-up and then every 3–6 months afterwards. The incidence and timing of disease progression at each site identified on pre-treatment imaging were scored using RECIST criteria [13]. Biopsy confirmation was not required for diagnosis of disease progression.

2.5. Statistical analyses

Rates of progression-free survival (PFS) and OS following initiation of CRT were calculated using the Kaplan–Meier method. Pre-treatment composite PET metrics (total SUVmax, total MTV) were tested as predictors of these clinical outcomes using the Logrank test after sorting patients into two groups of equal size.

Scatter plots were generated to depict the relationship between pre-treatment PET metrics, RT dose, and disease progression for individual lesions. Odds ratios (ORs) were calculated to describe the association between MTV and SUVmax with risk of local disease progression, using cutoffs selected based on visual inspection of these graphs. Receiver operating characteristic (ROC) curves were generated to examine the utility of pre-treatment SUVmax and MTV for identifying lesions destined to be the first site of disease progression.

Cumulative incidence rates (CIRs) of local disease progression in individual lesions identified on pre-treatment imaging were calculated using the Fine and Gray's proportional subhazards model [14]. Disease progression in other lesions visualized prior to treatment, development of disease outside of the treatment fields, and mortality due to any cause were treated as competing risks. CIR curves were generated for lesions with pre-treatment MTVs below and above 25 cc. This cutoff was chosen based on preliminary work using other datasets. These curves were compared using Gray's test.

For all analyses, p-values less than 0.05 were considered statistically significant. All analyses were performed using Matlab (The Mathworks, Natick, MA, USA).

3. Results

3.1. Patient characteristics

We initially identified 43 patients who underwent CRT for stage III NSCLC. 28 subjects met all inclusion criteria for this analysis (Fig. 1). Patient characteristics are summarized in Table 1. All patients received RT doses of 59.4–66.6 Gy in daily fractions of 1.8

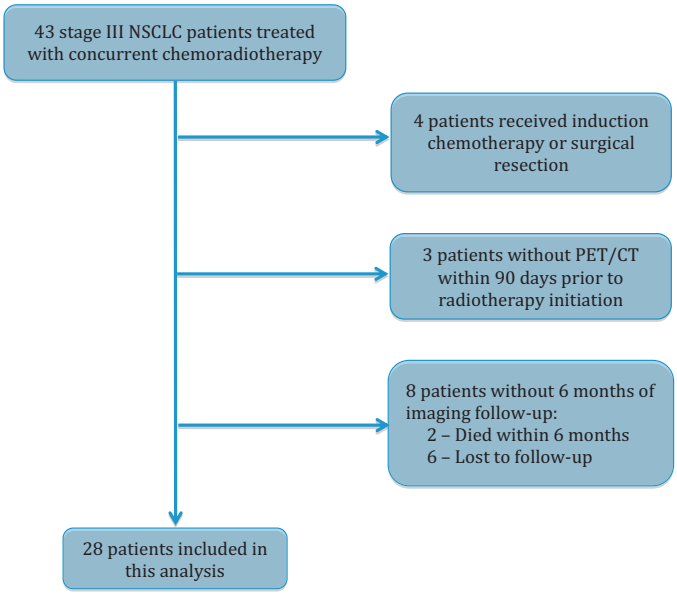

Fig. 1. Patient selection.