Outcomes of Modestly Hypofractionated Radiation for Lung Tumors: Pre- and Mid-Treatment Positron Emission Tomography-Computed Tomography Metrics as Prognostic Factors

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Abstract

Many patients with lung tumors have tumors too large for stereotactic ablative radiotherapy and comorbidities precluding concurrent chemotherapy. We report the outcomes of 29 patients treated with hypofractionated radiotherapy (RT) to 60 to 66 Gy in 3-Gy fractions. We also report an exploratory analysis of the prognostic value of the pre- and mid-RT positron emission tomography-computed tomography.

Introduction: Modestly hypofractionated radiation therapy (HypoRT; 60-66 Gy in 3-Gy fractions) allows patients with locally advanced thoracic tumors and poor performance status to complete treatment within a shorter period without concurrent chemotherapy. We evaluated the outcomes and imaging prognostic factors of HypoRT. **Materials and Methods:** We retrospectively reviewed the data from all patients with primary and metastatic intrathoracic tumors treated with HypoRT from 2006 to 2012. We analyzed the survival and toxicity outcomes, including overall survival (OS), progression-free survival (PFS), local recurrence (LR), and distant metastasis. We also evaluated the following tumor metrics in an exploratory analysis: gross tumor volume (GTV), maximum standardized uptake value (SUV_{Max}), and metabolic tumor volume using a threshold of $\geq$ 50% of the SUV_{Max} ($MTV_{50\%}$) or the maximum gradient of fluorine-18 fluorodeoxyglucose uptake (MTV_{Edge}). We assessed the association of these metrics and their changes from before to mid-RT using positron emission tomography-computed tomography (PET-CT) with OS and PFS. **Results:** We identified 29 patients, all with pre-RT and 20 with mid-RT PET-CT scans. The median follow-up period was 15 months. The 2-year overall and non–small-cell lung cancer-only rate for OS, PFS, and LR, was 59% and 59%, 52% and 41%, and 27% and 32%, respectively. No grade $\geq$ 3 toxicities developed. The median decrease in GTV, SUV_{Max}, and MTV_{Edge} was 11%, 24%, and 18%, respectively. Inferior OS was associated with a larger pre-RT MTV_{Edge} ($P = .005$) and pre-RT $MTV_{50\%}$ ($P = .007$). Inferior PFS was associated with a larger mid-RT SUV_{Max} ($P = .003$). **Conclusion:** These findings add to the growing body of data demonstrating promising outcomes and limited toxicity with HypoRT. The pre- and mid-RT PET-CT metrics could be useful for prognostic stratification in future clinical trials.

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Introduction

Modestly hypofractionated radiation therapy (HypoRT) allows for treatment completion within a shorter period and could be advantageous for patients with locally advanced lung tumors and a poor performance status or an inability to tolerate concurrent chemotherapy. HypoRT results in fewer daily treatments and a reduced cost compared with conventionally fractionated RT (CFRT) or combined chemotherapy and RT (chemoRT). Although small tumors can be treated effectively and safely with stereotactic ablative radiotherapy (SABR), a more fractionated approach is generally considered necessary for safe treatment of more advanced disease. Studies have shown effective treatment is attained with HypoRT for both early-stage non–small-cell lung cancer (NSCLC) and late-stage NSCLC and, with more accelerated courses, for oligometastatic lung cancer.[1-10] One concern is the potential for increased toxicity from HypoRT. However, the reported toxicities have generally been found to be acceptable compared with CFRT with appropriate patient selection and conformal radiation techniques. Although HypoRT can be effective, currently, limited prognostic factors are available to guide treatment and predict the outcomes.

Fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) combined with computed tomography (PET-CT) is an important tool for staging primary lung cancer and could potentially be used as a prognostic indicator of disease control and patient survival. Determining the metrics for tumor response could be used to tailor and potentially adjust treatment. Previous studies have demonstrated the usefulness of the CT-determined gross tumor volume (GTV) and metabolic tumor volume (MTV) for predicting the outcomes for NSCLC after both CFRT and SABR.[11-16] Additionally, analysis of the mid-RT PET-CT findings of different radiation fractionations and doses for lung tumors has shown that a decrease in FDG uptake is associated with improved outcomes.[17-20] To our knowledge, no other studies have been conducted that examined the benefit of mid-RT PET-CT with regard to MTV or as a prognosticator for patients undergoing HypoRT.

We sought to demonstrate the prognostic usefulness of pre- and mid-RT PET-CT metrics and to share our institutional experience of patients with lung cancer treated with a modestly hypofractionated course (60-66 Gy in 3-Gy fractions) of RT.

Materials and Methods

Patient Population

After approval by our institutional review board, we reviewed the medical records of all patients with an intrathoracic tumor treated with a modestly hypofractionated course of RT (60-66 Gy in 3-Gy fractions) using either 3-dimensional conformal (3D-CRT) or intensity-modulated RT (IMRT) at the Stanford Cancer Institute from January 2006 to January 2012. Intrathoracic tumors were those located in the lung cavity or thoracic lymph nodes. The patients included those with both primary or metastatic tumors. During this period, HypoRT was selected for patients with locally advanced or limited metastatic disease. This included patients with stage I lung cancer with a tumor volume too large for SABR and patients with nodal disease and a relatively compact overall planning target volume (PTV), who were considered poor candidates for chemoRT owing to a poor performance status. The pathologic specimens were reviewed at our institution. All patients underwent a pre-RT PET-CT scan within 1 month before RT. No exclusions were made for age, race, gender, or performance status.

Evaluation and Treatment

The pre-RT evaluation included history, physical examination, and diagnostic PET-CT. A total of 29 patients were identified. RT planning and delivery was by either IMRT or 3D-CRT: 19 patients were treated with conventional IMRT, 9 with volumetric modulated arc therapy, and 1 with 3D-CRT. Of the 29 patients, 28 were considered inoperable, and 1 patient underwent upper and lower wedge resections for a stage T2aN0M0 bronchogenic carcinoma followed by RT for positive surgical margins. This patient was not a candidate for lobectomy because of major chronic obstructive pulmonary disease comorbidity. For patients with stage I to III disease, treatment was with the intent to cure. For those with stage IV cancer, all known disease sites were targeted with definitive intent, except for 1 patient, who was treated with palliative intent. That patient had several metastatic lesions from a primary rectal adenocarcinoma and had received treatment to a mediastinal nodal mass causing new-onset left recurrent laryngeal nerve palsy. Six patients had undergone chemotherapy before RT, and 3 patients had undergone chemotherapy after RT. No patient was treated concurrently.

The GTV was contoured on axial slices of the planning CT scans, with a pulmonary window setting for pulmonary parenchymal lesions and a mediastinal window setting for mediastinal lesions, with the aid of fused PET-CT. No explicit expansion was made for microscopic extension to form the clinical target volume to minimize the normal tissue toxicity in a relatively frail patient population using this hypofractionated regimen. However, the multibeam arrangements used resulted in a relatively isotropic dose gradient such that the microscopic control doses (45-50 Gy in accelerated fractionation) typically extended $\geq$ 0.5 to 1 cm beyond the high-dose PTV. Respiratory motion was managed using a motion-inclusive internal target volume (ITV), determined using 4-dimensional CT. The ITV was expanded by a 0.5-cm circumferential margin to define the PTV. The treatment planning goals included $\geq$ 95% PTV coverage with the prescription dose, with a minimum dose of $\geq$ 90% (ideally $\geq$ 95%) and maximum dose of $\leq$ 115% (ideally $\leq$ 110%) of the prescription dose. All treatments were delivered using 6-MV photons. Image guidance was performed using daily pretreatment orthogonal kilovoltage imaging and at least weekly (typically twice weekly) cone-beam CT.

The dose regimens ranged from 60 to 66 Gy, delivered in 3-Gy fractions. Because ours was not a prospective trial, the normal tissue constraints were at the discretion of the treating physicians. However, given the accelerated schedule, they were generally more conservative than the ideal constraints we have typically used in our clinic for conventionally fractionated thoracic IMRT to $\geq$ 60 Gy (eg, percentage of lung volume receiving 20 Gy $\leq$ 30%, mean lung dose $\leq$ 18 Gy, mean esophageal dose $\leq$ 25 Gy, maximum spinal cord dose $\leq$ 45 Gy, percentage of heart volume receiving 30 Gy $\leq$ 50%). In most cases, the doses achieved were substantially lower than these constraints, reflecting the high conformity of the plans. However, in individual cases, structures overlapping the PTV could receive doses exceeding them within a small volume of tissue.