Original Study

Hypofractionated Intensity-Modulated Radiotherapy for Patients With Non–Small-Cell Lung Cancer

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Abstract

Alternative treatments are needed for patients with non–small-cell lung cancer who cannot tolerate standard definitive therapy but have potential for intermediate-term survival and could benefit from durable control of their intrathoracic disease. We found that hypofractionated intensity-modulated radiotherapy without concurrent chemotherapy provides favorable rates of local control, survival, and toxicity.

Background: Alternative treatment regimens are needed for patients with non-small cell lung cancer (NSCLC) who cannot receive definitive treatment with concurrent chemoradiotherapy, surgery, or stereotactic ablative radiotherapy (SABR). **Patients and Methods:** We report survival, patterns of failure and toxicity outcomes for patients with NSCLC who were not eligible for surgical resection, concurrent chemoradiotherapy, or SABR and underwent hypofractionated intensity-modulated radiotherapy (IMRT). Kaplan-Meier survival analysis was used to evaluate the progression-free and overall survival. Competing risk analysis was used to evaluate in-field, locoregional, and distant failure. **Results:** A total of 42 patients treated to 52.5 to 60 Gy in 15 fractions were included. Most of the patients had metastatic or recurrent disease (64%) and a relatively large, centrally located tumor burden (74%). The median follow-up period was 13 months (interquartile range, 6-18 months). All patients received the total prescribed dose. The median survival was 15.1 months. The overall and progression-free survival rates at 1 year were 63% and 22.5%, respectively. The pattern of failure was predominantly distant, with only 2% of patients experiencing isolated in-field recurrence. The cumulative incidence of in-field failure at 6 and 12 months was 2.5% (95% confidence interval, 0.4%-15.6%) and 16.1% (95% confidence interval, 7.5%-34.7%), respectively. The risk of esophageal toxicity was associated with the esophageal mean dose, maximal point dose, and dose to the 5 cm^3 volume. The risk of pneumonitis was associated with the lung mean dose and volume receiving 18 Gy. **Conclusion:** Hypofractionated IMRT without concurrent chemotherapy provides favorable rates of local control and survival for well-selected patients with NSCLC who cannot tolerate standard definitive therapy.

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Introduction

Surgery and concurrent chemoradiotherapy are standard treatment options for patients with early-stage and locally advanced non–small-cell lung cancer (NSCLC), respectively. Stereotactic ablative radiotherapy (SABR), also known as stereotactic body radiotherapy (SBRT), has also become increasingly accepted as a definitive treatment option for patients with early-stage, inoperable NSCLC.[1,2]

For patients with locally advanced NSCLC, concurrent chemoradiotherapy improves survival compared with sequential chemoradiotherapy.[3] However, concurrent chemoradiotherapy is associated with high rates of acute toxicity, in particular, esophageal

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and pulmonary toxicity.[4] Because many patients diagnosed with NSCLC are often of advanced age with multiple medical comorbidities and poor performance status, a substantial proportion of these patients are unable to tolerate concurrent chemotherapy with radiation (RT). In addition, many patients with early-stage, inoperable NSCLC are not candidates for SABR because of the size and/or location of the tumor. A phase II trial found excessive pulmonary toxicity in patients with centrally located tumors treated with the most dose-intensive SABR regimens.[5] Although low toxicity rates have been shown with properly dose-adjusted SABR for central and even ultra-central tumors,[6] the safety of SABR is still questionable for patients with a significant burden of intrathoracic and mediastinal disease.

Alternative treatment regimens are needed for these patients who cannot receive concurrent chemoradiotherapy, surgical resection, or SABR. Conventionally fractionated radiation alone has been associated with poor response rates and local control.[7] The University of Texas Southwestern Medical Center (UTSW)/Stanford phase I trial for patients with a poor performance status and NSCLC demonstrated that doses up to 60 Gy in 15 fractions were well-tolerated.[8] These results were consistent with those from other studies investigating dose intensification for locally advanced NSCLC, although most of the studies did not deliver a dose radiobiologically equivalent to 60 Gy in 15 fractions.[9-12]

This hypofractionated regimen has been adopted at our institution for patients who cannot receive standard of care treatment for their lung cancer either because of comorbidity or the tumor size and location. Patients with a low burden of distant metastatic disease and a good performance status who were at risk of symptomatic intrathoracic progression were also eligible for this treatment regimen. We report our experience with hypofractionated intensity-modulated RT (IMRT), including survival, patterns of failure and toxicity outcomes.

Patients and Methods

Patients and Follow-Up Protocol

With institutional review board approval, we conducted a retrospective review of patients with NSCLC who were not eligible for resection, concurrent chemoradiotherapy, or SABR and who had undergone hypofractionated IMRT (15 fractions of $\geq$ 3 Gy per fraction) at our institution. The patients were allowed sequential, but not concurrent, chemotherapy. The patients were examined once per week during the RT course and routinely underwent a chest computed tomography (CT) and positron emission tomography (PET) follow-up examination 3 months after RT completion. Repeat imaging studies and clinical follow-up examinations were typically performed every 3 months for the first 2 years.

Radiology reports and radiologic examinations were reviewed to determine the patterns of failure. Tissue biopsy was not required for confirmation. Locoregional failure was defined as recurrent or persistent disease involving the ipsilateral lung, hilum, or mediastinum. Supraclavicular and contralateral lung recurrence was considered distant failure. Locoregional failure was considered to be in-field if occurring within the 95% isodose line. In-field and locoregional failure were not censored by distant progression, and the patterns of failure were scored for as long as follow-up imaging data were available. Toxicity was graded according to the Common Terminology Criteria for Adverse Events, version 4.03.

Radiation Planning and Treatment

Patients underwent supine fluorodeoxyglucose PET, CT with contrast, and 4-dimensional (4D) CT simulation with a custom-made vacuum-based and wing board immobilization system.

The gross tumor volume was defined as the primary tumor and involved lymph nodes seen on CT and PET. The UTSW/Stanford phase I trial recommended, but did not mandate, a 5- to 10-mm expansion to form the clinical target volume. Elective nodal irradiation was not permitted. We typically added no additional margin for the clinical target volume. The internal target volume was defined on the 4D-CT scan to encompass tumor motion throughout the respiratory cycle. If the tumor motion on the 4D-CT scan exceeded 1 cm in any direction, respiratory gating techniques were implemented to reduce the internal target volume margin. The planning target volume (PTV) expansion was typically 5 mm.

RT was delivered by a linear accelerator using 6-MV photon beams and an IMRT technique. Daily image guidance (image-guided RT), which consisted of cone-beam CT, kilovoltage radiographs, or fluoroscopy, was required.

We used the dose constraints for the organs at risk (ie, spinal cord, lung, esophagus, brachial plexus, heart/pericardium, great vessels, trachea, bronchial tree, ribs, and skin) that the UTSW/Stanford Phase I trial used,[8] which were derived from the universal survival model, along with published tissue properties. If our target overlapped organs at risk other than the spinal cord, the small portion of the organs within the overlap region was allowed to receive the prescription dose. For patients who had received previous thoracic RT, cumulative plans were generated and constraints applied to the cumulative dose.

Statistical Analysis

Descriptive statistics and the unpaired *t* test were used for dose analysis. The dosimetric parameters examined included the lung volume receiving $\geq$ 18 Gy (V18), a more conservative constraint than typically used for a more fractionated regimen. We also considered the dose to the 5 cm^3 esophageal volume (D5cc), defined as the minimum dose to the hottest 5 cm^3 volume of esophagus; maximal esophageal dose, defined as the minimum dose to the hottest 0.035 cm^3 of the esophagus; and mean esophageal and lung dose. Kaplan-Meier survival analysis was used to evaluate progression-free and overall survival, and competing risk analysis was used to evaluate in-field, locoregional, and distant failure, with death as a competing risk. The time-to-event was defined from the start date of RT. All statistical analyses were performed using SAS software (SAS Institute, Cary, NC).

Results

Patient, Tumor, and Treatment Characteristics

A total of 42 patients were treated from March 2011 to December 2014. A summary of the patient, tumor, and treatment characteristics is listed in Table 1. Eleven patients (26%) were treated prospectively in a phase I dose escalation trial.[8] Most patients (79%) had locally advanced, metastatic, or recurrent disease. Patients with early-stage disease were either inoperable because of