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Stereotactic Body Radiotherapy for Medically Inoperable Stage I-II Non–Small Cell Lung Cancer: The Mayo Clinic Experience

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Abstract

Objective: To examine disease control and survival after stereotactic body radiotherapy (SBRT) for medically inoperable, early-stage non–small cell lung cancer (NSCLC) and determine associations of pretreatment ^{18}F-fluorodeoxyglucose–positron emission tomography (FDG-PET) maximum standardized uptake values (SUVmax), biologically effective dose, and mediastinal staging with disease control and survival outcomes.

Patients and Methods: We retrospectively reviewed the cases of consecutive patients with FDG-PET–staged, medically inoperable NSCLC treated with SBRT at our institution between January 1, 2008, and August 4, 2014. Cumulative incidences of recurrence were estimated, accounting for the competing risk of death. Associations of SUVmax, biologically effective dose, and mediastinal staging with outcomes were evaluated using Cox proportional hazards regression models.

Results: Among 282 patients, 2-year cumulative incidences of recurrence were 4.9% (95% CI, 2.6%-8.3%) for local, 9.8% (95% CI, 6.3%-14.2%) for nodal, 10.8% (95% CI, 7.0%-15.5%) for ipsilateral lung, 6.0% (3.3%-9.8%) for contralateral lung, 9.7% (95% CI, 6.3%-14.0%) for distant recurrence, and 26.1% (95% CI, 20.4%-32.0%) for any recurrence. The 2-year overall survival was 70.4% (95% CI, 64.5%-76.8%), and the 2-year disease-free survival was 51.2% (95% CI, 44.9%-58.5%). Risk of any recurrence was significantly higher for patients with higher SUVmax (hazard ratio [per each doubling], 1.29 [95% CI, 1.05-1.59]; P=.02). A similar association with SUVmax was observed when considering the composite outcome of any recurrence or death (hazard ratio, 1.23 [95% CI, 1.05-1.44]; P=.01). The SUVmax was not significantly associated with other outcomes ($P \geq 0.69$). Two-year cumulative incidences of local recurrence for patients receiving 48 Gy in 4 fractions, 54 Gy in 3 fractions, or 50 Gy in 5 fractions were 1.7% (95% CI, 0.3%-5.6%), 3.7% (95% CI, 0.7%-11.4%), and 15.3% (95% CI, 5.9%-28.9%), respectively (P=.02); this difference was independent of lesion size (P=.02).

Conclusion: Disease control was excellent for patients who received SBRT for early-stage NSCLC, and this series represents the largest single-institution experience from the United States on SBRT for early-stage inoperable NSCLC. Higher pretreatment FDG-PET SUVmax was associated with increased risk of any recurrence, and the 50 Gy in 5 fractions dose prescription was associated with increased risk of local recurrence.

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Non–small cell lung cancer (NSCLC) is the leading cause of cancer death in the United States.[1] For patients with early-stage disease, the standard treatment recommendation is surgical resection with mediastinal lymph node dissection or systematic sampling.[2] However, many patients with NSCLC have cardiac or pulmonary comorbid conditions that prevent them from being appropriate candidates for surgery. Many prospective and retrospective reports with limited follow-up have been published

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regarding the efficacy of stereotactic body radiotherapy (SBRT) in providing local control (LC) in patients with both medically inoperable and operable NSCLC.[3-6] In more recent series, the LC rates exceed 90%. Multiple studies have shown that delivering a higher biologically effective dose (BED) leads to better outcomes.[7,8]

The National Comprehensive Cancer Network guidelines provide options for adjuvant therapy after surgical resection on the basis of tumor size, lymphovascular space invasion, tumor grade, and lymph node involvement.[2] Many patients undergoing SBRT, however, have limited tissue to evaluate these pathologic risk factors to guide adjuvant therapy decisions. Furthermore, many patients have a clinical diagnosis based solely on radiographic suspicion and patient history, given that biopsy is often considered high risk because of comorbid conditions and poor lung function. In these patients, with the limited prognostic information available other than tumor size, metabolic parameters from pretreatment positron emission tomography (PET) have been evaluated as promising prognosticators. Investigators have found mixed results, however, regarding the prognostic capability of different PET parameters: some studies have found no prognostic value,[9-12] whereas others have found that PET parameters such as maximum standardized uptake value (SUVmax), total lesion glycolysis, and metabolic tumor volume may predict disease control as well as survival.[13-17]

Unlike surgery, which includes pathologic lymph node assessment, SBRT does not address or treat the potential spread of malignant cells into regional lymph nodes. Therefore, regional lymph node evaluation is needed to determine whether patients are appropriate candidates for SBRT. ^{18}F-fludeoxyglucose–PET (FDG-PET) has been shown to have excellent diagnostic accuracy, with a negative predictive value of 91%—an improvement compared with computed tomography (CT) alone.[18] Many patients also undergo histologic evaluation of lymph nodes with mediastinoscopy or, more commonly, endobronchial ultrasonography (EBUS). This further improves the chances of accurately staging disease. It is unknown whether histologic evaluation of lymph nodes before SBRT may decrease the risk of subsequent regional failure. In one study of patients referred for SBRT after lymph node–negative PET-CT results, 16% of patients undergoing EBUS had lymph node involvement.[19] If not evaluated with EBUS, these involved nodes would have posed a risk of subsequent regional failure after treatment with SBRT alone.

In this retrospective study, we report outcomes after SBRT for patients with medically inoperable NSCLC at our institution. The primary aim was to evaluate disease control and survival outcomes after SBRT, with secondary aims of evaluating potential associations between outcomes and FDG-PET SUVmax, BED, and mediastinal staging. Toxicity associated with SBRT will be the subject of a separate future analysis.

PATIENTS AND METHODS

Study Population

Institutional review board approval was obtained for this retrospective review of consecutive patients with NSCLC treated with SBRT at 3 geographically separate campuses of our institution (designated sites 1, 2, and 3) between January 1, 2008, and August 4, 2014. Patients were included if they had American Joint Committee on Cancer clinical stage I or II, T1-T3N0M0 NSCLC, as determined by either clinical suspicion or pathologic diagnosis. Patients were excluded if they did not undergo FDG-PET staging, if they had a synchronous lung cancer lesion, prior lung cancer, history of other cancer that was possibly presenting as a lung metastasis, or if they did not have any follow-up after SBRT treatment.

All patients underwent pretreatment PET. Patients were required to have follow-up chest CT, most often performed every 3 months. Measured outcomes included local recurrence, nodal recurrence, ipsilateral lung recurrence, contralateral lung recurrence, distant recurrence, any recurrence, disease-free survival (DFS), and overall survival (OS). The baseline time point for all outcomes was the day of the first SBRT treatment.

Radiation Treatment

Patients were treated with target definitions and treatment planning consistent with Radiation Therapy Oncology Group (RTOG) protocols.[20-23] In most cases, a gross tumor volume was created based on lung windows from

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