Original Study

Recurrence Patterns and Second Primary Lung Cancers After Stereotactic Body Radiation Therapy for Early-Stage Non–Small-Cell Lung Cancer: Implications for Surveillance

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Abstract

The optimal surveillance regimen remains unclear for patients treated with stereotactic body radiation therapy (SBRT) for early-stage non–small-cell lung cancer (SCLC). We assessed 366 patients with early-stage NSCLC treated with SBRT. In patients with progression after SBRT, 84% of cases occurred within the first 2 years. In patients who experienced second primary lung cancers, 33% of cases occurred after 2 years. Close monitoring beyond 2 years may be necessary in patients treated with SBRT.

Background: Patients treated with stereotactic body radiation therapy (SBRT) for early-stage non–small-cell lung cancer (NSCLC) are subject to locoregional and distant recurrence, as well as the formation of second primary lung cancers (SPLCs). The optimal surveillance regimen for patients treated with SBRT for early-stage NSCLC remains unclear; we therefore investigated the posttreatment recurrence patterns and development of SPLCs. **Methods:** Three hundred sixty-six patients with pathologically proven inoperable early-stage NSCLC treated with SBRT between 2006 and 2013 were assessed. Patients underwent a computed tomographic (CT) scan of the chest every 3 months during years 1 and 2, every 6 months during years 3 and 4, and annually thereafter. Competing risk analysis was used for all time-to-event analyses. **Results:** With a median follow-up of 23 months, the 2-year cumulative incidence of local, nodal, and distant treatment failures were 12.2%, 16.1%, and 15.5%, respectively. In patients with disease progression after SBRT (n = 108), 84% (n = 91) of cases occurred within the first 2 years. Five percent (n = 19) of patients experienced SPLCs. The median time to development of an SPLC was 16.5 months (range, 6.5-71.1 months), with 33% (n = 6) of these patients experiencing SPLCs after 2 years. None of the never smokers, but 4% of former tobacco smokers and 15% of current tobacco smokers, experienced an SPLC ($P = .005$). **Conclusion:** Close monitoring with routine CT scans within the first 2 years after SBRT is effective in detecting early disease progression. In contrast, the risk for the development of an SPLC remains elevated beyond 2 years, particularly in former and current smokers.

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Introduction

Stereotactic body radiation therapy (SBRT) has resulted in unprecedented local control in patients with inoperable early-stage non–small-cell lung cancer (NSCLC). This has significantly shifted practice patterns, resulting in an exponential rise in the use of SBRT, which has been associated with improvements in overall

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survival (OS).[1,2] In parallel, CT screening in the high-risk population has resulted in an increase in detection of early-stage NSCLC and associated improvement in OS.[3] For these reasons, it is likely that the use of SBRT for early-stage NSCLC will continue to rise.

SBRT consistently results in long-term local control rates of approximately 90%, and surveillance is important not only to monitor the primary tumor site but also to detect the considerable number of regional and distant treatment failures that occur in this population.[2] Furthermore, second primary lung cancers (SPLCs) develop at an estimated crude rate of approximately 6%.[4] Early detection and intervention for SPLCs is likely important for these patients, because even early-stage lung cancer results in a median survival time of only 14 months when left untreated.[5] Thus, it is critical to understand the temporal development of SPLCs. However, because of the rapid adoption of this technology, the optimal posttreatment surveillance regimen has yet to be established.

To address the void in data on timing of recurrence and formation of SPLCs, we aimed to investigate and understand the appropriate surveillance regimen for patients treated with SBRT. We report a detailed analysis of recurrence and the development of new SPLCs in a large cohort of patients with NSCLC uniformly treated with SBRT at a single institution.

Methods

Patient and Study Details

This study was approved by the Institutional Review Board at Memorial Sloan Kettering Cancer Center. We identified 366 consecutive patients who received SBRT for inoperable biopsy-proven stage I NSCLC (T1-2aN0M0) at our institution between 2006 and 2013. Pathologic confirmation is required before SBRT is undertaken for all patients.

Radiation Therapy

Our radiation therapy methods have been described previously. Briefly, patients were immobilized with an alpha cradle with the arms raised above the head. They then underwent a 4-dimensional CT simulation. Treatment planning was performed using our in-house treatment planning software. Target delineation was based on standard International Commission of Radiation Units and Measurements definitions. The gross tumor volume was defined on free-breathing computed tomography and modified based on the 4-dimensional CT scan to create an internal target volume for all patients. The internal target volume was expanded with a 2- to 3-mm margin for microscopic disease extension to create a clinical target volume, which was then expanded 5 mm to the planning target volume. Dose was prescribed to the 100% isodose line surrounding the planning target volume using inhomogeneity corrections. The median dose prescribed was 48 Gy, ranging from 45 to 60 Gy in 3 to 5 fractions. Tumors were typically treated with a risk-adapted approach using 9 to 10 Gy × 5 fractions (n = 94) for tumors within 2 cm of the proximal bronchial tree, 12 Gy × 4 fractions (n = 123) for tumors within 1 cm of the chest wall, and 18 to 20 Gy × 3 fractions (n = 135) for all other peripherally located tumors. Fourteen patients received alternative dose/fractionation schedules. All patients had treatment every other day. Treatment setup was verified using cone-beam computed tomography, and adjustments and shifts were performed for optimal alignment.

Follow-Up

Patients typically underwent a CT scan of the chest and upper abdomen, including the adrenal glands and liver every 3 months during years 1 and 2, every 6 months during years 3 and 4, and annually thereafter. Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) was performed at baseline and was only performed again if there was radiographic suspicion of recurrence on CT scan. Recurrences were documented by biopsy procedures unless there was clear evidence of metastatic disease on CT or PET/CT scan.

End Points and Statistics

Recurrences were defined as local with treatment failure of the irradiated primary tumor in or adjacent to the planning target volume; nodal with treatment failure in intrathoracic, mediastinal, or supraclavicular lymph nodes; or distant with treatment failure at all other sites. Second primary tumors were defined using all available radiologic and pathologic information according to a modified version of the criteria of Martini and Melamed. We defined them as a new pulmonary malignancy occurring in a different lobe or lung from the first tumor with no intervening lymph nodes and no evidence of metastases, a different histologic type or subtype, molecular genomic differences, or a combination of these factors.[6] However, we did not mandate a minimum interval of 2 years between the first tumor and the SPLC. We also considered second primary tumors in the same lobe of the lung when they were of different histologic type or outside the previous radiation field.

The associations between variables and the risk of local failure, nodal failure, distant failure, and SPLC were evaluated using competing risk analyses. The risk of each event was estimated using a cumulative incidence function that accounted for death without the event of interest. The analysis of SPLCs included a second competing event, ie, other progression. Cumulative incidence comparisons across subgroups were analyzed using the Gray test. The Fine and Gray method was used for multivariate analyses. Kaplan-Meier analysis was used to estimate OS, and patients who were still alive were censored at the date of last available follow-up. All end points were determined from the date of the last fraction of SBRT. Candidate factors with $P < .20$ on univariate analysis were incorporated into a multivariate model for each end point. Statistical significance for all analyses was 2-sided and used a 5% significance level ($P < .05$). Statistical analyses were performed using R, version 3.0.1 (The R Project for Statistical Computing, Vienna, Austria) with the "survival" and "cmprsk" packages.

Results

The median age of the cohort was 77 years (range, 50-95 years); 170 (46%) were men and 196 (54%) were women (Table 1). The majority of patients (n = 263 [72%]) had a Karnofsky performance status (KPS) of ≥ 80. Most patients presented with a stage T1 tumor (n = 297 [81%]), and 257 (70%) had an adenocarcinoma histologic type. The median tumor size was 2 cm (range, < 0.5-5 cm). Thirty-seven (10%) patients were never smokers, 290 (79%) were former tobacco smokers, and 39 (11%) were current tobacco smokers. A total of 121 patients had had previous lung surgery for a primary NSCLC, and 30 had had previous conventionally