ORIGINAL ARTICLE

Isolated Nodal Failure after Stereotactic Body Radiotherapy for Lung Cancer: The Role for Salvage Mediastinal Radiotherapy

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ABSTRACT

Introduction: Isolated nodal failure (INF) without synchronous local or distant failure is an uncommon occurrence after stereotactic body radiation therapy (SBRT) for lung cancer. Here we review the natural history and patterns of failure after post-SBRT INF with or without salvage mediastinal radiotherapy (SvRT).

Methods: Patients treated with SBRT for non–small cell lung cancer with definitive intent were identified. Patients who experienced hilar or mediastinal INF without synchronous distant, lobar, or local failure were included and grouped according to the use of SvRT. The rates of subsequent locoregional control, distant metastases, progression-free survival (PFS), and overall survival were assessed.

Results: Of 797 patients treated with definitive SBRT, 24 (3%) experienced INF and 15 (63%) received SvRT. The most common SvRT regimen (53%) was 45 Gy in 15 fractions. The median follow-up after INF was 11.3 months for survivors. There were no grade 3 or higher toxicities after SvRT. The 1-year Kaplan-Meier PFS and overall survival estimates were 33% and 56% for patients not receiving radiotherapy and 75% and 73% with SvRT. After SvRT, the rate of locoregional control at 1 year was 84.4%. Crude rates of distant failure were 20.0% with SvRT and 22.2% with no radiotherapy. Of the 13 deaths observed, five (38%) were related to distant progression of lung cancer, four (31%) to comorbidities, three (23%) to mediastinal progression, and one (8%) to an unknown cause.

Conclusions: INF is uncommon after SBRT. Despite the significant comorbidities of this population, intrathoracic progression remains a contributor to morbidity and mortality. SVRT for INF is well tolerated and may improve PFS.

Keywords: Nodal failure; SBRT; Salvage; NSCLC; Medically inoperable

Introduction

Over the past decade stereotactic body radiotherapy (SBRT) has emerged as the standard therapeutic option for medically inoperable patients with early-stage non–small cell lung cancer (NSCLC). SBRT is associated with excellent control rates at the primary site and the involved lobe, with distant failure emerging as the most common site of recurrence.[1] Isolated nodal failure (INF) within the hilum or mediastinum in the absence of local, lobar, or distant failure is an uncommon event, occurring in 2% to 5% of patients.[1–3]

It is unclear whether patients who experience an INF represent a subset that remains salvageable with mediastinal radiation or whether INF is simply a precursor to distant failure. Furthermore, in the medically inoperable population, the competing risks of medical comorbidities may shift the risk-benefit ratio away from further tumor-directed therapy. In this study we report our experience with INF, including the natural course after INF in a medically inoperable population and the potential role for salvage mediastinal radiotherapy (SvRT) for these patients.

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Methods

Patients

From a prospectively maintained institutional review board–approved registry, patients with T1-4N0M0 NSCLC who were initially treated with definitive SBRT between October 1, 2003, and February 28, 2014, were identified. Patients treated for both peripheral and central lesions were included. As per Radiation Therapy Oncology Group 08-13, central lesions were defined as those within 2 cm of the tracheobronchial tree or within 5 mm of the mediastinal pleura.[4] Patients who later experienced an isolated hilar or mediastinal failure (INF) without simultaneous local, lobar, or distant failure were included in this series. When medically safe and feasible, biopsy to prove nodal failure was routinely attempted and repeat positron emission tomography/computed tomography (18F-FDG PET) was routine at the time of suspected nodal failure. Patients medically unfit for biopsy were considered to have experienced a nodal failure if 18F-FDG PET staging demonstrated new hilar or mediastinal lymphadenopathy measuring 1.0 to 1.5 cm or greater in the short-axis diameter or with a maximum standardized uptake value of 3.0 or greater.[5,6] These criteria are similar to those in previous SBRT studies including patients without pathologic confirmation.[7,8] Repeat imaging of the brain with either magnetic resonance imaging or contrast-enhanced computed tomography (CT) was physician dependent. Comorbidities were ranked using the Charlson score[9] and patients were staged per the seventh edition of the American Joint Committee on Cancer manual.[10] Patients were included regardless of whether they proceeded with salvage treatment or supportive care alone.

Salvage Treatment and Patterns of Failure

If salvage treatment was used, its details, including timing, dose, and fractionation of mediastinal radiotherapy, were recorded. Chemotherapy, if given, was noted to be either before, concurrent with, or after radiotherapy, or with palliative intent if radiotherapy was not given. Patterns of failure after SvRT, including subsequent local or lobar failure, mediastinal progression in the field of radiotherapy, or progression at distant sites, were recorded. The toxicity of SrVT was graded according to the Common Terminology Criteria for Adverse Events version 4.0 criteria.

Statistical Analysis

Patients were grouped according to the use of SrVT. Differences between the two cohorts were assessed using Student's t test, Wilcoxon's ranked sum test, or Pearson's chi-square test. End points collected included locoregional control (LRC), distant metastatic failure, and overall survival (OS). LRC was measured only for those treated with SrVT and defined as any progression within the original lung or the mediastinum. Progression-free survival (PFS) events were defined as any distant metastatic disease, locoregional progression, or death. Distant metastatic disease was considered any disease outside the thorax, a malignant pleural effusion, or disease spread to the contralateral lung. Time was measured from the date of diagnosis of failure (by biopsy or imaging) to the date of the event (failure or death). The length of follow-up was measured from the date of diagnosis of failure to the last date of clinical follow-up with imaging. Survival end points were assessed using the Kaplan-Meier technique, and when appropriate, differences were assessed using the log-rank test. Limited statistical power prevented multivariate analysis. All statistical analysis was performed using JMP software, version 10 (SAS Institute, Inc., Cary, NC). Study data were collected and managed using Research Electronic Data Capture electronic data capture tools hosted at the Cleveland Clinic.[11]

Results

Patients and Initial Therapy

Between October 1, 2003, and February 28, 2014, a total of 797 patients were treated with definitive SBRT with a median clinical follow-up of 18.0 months for survivors (range 0–100.3 months). Of these, 51 experienced a nodal failure, 24 of which were isolated and without simultaneous local, lobar, or distant failure. This represents a 3.0% crude rate of INF (95% confidence interval [CI]: 2.0–4.5 [Fig. 1]). As estimated by the Kaplan-Meier method, the cumulative incidence of INF was 4.4% (95% CI: 2.8–6.8).

Demographics and initial treatment details are presented in Table 1. No statistical differences were noted between patients with INF who did or did not receive SvRT. Of the 24 patients, 23 were considered medically inoperable at the time of initial diagnosis and one was considered high-risk for surgery and opted for SBRT. All patients were initially staged with 18F-FDG PET, except for one for insurance reasons. A biopsy was attempted in 83.3% of patients (20 of 24), with a tissue diagnosis of lung cancer in 75% (18 of 24). Of the six with either a nondiagnostic biopsy initially or a radiographic diagnosis, three underwent biopsy at the time of failure and were found to have adenocarcinoma.

Patterns of Nodal Failure and SrVT

Patient characteristics at the time of INF are presented in Table 2. Repeat imaging of the brain to screen for metastases at the time of INF was obtained for 37.5% of patients (nine of 24) and repeat 18F-FDG PET imaging of the body was obtained for 87.5% (21 of 24). In the