ORIGINAL ARTICLE

Absence of Pathological Proof of Cancer Associated with Improved Outcomes in Early-Stage Lung Cancer

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Received 14 January 2016; revised 15 March 2016; accepted 20 March 2016
Available online - 19 April 2016

ABSTRACT

Objectives: The purpose of this study was to assess the trends in use of clinical diagnosis and its impact on treatment outcomes in patients receiving radiation therapy for early-stage lung cancer.

Methods: The Surveillance, Epidemiology, and End Results registry was queried from 2004 to 2012 for patients at least 18 years old in whom stage I (clinical stage T1a–T2a) lung cancer had been diagnosed and who underwent radiation therapy alone. Trends in diagnostic confirmation patterns were characterized. A Cox proportional hazards model was used to assess overall survival, and competing risk regression analysis was used to assess cancer-specific survival (CSS).

Results: A total of 7050 patients were included; the disease of 6399 of them (90.8%) was pathologically diagnosed and that of 651 (9.2%) was clinically diagnosed. There was no significant change in the utilization of clinical versus pathologic diagnosis ($p = 0.172$) over time. Patients with T1 disease ($p < 0.001$), tumors 0 to 1.9 cm in size ($p < 0.001$), and upper lobe tumors ($p = 0.004$) were more likely to have been clinically diagnosed. On multivariable analysis, clinical diagnosis was associated with an improved CSS (hazard ratio [HR] = 0.82, 95% confidence interval [CI]: 0.71–0.96) but was not associated with an improved overall survival (HR = 1.01, 95% CI: 0.90–1.13). When stratified by T stage, patients whose disease had been clinically diagnosed as stage T1a had an improved CSS (HR = 0.75, 95% CI: 0.58–0.96, $p = 0.022$). There was a trend toward improved CSS in patients with clinical stage T1b tumors (HR = 0.74, 95% CI: 0.55–1.00, $p = 0.052$).

Conclusions: The improved CSS in patients with a clinical diagnosis suggests treatment of benign disease, particularly in smaller tumors. Prudent patient selection is needed to reduce the potential for overtreatment.

Keywords: SBRT; Lung cancer; Early stage; Biopsy; Radiation therapy

Introduction

Lung cancer is the most common cause of cancer mortality in the United States, with 158,040 expected deaths in 2015.[1] Approximately 15% of new lung cancer cases are clinically localized. For patients with early-stage disease, surgical resection has long been considered the accepted standard treatment. Poor lung function or multiple comorbidities may preclude a patient from undergoing surgical resection. Stereotactic body radiotherapy (SBRT) is an acceptable alternative treatment option for medically inoperable patients at high risk for surgical morbidity or mortality.[2]

In patients with poor pulmonary function or multiple comorbidities, obtaining pathologic confirmation of a presumed lung cancer may be difficult. Furthermore, tumor location or patient refusal to undergo an invasive procedure may encourage a clinician to treat without a pathologic diagnosis. Moreover, imaging may be equivocal, as benign causes (e.g., infection) may appear

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Disclosure: The authors declare no conflict of interest.

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ISSN: 1556-0864
http://dx.doi.org/10.1016/j.jtho.2016.03.024

as false positives on both computed tomography and positron emission tomography (PET) scans.[3] As a result, physicians often rely on a patient's clinical history and imaging studies to identify whether a lung nodule is a presumed malignancy. Multiple studies have demonstrated that SBRT may be a safe and effective treatment option in patients without pathologic confirmation of their disease.[4–7] The purpose of this analysis was to identify the trends in the utilization of a clinical diagnosis for lung cancer using a large national registry and to identify whether the method of diagnosis affects treatment outcomes for patients undergoing radiotherapy for stage I lung cancer. We hypothesized that patients receiving a clinical diagnosis may have improved treatment outcomes on account of a larger proportion of these patients not having a malignancy.

Materials and Methods

Patient Selection

The Surveillance, Epidemiology, and End Results (SEER) program is sponsored by the National Cancer Institute and collects cancer incidence, survival, and treatment information. The SEER registry covers approximately 28% of the U.S. population.[8] Specifically, the database includes clinical (age, race, sex, stage, and grade) and treatment (lymph nodes evaluated, type of surgery, and type of radiation) information. The SEER registry does not include data on comorbidities, performance status, margin status, radiation dose, or chemotherapy use. All data regarding treatment represent the first course of therapy and exclude treatment delivered at recurrence or progression.

The SEER registry was queried from 2004 to 2012 for patients who were at least 18 years old and undergoing external beam radiation therapy for stage I lung cancer (C34.0–C34.9) according to the seventh edition of the American Joint Committee on Cancer staging system.[9] Patients undergoing surgery, with tumors larger than 5 cm, with any previous cancer diagnosis, with 1 month or less of follow-up, or missing treatment information were excluded from the analysis. The SEER registry codes for method of diagnostic confirmation; patients with positive histologic, positive cytologic, or positive microscopic confirmation were considered to have a pathologic diagnosis. Patients with a positive laboratory test or marker, direct visualization without microscopic confirmation, positive findings by radiologic and other imaging techniques without microscopic confirmation, or clinical diagnosis were considered to have only a clinical diagnosis. Patients with an unknown confirmation status were excluded from the analysis.

Statistical Analysis

The primary objectives were to assess trends in diagnostic confirmation patterns in patients with stage I lung cancer and to assess whether the method of diagnostic confirmation impacts overall survival (OS) or cancer-specific survival (CSS). Chi-square tests were used to compare demographic and clinical characteristics between patients with pathologic and clinical diagnoses. Trends in rates of radiotherapy use over time were examined using the chi-square test for trend. Cause of death was classified as lung cancer mortality or non-cancer mortality. Survival estimates were generated using the Kaplan-Meier method with comparisons between groups by the log-rank test. Multivariable survival analyses for OS were performed with the Cox proportional hazards model controlling for type of diagnosis, age, race, sex, marital status, clinical T stage, laterality, tumor location, poverty level, income level, education status, and tumor size (according to quintiles). Given that Cox proportional hazards estimates for CSS may overestimate risk, we performed a Fine and Gray competing risk regression model to assess whether patients receiving a clinical diagnosis versus a pathologic diagnosis had a decreased CSS (presented as a standardized hazard ratio [sHR]) after adjustment for age, race, sex, marital status, clinical T stage, laterality, tumor location, poverty level, income level, and education status.[10] Statistical analysis was performed using STATA software, version 14.1 (StataCorp LP, College Station, TX). A p value of 0.05 or less was considered statistically significant. All statistical tests were two sided.

Results

Patient Population

A total of 7050 patients were included in the analysis; 6399 of them (90.8 %) had a pathologic diagnosis and 651 (9.2 %) received a clinical diagnosis. The median age was 75 (range 28–98) and the median follow-up time was 17 months (range 2–107). Most patients had clinical stage T1 disease (57.7%) and an upper lobe lesion (60.4%). Overall, more patients underwent radiation therapy as the study progressed, from 598 cases in 2004 to 959 in 2012. There was no significant change in the utilization of clinical diagnosis versus pathologic diagnosis ($p = 0.172$ [Fig. 1]) during this period. Of patients without a pathologic diagnosis, 554 (85.1%) received a diagnosis based on imaging, the disease of 93 (14.3%) was coded as having been diagnosed clinically only, and 4 (0.6%) had a diagnosis by direct visualization without microscopic confirmation. No patients had a diagnosis utilizing a positive laboratory test/marker.

Patients with clinical T1 disease ($p < 0.001$), tumors 0 to 1.9 cm in size ($p < 0.001$), and upper lobe tumors