ORIGINAL ARTICLE

A Histologic Basis for the Efficacy of SBRT to the lung

Neil M. Woody, MD,[a] Kevin L. Stephans, MD,[a] Martin Andrews, PhD,[a] Tingliang Zhuang, PhD,[a] Priyanka Gopal, MS,[b] Ping Xia, PhD,[a] Carol F. Farver, MD,[c] Daniel P. Raymond, MD,[d] Craig D. Peacock, PhD,[b] Joseph Cicenia, MD,[e] Chandana A. Reddy, MS,[a] Gregory M. M. Videtic, MD,[a] Mohamed E. Abazeed, MD, PhD[a,b,*]

[a]*Department of Radiation Oncology, Cleveland Clinic, Cleveland, Ohio*
[b]*Department of Translational Hematology Oncology Research, Cleveland Clinic, Cleveland, Ohio*
[c]*Pathology and Laboratory Medicine Institute, Cleveland Clinic, Cleveland, Ohio*
[d]*Department of Thoracic and Cardiovascular Surgery, Cleveland Clinic, Cleveland, Ohio*
[e]*Department of Pulmonary Medicine, Cleveland Clinic, Cleveland, Ohio*

Received 4 September 2016; revised 10 October 2016; accepted 3 November 2016
Available online - 22 December 2016

ABSTRACT

Purpose: Stereotactic body radiation therapy (SBRT) is the standard of care for medically inoperable patients with early-stage NSCLC. However, NSCLC is composed of several histological subtypes and the impact of this heterogeneity on SBRT treatments has yet to be established.

Methods: We analyzed 740 patients with early-stage NSCLC treated definitively with SBRT from 2003 through 2015. We calculated cumulative incidence curves using the competing risk method and identified predictors of local failure using Fine and Gray regression.

Results: Overall, 72 patients had a local failure, with a cumulative incidence of local failure at 3 years of 11.8%. On univariate analysis, squamous histological subtype, younger age, fewer medical comorbidities, higher body mass index, higher positron emission tomography standardized uptake value, central tumors, and lower radiation dose were associated with an increased risk for local failure. On multivariable analysis, squamous histological subtype (hazard ratio = 2.4 $p = 0.008$) was the strongest predictor of local failure. Patients with squamous cancers fail SBRT at a significantly higher rate than do those with adenocarcinomas or NSCLC not otherwise specified, with 3-year cumulative rates of local failure of 18.9% (95% confidence interval [CI]: 12.7–25.1), 8.7% (95% CI: 4.6–12.8), and 4.1% (95% CI: 0–9.6), respectively.

Conclusion: Our results demonstrate an increased rate of local failure in patients with squamous cell carcinoma. Standard approaches for radiotherapy that demonstrate efficacy for a population may not achieve optimal results for individual patients. Establishing the differential dose effect of SBRT across histological groups is likely to improve efficacy and inform ongoing and future studies that aim to expand indications for SBRT.

Keywords: SABR; precision; heterogeneity; personalized

Introduction

Clinical outcomes after surgery for patients with early-stage NSCLC are favorable, with 5-year survival rates ranging from 60% to 80%.[1] However, high rates of comorbid disease that could result in significant perioperative morbidity and affect long-term quality of life often disqualify many patients from surgery. In this milieu, noninvasive treatments such as stereotactic body radiotherapy (SBRT) to the lung were developed and expanded. To date, several prospective phase II

*Corresponding author.

Disclosure: The authors declare no conflict of interest.

Address for correspondence: Mohamed E. Abazeed, MD, PhD, Cleveland Clinic Foundation, 9500 Euclid Ave./R40-005, Cleveland, OH 44195. E-mail: abazeem@ccf.org

ISSN: 1556-0864
http://dx.doi.org/10.1016/j.jtho.2016.11.002

trials using SBRT have been conducted in medically inoperable patients with excellent results, specifically, with 2- to 3-year local tumor control rates between 93% and 98%.[2–4] These successes have established SBRT as the standard of care in medically inoperable patients, and studies have begun to explore a role for SBRT in healthier patients with early-stage NSCLC.[5–10]

The use of SBRT for NSCLC has been optimized by the identification of tumor- and treatment-related factors that predict failure, including larger tumor size and lower radiation doses.[11–14] However, whether groups within NSCLC are more or less likely to respond to treatments remains unclear. NSCLCs are characterized by substantial genetic diversity, and the optimal therapeutic approach is likely to vary depending on the genetic features of individual cancers.[15,16] Indeed, the stratification of patients with NSCLC into more homogenous populations has resulted in a greater likelihood of response to specific agents.[17–22] In the same manner, histological and molecular profiling of tumors may reveal subpopulations that are more or less likely to achieve local control after SBRT. Elucidating the interaction between radiation dose and NSCLC subtypes is critical for SBRT's optimization for indications beyond its current role in the treatment of medically inoperable patients with early-stage disease.

NSCLC is composed of two predominant histological subtypes, adenocarcinoma (~50%) and squamous cell carcinoma (SqCC) (~30%).[23] Histological characterization separates NSCLC into more homogeneous subtypes,[24] and there are important differences in the genetic and microenvironments of tumors from glandular origin (adenocarcinomas) and those of tumors with squamous differentiation.[15,16,25] Therefore, we posited that the histological subtype of lung cancer may affect the efficacy of SBRT. Herein, we used competing risk analysis to identify tumor and treatment factors that are predictive of local failure after SBRT.

Material and Methods

Patients

From an institutional review board–approved database of 1084 patients treated with lung SBRT from 2003 to 2015, we included patients with clinical stages T1N0M0 to T3N0M0 (seventh edition of American Joint Committee on Cancer staging) lung cancer and excluded patients with tumors that invaded the chest wall, synchronous primary tumors, and cases treated with the intent to salvage recurrent tumor after prior radiotherapy (RT) or surgery. Patients were treated on the basis of either a pathologic or radiographic diagnosis. A diagnosis of lung cancer was confirmed by histological examination of biopsy specimens for 69.8% of the patients studied. A general surgical pathologist or a pulmonary pathologist diagnosed cases from 2003 to July 2014. A staff pulmonary pathologist classified all lung cancer cases after July 2014. The World Health Organization classification system was used from 2003 to 2011.[26,27] After 2011, the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification system was used.[28] In most cases, a diagnosis of adenocarcinoma and SqCC was made solely on the basis of morphologic criteria. A histological or immunohistochemical staining panel was used to better define the diagnosis if the morphology was not distinctly that of SqCC or adenocarcinoma. In some cases, this resulted in diagnoses of NSCLC–favor adenocarcinoma or NSCLC–favor SqCC. These cases were grouped with their respective "favored" diagnosis. NSCLC not otherwise specified (NOS) was reserved for cases with strong, concurrent features of both adenocarcinoma and SqCC and cases without any definitive morphologic or immunohistochemical features of either adenocarcinoma or SqCC. Cases of large cell carcinoma before 2011 were reclassified as NSCLC NOS for consistency with the current terminology.

In 30.1% of patients who did not have a confirmed pathologic diagnosis (n = 223), an attempt at a biopsy did not result in confirmation of malignant disease in 39% of cases (n = 87 [11.8% of the overall population]). A radiographic diagnosis was established in cases in which a biopsy was contraindicated or was nondiagnostic. The criteria for a radiographic diagnosis included serial growth of a single lesion on computed tomography (CT) scans and a positron emission tomography (PET) standardized uptake value (SUV) that exceeded 3.0.

In all cases, an experienced thoracic surgeon and/or pulmonologist established medical inoperability. For each patient, the Charlson comorbidity index (CCI) was documented to assess comorbid illness, and baseline pulmonary function testing results were obtained. All patients were staged using a CT scan of the chest; PET/CT and imaging of the brain (magnetic resonance imaging or CT) were used when clinically indicated. In cases in which imaging revealed mediastinal or hilar lymph nodes enlarged by accepted radiographic criteria or in which the standardized uptake value (SUV) exceeded a value of 3.0 on PET, pathologic mediastinal evaluation with endobronchial ultrasound was requested.[29] The use of chemotherapy after SBRT in patients considered at risk for distant failure was not routinely recommended given patient comorbidities. A small fraction of patients (8.8%) did receive chemotherapy at the discretion of the multidisciplinary treatment team.

Treatment

Our institutional approach for lung SBRT consists of immobilization in a Bodyfix vacuum system with