ORIGINAL ARTICLE

Histology, Tumor Volume, and Radiation Dose Predict Outcomes in NSCLC Patients After Stereotactic Ablative Radiotherapy

Kevin Shiue, MD,[a] Alberto Cerra-Franco, MD,[a] Ronald Shapiro, MD,[b] Neil Estabrook, MD,[a] Edward M. Mannina, MD,[a] Christopher R. Deig, MD,[a] Sandra Althouse, MS,[c] Sheng Liu, PhD,[d,e] Jun Wan, PhD,[d,e] Yong Zang, PhD,[c,f] Namita Agrawal, MD,[a] Pericles Ioannides, MD,[a] Yongmei Liu, MD,[a] Chen Zhang, MD,[g] Colleen DesRosiers, PhD,[a] Greg Bartlett, CMD,[a] Marvene Ewing, CMD,[a] Mark P. Langer, MD,[a] Gordon Watson, MD,[a] Richard Zellars, MD,[a] Feng-Ming Kong, MD,[a] Tim Lautenschlaeger, MD[a,*]

[a]*Department of Radiation Oncology, Indiana University School of Medicine, Indianapolis, Indiana*
[b]*Department of Radiation Oncology, Richard L. Roudebush VAMC, Indianapolis, Indiana*
[c]*Department of Biostatistics, Indiana University School of Medicine, Indianapolis, Indiana*
[d]*Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, Indiana*
[e]*Collaborative Core for Cancer Bioinformatics, Indiana University Simon Cancer Center, Indianapolis, Indiana*
[f]*Center for Computational Biology and Bioinformatics, Indiana University School of Medicine, Indianapolis, Indiana*
[g]*Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, Indiana*

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ABSTRACT

Introduction: It remains unclear if histology should be independently considered when choosing stereotactic ablative body radiotherapy dose prescriptions for NSCLC.

Methods: The study population included 508 patients with 561 lesions between 2000 and 2016, of which 442 patients with 482 lesions had complete dosimetric information. Eligible patients had histologically or clinically diagnosed early-stage NSCLC and were treated with 3 to 5 fractions. The primary endpoint was in-field tumor control censored by either death or progression. Involved lobe control was also assessed.

Results: At 6.7 years median follow-up, 3-year in-field control, involved lobe control, overall survival, and progression-free survival rates were 88.1%, 80.0%, 49.4%, and 37.2%, respectively. Gross tumor volume (GTV) (hazard ratio [HR] = 1.01 per mL, $p = 0.0044$) and histology ($p = 0.0225$) were independently associated with involved lobe failure. GTV (HR = 1.013, $p = 0.001$) and GTV dose (cutoff of 110 Gy, biologically effective dose with $\alpha/\beta = 10$ [BED10], HR = 2.380, $p = 0.0084$) were independently associated with in-field failure. For squamous cell carcinomas, lower prescription doses were associated with worse in-field control (12 Gy × 4 or 10 Gy × 5 versus 18 Gy or 20 Gy × 3: HR = 3.530, $p = 0.0447$, confirmed by propensity score matching) and was independent of GTV (HR = 1.014 per mL, 95% confidence interval: 1.005–1.022, $p = 0.0012$). For adenocarcinomas, there were no differences in in-field control observed using the above dose groupings ($p = 0.12$ and $p = 0.31$, respectively).

Conclusions: In the absence of level I data, GTV and histology should be considered to personalize radiation dose for stereotactic ablative body radiotherapy. We suggest lower prescription doses (i.e., 12 Gy × 4 or 10 G × 5) should be avoided for squamous cell carcinomas if normal tissue tolerances are met.

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Keywords: Stereotactic body radiation therapy; Stereotactic ablative radiotherapy; Histology; NSCLC

*Corresponding author.

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Address for correspondence: Tim Lautenschlaeger, MD, 535 Barnhill Dr RT 041, Indianapolis, Indiana 46202. E-mail: timlaut@iupui.edu

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Introduction

NSCLC represents approximately 84% of lung cancer cases in the United States.[1] Approximately 30% of early-stage NSCLC patients are inappropriate for or refuse surgical resection. Historically, such patients received conventionally fractionated radiotherapy with expected 3-year overall survival (OS) rates between 20% and 35% and local failure rates between 40% and 60%.[2,3] In an attempt to improve outcomes, stereotactic ablative body radiation (SABR; also called stereotactic body radiation therapy) was initially explored in medically inoperable patients with one of the first trials originating from Timmerman et al.[4] at Indiana University. Subsequently, the Radiation Therapy Oncology Group (RTOG) conducted a phase II trial (RTOG 0236) evaluating the efficacy of SABR for patients with peripherally located tumors. The reported 3-year local control (LC) rate was 98% with a 3-year OS of 56% and a median OS of 4 years.[2] Other prospective and retrospective studies have corroborated these findings.[5-7] A pooled analysis of two prematurely closed randomized trials comparing SABR versus lobectomy for operable stage I (T1-2aN0M0) NSCLC patients suggested clinical equipoise between SABR and surgery, with a 3-year OS of 95% versus 79%, respectively.[8]

Risk factors for recurrence have been explored in surgical series, and findings suggest that outcomes are dependent on extent of resection and histology, including worse outcomes in squamous cell carcinomas and differing outcomes based on adenocarcinoma subtypes.[9-14] Similar analyses for SABR are limited. Evidence suggests that biologically effective dose ($\alpha/\beta = 10$, BED_{10}) cutoffs predict better control.[5,15-23] In addition, recent publications suggest histology may also play a role for predicting treatment response following SABR.[6,24] We aim to identify risk factors for recurrence using our institution's 16-year experience using SABR for NSCLC to allow personalization of dose prescriptions according to patient, tumor, and treatment-specific characteristics.

Materials and Methods

Study Population

This study is an Institutional Review Board–approved retrospective review of outcomes after SABR for NSCLC. We included patients treated from 2000 to 2016 who were identified by medical billing codes and relevant billing information.

Eligible patients were 18 years of age or older with histologically or clinically diagnosed early-stage NSCLC; synchronous and metachronous lesions were included, the latter of which only if a previously treated NSCLC was felt to be cured.[25] Clinical diagnosis was based on radiographic suspicion, most often via tumor board consensus.[26,27] Patients were either inoperable or had elected against surgery. Patients were excluded if they had systemic spread of lung cancer at the time of SABR.

Treatment Details

Treatment planning and delivery evolved during the study period. All patients underwent computed tomography (CT) simulation in the supine position with immobilization for stereotactic treatment. Heterogeneity corrections were taken into account starting in 2007. Radiation plans were calculated using the analytical anisotropic algorithm (AAA) (Eclipse Treatment Planning System, Varian Medical Systems, Palo Alto, California) with heterogeneity corrections, AAA (Eclipse) without heterogeneity corrections, pencil beam (Precise Plan, Elekta, Stockholm, Sweden) without heterogeneity corrections, or convolution/superposition (XiO, Elekta, Stockholm, Sweden) without heterogeneity corrections. Radiation was delivered in 3 to 5 fractions with at least 1 day between fractions. Gross tumor volume (GTV) was defined as visible tumor on CT using lung windows. Other imaging was used as needed. Internal target motion was taken into account with fluoroscopy initially and four-dimensional CT more recently to generate an internal target volume, and margins were added to generate the planning target volume (PTV). Prescriptions typically were to the 80% isodose line, and the prescription typically covered at least 95% of the PTV. More recently in the intensity-modulated radiation therapy setting, prescriptions were typically 95% of the PTV receiving 100% of the prescription and 99% of the internal target volume receiving at least 110% of the prescription. Radiation doses are represented as Gy BED_{10} except when dose is stated as "dose per fraction × # of fractions." A small proportion of the study cohort received suboptimal doses (i.e., prescription dose <100 Gy) according to current standards (n = 30 patients and lesions in the study cohort; n = 23 patients and lesions in the dosimetric cohort) as they were enrolled on dose escalation trials.

Data Collection

The date of diagnosis was defined as the date of tumor sampling for those with histologic diagnosis or the date of imaging prompting additional workup for those with clinical diagnosis. In total, 15.3% (n = 86) of lesions were diagnosed clinically, of which 12.7% (n = 71) had no biopsy and 2.7% (n = 15) had no pathology report available for review. The date of last follow-up was defined as the date the patient last visited with a radiation oncologist, medical oncologist, surgical oncologist, or pulmonologist. The T stage was updated for all lesions to be consistent with the American Joint Committee on Cancer seventh edition (AJCC 7e) staging.

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