Predictors of Distant Failure After Stereotactic Body Radiation Therapy for Stages I to IIA Non–Small-Cell Lung Cancer

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Abstract

Stereotactic body radiation therapy (SBRT) is an effective treatment modality for early-stage non–small-cell lung cancer, with excellent rates of local control. Despite this, the predominant pattern of failure in these patients is distant. We sought to identify factors that may help to predict which of these patients are at highest risk of distant failure following SBRT. We retrospectively reviewed 292 patients treated with SBRT for early-stage non–small-cell lung cancer. The primary endpoint was distant failure. We classified patients according to T-stage, tumor size, location and histology, pretreatment positron emission tomography/computed tomography standardized uptake value, smoking status, and age. The 2-year distant failure rate was 22.0%, and the 2-year overall survival was 61.0%. For every 1-year increase in patient age, the hazard of distant failure at any given time was 3% lower (hazard ratio, 0.97; 95% confidence interval, 0.94-0.99; $P = .04$). No other clinical factors emerged as significant predictors, and additional molecular studies may be needed to identify the patients with early-stage lung cancer at highest risk of distant failure.

Purpose: The use of stereotactic body radiation therapy (SBRT) has emerged as an effective treatment modality for patients with early-stage non–small-cell lung cancer (NSCLC), with excellent local control rates. Despite this, there is a predominant pattern of distant failure. We sought to identify factors that help predict which patients with stages I to IIA NSCLC treated with SBRT are at highest risk of distant failure, so that we may utilize these factors in the future to help determine which patients may benefit from the addition of systemic therapies. **Patients and Methods:** We retrospectively reviewed 292 patients treated with SBRT for early stage NSCLC from 2006 to 2016 at 2 institutions. Patients were classified by T stage, tumor size, location and histology, pretreatment positron emission tomography/computed tomography (PET/CT) standardized uptake value (SUV), smoking status, and age. The primary endpoint of the study was distant failure. We aimed to analyze if patient characteristics could be identified that predicted for distant failure through the use of competing risk analysis. **Results:** The median follow-up was 21.9 months. The median dose of radiation and fractionation delivered was 50 Gy (range, 45-65 Gy) in 5 fractions (range, 3-13 fractions). The median patient age was 72.8 years (interquartile range, 65.4-79.7 years). The 2-year distant failure was 22.0%, and overall survival at 2 years was found to be 61.0%. For every 1-year increase in patient age, the hazard of distant failure at any given time was 3% lower (hazard ratio, 0.97; 95% confidence interval, 0.94-0.99; $P = .04$). None of the remaining characteristics emerged as significant risk factors for distant failure on univariable or multivariable analysis. **Conclusions:** Overall, our cohort had distant failure and survival rates comparable with what has been described in the literature. Although we were unable to identify factors outside of age that correlated to risk of distant failure, this topic warrants further investigation, as distant failure is the primary pattern of failure with SBRT when used as the primary management for early-stage NSCLC. Additional molecular studies are needed to further inform on the role of systemic therapy in patients with early-stage NSCLC to improve clinical outcomes.

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Introduction

Non–small-cell lung cancer (NSCLC) is the leading cause of cancer death, with about 20% of newly diagnosed NSCLC representing early-stage lung cancers.[1] With the increasing use of low-dose screening computed tomography (CT) scans for high-risk populations, the diagnosis of early-stage lung cancer will likely continue to increase in years to come. Although surgical resection with lobectomy and lymph node dissection has been the standard of care for early-stage NSCLC, radiotherapy has been an alternative method for those who are medically inoperable or who refuse surgery.[2] Historically, patients treated with conventional radiotherapy alone for the treatment of stage I NSCLC had poor outcomes, with 5-year cause-specific survival rates ranging from 13% to 32% and local failure rates of 42% to 49%.[3-5] However, in more recent years, the technique of stereotactic body radiation therapy (SBRT), using high ablative doses per fraction with a steep dose fall-off, has emerged as a lone treatment modality for these patients with early-stage NSCLC, with improved local control and decreased toxicity.[6-10]

Prospective trials have proven both the efficacy and safety of SBRT with impressive local control rates. Various doses and fractionation schedules have been used in several studies with similar rates of local, regional, and distant failure. Local control rates are routinely $\geq$ 85% at 3 years.[2,6,7] Despite these high local control rates, there continues to be a predominant pattern of distant failure within this group of patients with ranges of 12.9% to 33% at 3 years.[7,10-12] Given that the primary pattern of failure is distant, the aim of this study is to identify clinicopathologic factors in patients with early-stage NSCLC treated with SBRT that are associated with highest risk of distant failure.

Methods and Materials

We retrospectively reviewed 292 patients treated with SBRT for early stage NSCLC, who were treated from 2006 to 2016 at 2 institutions (Loyola University Medical Center and Edward Hines Jr. VA Hospital). Both Institutional Review Boards approved this study. Patient and tumor characteristics that were obtained included T stage, tumor size, tumor location, histology, pretreatment 2-deoxy-2-[^{18}F] fluoro-D-glucose (FDG) positron emission tomography (PET)/CT standardized uptake values (SUVs), smoking status, and age.

Treatment Planning and Delivery

Patients were treated with SBRT if they were determined to be medically inoperable based on multidisciplinary evaluation or if the patient declined surgical intervention. For treatment planning, all patients were immobilized and then underwent simulation with 4-dimensional CT (4DCT). Motion management strategies with abdominal compression and/or respiratory gating were utilized for excessive tumor motion during respiration at the discretion of the treating physician. All patients were treated using either 3D conformal technique or volumetric modulated arc therapy. An internal target volume was created by defining the gross tumor volume utilizing multiple phases of the respiratory cycle from the 4DCT, most commonly on a merged dataset of the maximum intensity projection, to account for motion of tumor with breathing. A planning target volume was defined as the internal target volume with a 5-mm uniform margin to account for uncertainty with planning or treatment delivery.

Follow-up and Endpoints

Patients were seen in follow-up at regular intervals, with chest CT obtained every 3 to 6 months for year 1, every 6 months for years 2 to 3, every 6 to 12 months until year 5, and then annually. Dates and sites of local, regional, and distant failure were recorded and analyzed by a dedicated multidisciplinary tumor board in the majority of cases. The primary endpoint of the study was distant failure rate. Distant failure was defined as any failure outside of the thorax based upon imaging and/or biopsy. Biopsy of distant recurrence was obtained to verify diagnosis whenever feasible. Progression-free survival (PFS) was defined as absence of local failure, nodal failure, distant failure, and death.

Statistical Methods

Univariable and multivariable Cox proportional hazards models were used to estimate the hazard of distant failure at any given time as a function of patient demographics and clinical measures. In these models, death preceding failure was considered a competing event, and a cause-specific hazard for distant failure was estimated. The proportional hazards assumption for each event type (distant failure and death) was assessed as described by Cox and Oakes, and the proportional hazards assumption for each risk factor was assessed as described by Lin, Wei, and Ying.[13,14] All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

Results

A total of 292 patients were retrospectively reviewed on our database. The median follow-up was 21.0 months (interquartile range, 10.6-32.7 months). A summary of the patient characteristics can be seen in Table 1. The median patient age was 72.8 years (interquartile range, 65.4-79.7 years), and 65.4% of patients were male. The median dose and fractionation of radiation delivered was 50 Gy (range, 45-65 Gy) in 5 fractions (range, 3-13 fractions). Patients were well-distributed between both treatment sites, with 168 (57.5%) patients treated at Loyola University Medical Center and 124 (42.4%) patients treated at Edward Hines Jr. VA Hospital.

Sixty-one (20.9%) patients ultimately developed a distant recurrence. The 2-year estimate of distant failure was 22.0%, as shown in Figure 1. PFS estimates, stratified according to the 2 most prevalent histologies in our cohort, showed an 80.0% and a 65.0% PFS estimate at 2 years for adenocarcinoma and squamous cell carcinoma, respectively. Of the 246 patients with known living status, 132 (53.7%) patients had died at time of this analysis. Overall survival rates, as shown in Figure 2, were found to be 85.0% and 61.0% at 1 and 2 years, respectively.

Table 2 presents the univariable and multivariable analysis for risk of distant failure. On univariable analysis, for every 1-year increase in patient age, the hazard of distant failure at any given time was 3% lower (hazard ratio, 0.97; 95% confidence interval, 0.94-0.99; $P = .04$). None of the remaining patient demographic or clinical characteristics emerged as significant risk factors for distant failure on univariable analysis. Patient age, pretreatment SUV, location, histology, and T stage were also evaluated on multivariable

Table 1 Descriptive Summary of Patient Characteristics

Characteristic	Total (N = 292), n (% or std dev)
Gender	292
Female	101 (34.6)
Male	191 (65.4)
Smoker status	226
Current smoker	55 (24.3)
Former smoker	156 (69.0)
Never smoker	15 (6.6)
Tumor location	264
Multiple/bilateral	4 (1.5)
Nodes/hilum	3 (1.1)
RML/RLL/LLL	90 (34.1)
RUL/LUL/lingula	167 (63.3)
Pathology	292
Adenocarcinoma	91 (31.2)
Squamous cell carcinoma	71 (24.3)
Large cell	3 (1.0)
No pathology	92 (31.5)
NSCLC NOS	35 (12.0)
T stage	274
1	203 (74.1)
2	56 (20.4)
3	7 (2.6)
4	8 (2.9)
Tumor	267
Central	70 (26.2)
Peripheral	197 (73.8)
Dose	292
50 Gy in 5 fractions	209 (71.6)
60 Gy in 5 fractions	58 (19.8)
54 Gy in 3 fractions	7 (2.4)
Other	18 (6.2)
Smoking pack-years[a] (n = 194)	57.4 (34.1)
Maximum tumor dimension[a] (n = 266)	2.31 (1.15)
Pretreatment PET/CT SUV[a] (n = 185)	7.50 (4.81)
Age, y[a] (n = 257)	72.8 (9.1)

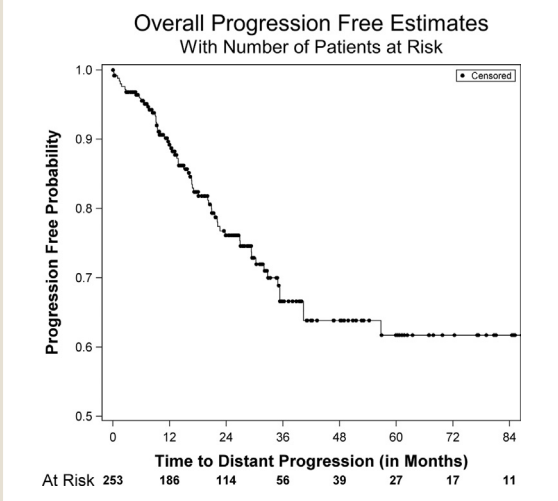
Abbreviations: std dev = standard deviation; LLL = left lower lobe; LUL = left upper lobe; LUMC = Loyola University Medical Center; RLL = right lower lobe; RML = right middle lobe; RUL = right upper lobe.
[a]Continuous variables expressed as means and standard deviations.

analysis to further investigate possible interactions associated with tumor progression. Although histology trended toward borderline marginal significance using this approach, the results largely confirmed initial univariable findings.

Discussion

SBRT has proven to be a valuable tool in the treatment of early stage NSCLC, particularly in patients who are medically inoperable or who refuse surgery, with excellent control rates and acceptable toxicity profiles. In addition, several dose and fractionation schemas have been tested and emerged as proven variations, all with nearly

Figure 1 Distant Progression-free Probability



equivalent rates of local control and toxicities.[15-17] With these consistently high rates of local control with modern radiotherapy, we have now pushed the pattern of failure to distant. As discussed by Bradley et al, the main predictor of overall survival in early-stage NSCLC is distant failure.[18] With distant failure rates ranging from 12.9% to 33% and local failures ranging from 9% to 13% at 3 years, respectively, additional therapies are needed to address the competing pattern of distant failure.[19] With high rates of distant failure, one would advocate for the role of systemic therapy in these patients; however, many patients who are medically inoperable upfront are also poor candidates for chemotherapy. In addition, surgical series have failed to add a benefit with the addition of adjuvant chemotherapy following surgical resection of early, stage IB NSCLC, per the American Joint Committee on Cancer fifth edition staging, with the exception of selected patients with IB

Figure 2 Overall Survival

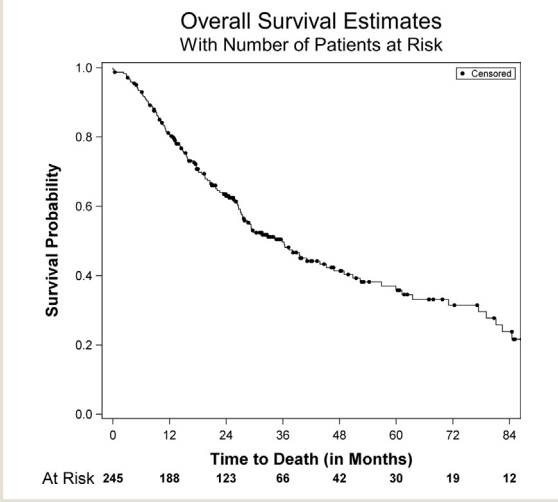


Table 2 Univariable and Multivariable Cox Proportional Hazards Model Results

	Valid N	HR (95% CI)	*P*	AHR (95% CI)	*P*
Age	228	0.97 (0.94-0.99)	.04	0.97 (0.93-1.00)	.05
Gender	233				
Female		1.23 (0.72-2.09)	.44		
Male (Ref)		—			
Smoker status	203		.87		
Current smoker		0.76 (0.24-2.36)			
Former smoker		0.87 (0.31-2.46)			
Never smoker (Ref)		—			
Tumor location	224		.20		
Nodes/hilum		3.32 (0.80-13.80)			
RML/RLL/LLL		0.87 (0.49-1.54)			
RUL/LUL/linguala (Ref)		—			
Histology	237		.39		.12
Adenocarcinoma (Ref)		—		—	
NSCLC		0.96 (0.42-2.19)		0.70 (0.23-2.18)	
No pathology		0.74 (0.37-1.51)		0.49 (0.18-1.32)	
Squamous cell carcinoma		1.39 (0.73-2.65)		1.55 (0.73-3.26)	
T stage	241		.80		.87
1 (Ref)		—		—	
2		1.28 (0.66-2.47)		1.13 (0.50-2.55)	
3		1.73 (0.42-7.14)		2.40 (0.29-20.28)	
4		1.09 (0.26-4.49)		1.27 (0.16-9.85)	
Tumor	237				
Central		1.44 (0.83-2.49)	.19	0.86 (0.40-1.85)	.70
Peripheral (Ref)		—		—	
Dose	251		.56		
50 Gy (Ref)		—			
54/60 Gy		1.37 (0.72-2.60)			
Unknown		1.46 (0.45-4.74)			
Smoking pack-years	174	1.00 (0.99-1.01)	.88		
Maximum tumor dimension	239	0.99 (0.78-1.27)	.96		
Pretreatment PET SUV	168	1.00 (0.94-1.07)	.96	0.98 (0.91-1.06)	.66

Abbreviations: AHR = Adjusted hazard ratio; CI = confidence interval; HR = hazard ratio; LLL = left lower lobe; LUL = left upper lobe; NSCLC = non–small-cell lung cancer; PET = positron emission tomography; Ref = reference; RLL = right lower lobe; RML = right middle lobe; RUL = right upper lobe; SUV = standardized uptake value.

disease who had tumors $\geq$ 4 cm in diameter,[20,21] further muddying its role in combination with SBRT. Finally, systemic therapy is not without cost, both to patient health and quality of life, in addition to increased financial burden to the health care system, making it even more prudent to identify factors that may help establish its role. This is another opportunity where molecular subtyping may identify patients who are most likely to benefit from systemic therapy.

On literature review, other studies have tried to identify variables that may predict distant failure. One study by Zhou et al sought to predict early distant failure in early-stage NSCLC treated with SBRT through the use of machine learning-based models, using similar characteristics to those utilized in our database. Clinical parameters, including demographics, tumor characteristics, treatment parameters, and pretreatment medications, were used in a predictive model, and, through use of the support vector machine model, which analyzes data for both classification and regression, one could predict for early distant failure in patients treated with definitive SBRT with high rates of sensitivity and specificity.[22] Clarke et al found that, in medically inoperable patients with early-stage NSCLC treated with SBRT, baseline maximum SUV on FDG-PET prior to therapy predicted for distant failure, with higher rates of failure correlating to a baseline maximum SUV above 5.[23]

We sought to identify patients at highest risk of distant failure, through exploration of patient profiles and tumor characteristics, to create a clinically applicable method of stratifying patients for everyday use and to ideally identify a subset of patients who could receive early intervention with upfront systemic therapy and improve rates of distant failure. In our study, advanced age was the only notable factor we were able to find. Central tumor location trended toward higher likelihood of distant failure, though this did not reach significance. It is possible that with a larger sample size,

small differences in in distant metastases could be detected. Our distant failure rates were comparable with other studies, so there did not appear to be an unusually low percentage of events.

There are several potential limitations in this study. These include the retrospective design of the study. It could be underpowered to detect small differences in distant metastases and would benefit from evaluation with greater patient numbers in a multi-institutional setting. It is also limited to patients treated with SBRT who are routinely medically inoperable. This makes the competing risk of death greater for such patients with advanced age, greater comorbidities, and/or poorer lung function relative to a surgical population.

Chaudhuri et al looked at circulating tumor DNA (ctDNA) in the blood of patients with localized primary lung cancer, before and after treatment with either radiotherapy or surgery. They found patients with detectable ctDNA post treatment had significantly worse outcomes and suggested that detection of ctDNA post-therapy could be an indication for administration of a first-line targeted therapy.[24] There is increasing utilization of molecular testing to determine epidermal growth factor receptor/anaplastic lymphoma kinase/ROS status and programmed death-ligand 1 expression on advanced stage and metastatic NSCLC patients, to determine who may benefit from addition of targeted agents. At the present time though, such testing is under investigation for patients with early-stage disease.[25-27] The current ALCHEMIST trial (The Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials) is looking at such factors and requires upfront genotyping for epidermal growth factor receptor mutations and anaplastic lymphoma kinase rearrangement in patients with surgically treated non−small-cell carcinoma of the lung. Patients who test positive are subsequently treated with adjuvant erlotinib or crizotinib, pending their receptor status, following complete resection with lobectomy. Patients without an actionable mutation can be enrolled and randomized to immunotherapy or observation.[28] Perhaps the next frontier should be to pursue something similar with SBRT. In addition, instead of focusing on patient clinicopathologic features, perhaps the focus should be on precision molecular features to create predictive assays for distant failure.

Conclusion

In early-stage lung cancer, SBRT provides excellent local control, but the primary pattern of failure is distant. This retrospective, multi-institutional study sought to assess whether clinical parameters, such as tumor size, location and histology, PET/CT SUV, and age, could help predict which patients are at highest risk for distant failure. Although younger age was the only parameter that we found to be significant in predicting for higher rates of distant failure, there is the competing risk of death for older patients. Future studies should utilize molecular analyses, in addition to tumor characteristics, to guide management and perhaps identify those patients who may benefit from a combination of upfront SBRT and systemic therapy to improve distant failure rates.

Clinical Practice Points

- At this time, we know that the use of SBRT is an effective means of primary therapy for early-stage NSCLC with excellent rates of local control. Despite high rates of local control, a majority of these patients will fail distantly. Currently, we do not offer any additional therapy to these patients.
- This study sought to determine if there were any factors that helped predict which patients were more likely to fail distantly, so that those characteristics could be utilized in the future to help define a subset that may benefit from other treatment modalities. Although we were only able to find age as a significant risk factor, we feel this area warrants more research, particularly in the new era of combined immunotherapy and radiotherapy.
- It is important to now address that the primary pattern of failure in these patients is distant, and perhaps other molecular analyses should be done, in addition to focusing on patient and tumor characteristics, in these patients to identify those patients at highest risk of failure that may benefit from other systemic therapy to improve rates of distant failure.

Disclosure

The authors have stated that they have no conflicts of interest.

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