Use of Frailty to Predict Survival in Elderly Patients With Early Stage Non-Small-Cell Lung Cancer Treated With Stereotactic Body Radiation Therapy

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Scholarly Report Title: Use of Frailty to Predict Survival in Elderly Patients with Early Stage Non-Small-Cell Lung Cancer Treated with Stereotactic Body Radiation Therapy

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Abstract

TITLE: Use of Frailty to Predict Survival in Elderly Patients with Early Stage Non-Small-Cell Lung Cancer Treated With Stereotactic Body Radiation Therapy

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Purpose: Frailty has been shown to increase morbidity and mortality independent of age, but studies are lacking in radiation oncology. This study evaluates a modified frailty index (mFI) in predicting overall survival (OS) and non-cancer death for Stage I/II [N0M0] Non-Small-Cell Lung Cancer (NSCLC) patients treated with Stereotactic Body Radiation Therapy (SBRT).

Methods: Medical records for all patients with Stage I/II NSCLC treated at our institution with SBRT from 2009-2014 were reviewed. A validated mFI score, consisting of 11 variables was calculated, classifying patients as non-frail (0-1) or frail (≥2). Primary endpoint (OS) was analyzed using Kaplan-Meier method and log-rank. Secondary endpoint, non-cancer death, was analyzed using Fine-Gray's method, with death from lung cancer as a competing risk.

Results: Patient cohort consisted of 38 (27.3%) non-frail and 101 (72.7%) frail [median total mFI score 3.0 (range 0-7)]. Median age and pack-year history was 74 and 46 years, respectively. Median follow-up among survivors was 38.5 months (range 4.0-74.1 months). Frailty was associated with a lower 3-year OS (37.3% vs. 74.7%; p=0.004) and 3-year cumulative incidence of non-cancer death (36.7% vs. 12.5%; p=0.02). Frailty remained significant in the multivariate model [OS HR for mFI ≥2: 2.25 (1.14-4.44); p=0.02].

Conclusion: Frailty is associated with lower OS in elderly patients with early stage NSCLC treated with SBRT, yet frail patients survived a median 2.5 years, and were more likely to die of causes unrelated to the primary lung cancer, suggesting SBRT should be considered even in older patients deemed unfit for surgery.

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Glossary:

CI: Cummulative Index

CT: Computed Tomography

CTCAE: Common Terminology Criteria for Adverse Events

Gy: Gray

mFI: Modified Frailty Index

NSCLC: Non-Small-Cell Lung Cancer

OS: Overall Survival

RTOG: Radiation Therapy Oncology Group

SBRT: Stereotactic Body Radiation Therapy

Contributions to the work:

As the first author on this manuscript, I had the principal role designing the project, including initial formulation of the goals and aims of the paper. With the assistance of the project mentor, Dr. Raymond Mak, we decided to study the role of frailty in outcomes for early stage lung cancer patients and I set out to conduct literature reviews on appropriate indices and what was known in the field. I found that frailty had not been explored within radiation oncology, but similar fields including medical oncology and surgical oncology had applicable data on the role of frailty in cancer patients and treatment outcomes. Based on the similarity of the patient population to the surgical early non-small-cell lung cancer population I decided that the modified frailty index (mFI), previously studied in surgical oncology, could serve as an appropriate metric for our outcome of interest. I used the existing database created to evaluate outcome of Stereotactic Body Radiation Therapy on lung cancer patients and added the eleven variables needed to determine the composite mFI. This database was maintained at the time by the research assistant, John Romano, who helped design the software for data collection. In addition to the frailty variables, outcomes and descriptive variables were also necessary and were collected and recorded in the medical record by the radiation oncologist and surgical oncologist that also served as collaborators on the project: Drs. Elizabeth Baldini, Aileen Chen, Yolonda Colson, David Kozono, Jon Wee and Raymond Mak. Data was extracted and entered into the RedCap Software by myself, Fallon Chipidza, Vishesh Agrawal, John Romano, and Ying Hou. Once all the data was recorded I went through and verified that all entries were correct and valid. I then performed data cleaning and initial statistical analysis in SAS, with Drs. Raymond Mak and Vishesh Agrawal helping me troubleshoot and think through how to best approach the research question including conducting a secondary analysis for competing risks. Once I had completed the initial analysis, I completed descriptive tables and figures and took the code to our statistician, Yu-Hui Chen, who verified the statistical output and helped me create the final figures and tables for the manuscript submission. Once all this was completed I composed the first draft of the paper which was sent out to all the co-authors for feedback and additional guidance. All authors provided valuable feedback in manuscript structure and data presentation. Drs. Elizabeth Baldini, Aileen Chen, Yolonda Colson, David Kozono, Jon Wee and Raymond Mak provided expert opinions on technical aspects of the paper and valuable references to include in the final submission. Once the paper had undergone multiple revisions all authors approved the final manuscript and suggested potential reviewers. The project mentor and I reviewed potential submission venues that were most appropriate for the manuscript topic and decided on the Journal of Geriatric Oncology. I then went through the submission process and am awaiting a final decision from the editors.

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Appendix 1:

Manuscript Submitted for Publication

1. Introduction

While cigarette smoking has continued to decline in the United States over the past decade, lung cancer remains the malignancy with the second highest incidence and highest number of estimated deaths for both men and women. Non-Small-Cell Lung Cancer (NSCLC), the most common type of lung cancer, composes 85-90% of lung cancers, with surgical resection as the treatment of choice. Yet, for many older patients, the risk of postoperative morbidity and mortality is not trivial, and radiation treatment has become an attractive modality in treating this sicker patient population.[1], [2], [3] and [4]

Although more than one-third of cancers are diagnosed in adults over age 70, chronological age alone appears to be a poor predictor of treatment tolerance and outcomes.[5] Functional status, cognition, and comorbidities are variable in older patients and can also influence tolerance to cancer therapy. Reports from the American Geriatric Society and National Institute on Aging have emerged in recent years highlighting the importance of understanding the clinical definition and physiological characteristics encompassing vulnerability intrinsic in frail adults.[6]

The multidomain definition of frailty, comprised of the cumulative effect of individual deficits in physical, cognitive, functional and social domains, has been used throughout the medical literature.[7] Frailty, defined through a modified frailty index (mFI), has gained popularity in the surgical field as a reliable means of predicting morbidity and mortality in vulnerable elderly populations. Multiple studies have shown the mFI to accurately stratify patients at increased risk of postoperative delirium, institutionalization, readmission, and increased length of stay.[8], [9], [10] and [11] This mFI, created by mapping 11 variables available in the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) to the Canadian Study of Health and Aging Frailty Index (CSHA-FI), has been shown to be useful in preoperative patient selection to minimize negative outcomes for early stage NSCLC patients undergoing lobectomy.[12] and [13]

Historically, conventional radiotherapy or watchful waiting were the only options available for non-surgical candidates.[14] and [15] A meta-analysis of conventional radiotherapy for NSCLC by Qiao et al. looking at 18 papers published between 1988 and 2000 found a 3-year OS of 34%.[16] Outcomes drastically improved with the development of Stereotactic Body Radiation Therapy (SBRT), and prospective studies have demonstrated substantially higher primary tumor control, with a low risk of severe toxicity, compared to conventional radiotherapy [17] and [18], making SBRT the guideline-recommended treatment of

choice for peripherally located, early stage NSCLC in medically inoperable patients, or those refusing surgery.[4]

Despite development of this effective treatment option for high-risk NSCLC patients, the current U.S. Preventive Services Task Force recommendation of annual CT screening for lung cancer excludes those patients unable or unwilling to have curative surgery.[19] This is likely due to high-risk patients having multiple competing causes of death, including chronic obstructive lung disease, coronary artery disease, and other smoking related diseases that outweigh the potential long-term benefits of cancer treatment.[18] The fact remains that overall risk-benefit ratios must be understood within the heterogeneous aging population to better guide treatments.

Despite the growing literature describing the usefulness of frailty in risk stratification for surgery and medicine, to our knowledge there are no prior studies assessing frailty within the field of Radiation Oncology. As the proportion of nonsurgical thoracic oncology patients continues to increase, it becomes crucial to incorporate baseline metrics of overall fitness, which are more predictive than age, to identify older cancer patients most at risk for adverse outcomes. The current study evaluates the use of the mFI in predicting overall survival and risk of non-cancer death for Stage I/II (N0M0) NSCLC patients treated with SBRT.

2. Materials and Methods

2.1 Patients

With Institutional Review Board approval, medical records for all patients with Stage I/II (N0M0) NSCLC treated with SBRT in our department from 2009-2014 were reviewed. NSCLC Stage I/II (N0M0) was defined per the American Joint Committee on Cancer (AJCC 7th edition)[20], with the highest classification as Stage IIA [T2b N0 M0]: tumor more than 5cm but 7cm or less in greatest dimension [T2b], no regional lymph node metastasis [N0], no distant metastasis [M0]. Patient, tumor, treatment characteristics, and outcomes data were collected. Patients who received SBRT for locally recurrent disease, local progression of advance stage disease, small cell lung cancer, or metastases to the lung from other sites of primary disease were excluded. In nine patients who underwent two SBRT treatments for two primary lung cancers, only data from the most recent SBRT treatment was used.

2.2 Endpoints

Data on patient vital statistics were updated through December 2015. Information on death was obtained from electronic medical records as well as the U.S. Social Security Death Index database.[21] Information on cause of death was obtained from the medical record, when available, and categorized as: death of disease, death of other causes, and death of unknown causes. There were no deaths due to treatment-related toxicity. The endpoints for overall survival (OS) in the survival analysis were calculated from the

start date of radiation therapy (SBRT) to the date of death or last date known alive. For competing risk analyses, other and unknown causes of death were combined and compared to death from lung cancer.

Data on recurrence was categorized as per RTOG 0236[17]: (1) primary tumor recurrence [tumor recurrence in-field or within 1 cm of planning target volume], (2) lobar recurrence [including primary tumor and recurrence in the same lobe], (3) local/regional recurrence [composite of lobar recurrence and hilar/mediastinal recurrences], and (4) distant metastases. Recurrence-Free Survival (RFS) was determined from date of first radiation treatment to date of any recurrence or death; whichever came first (with censoring of patients at last disease assessment who died without documented recurrence and death occurred greater than 6 months from date of last disease assessment). Toxicity was graded per CTCAE v4.0. Rib fracture was recorded as a binary variable.

2.3 Treatment Approach

All patients were evaluated by a thoracic surgeon and radiation oncologist and deemed to be inoperable or borderline operable, and opted for treatment with SBRT. Patients were treated with SBRT per institutional norms to a dose of 10 to 12 Gy x 5 fractions for tumors adjacent to chest wall or central tumors, and 18 Gy x 3 fractions for peripheral tumors. Follow-up occurred every 3 to 4 months after treatment for the first 2 years with a chest CT, then every 6 months for the next three years, and annually thereafter.

2.4 Modified Frailty Index

The validated mFI score, consisting of 11 variables was calculated by assigning one point for each of the following: performance status ≥2, impaired sensorium, diabetes mellitus, chronic/acute lung disease, myocardial infarction in past ≤ 6 months, hospitalization for congestive heart failure in past ≤6 months, coronary or cardiac disease, hypertension on medications, history of transient ischemic attack, cerebrovascular accident or stroke with neurological deficits, and peripheral vascular disease. Frailty status was defined as non-frail (score 0-1) and frail (score ≥2), as previously described in the literature.[9] and [10]

2.5 Statistical Analyses

Descriptive statistics were assessed for pre-treatment patient, tumor characteristics, and mFI components. The distribution of characteristics by frailty status was performed using Chi-square /Fisher's exact test or Wilcoxon Rank-Sum. Time-to-event outcomes were analyzed using the Kaplan-Meier method and log-rank test. Multivariate Cox Proportional Hazards model for OS was created via stepwise selection with p=0.15 as the inclusion and removal criteria. As a secondary analysis, the risk of non-cancer death was analyzed by frailty status using Fine-Gray's method with death from lung cancer as a competing risk.

Study data were collected and managed using REDCap electronic data capture tools hosted at our institution.[22] Statistics were performed using SAS version 9.4 (SAS Institute, Cary, NC) with competing risk analysis done in R version 2.10.0 (R Foundation, Vienna, Austria). Two-sided p-values were used, and p-values less than 0.05 were considered statistically significant.

3. Results

3.1 Patient Characteristics

The study cohort consisted of 139 patients with early stage NSCLC treated with SBRT. Pretreatment characteristics for all patients and comparison by frailty status are shown in Table 1. Median age was 74 years [Interquartile Range 66, 80], median pack-year smoking history was 46 [IQR 30, 65] and median Body Mass Index (BMI) was 25.7 [IQR 22.4, 30.5]. Fifty-two percent of the population consisted of women. Most common histology was adenocarcinoma at 43%, followed by squamous cell carcinoma at 25%. Over 85% of patients had Stage IA disease and 84.9% were T1. Comparisons by frailty status showed frail patients were older (54.5% vs. 34.2% above age 74; p=0.04) and had a more extensive smoking history (50 vs. 40 pack-years; p=0.01).

In looking at the entire patient cohort, with respect to the eleven components comprising the modified frailty index (mFI), seven factors were significantly higher in the frail group compared to the non-frail group (Table 2). These included: hypertension on medications (75.3% vs. 34.2%; p<0.0001), history of hospitalization due to chronic obstructive pulmonary disease or pneumonia ≤ 6 months (60.4% vs. 15.8%; p<0.0001), history of CAD (53.3% vs. 5.3%; p<0.0001), performance status ≥2 (49.5% vs. 5.3%; p<0.0001), history of diabetes mellitus (36.6% vs. 2.6%; p<0.0001), history of transient ischemic attack (16.8% vs. 0.0%; p=0.004) and history of peripheral vascular disease (26.7% vs. 2.6%; p=0.0008). The remaining four factors were not statistically different between groups.

3.2 Outcomes

The median follow-up time among survivors was 38.5 months (range 4.0-74.1 months). Outcomes are shown in Table 3. Frail patients had a statistically significant lower 3-year OS than non-frail patients (37.3% vs. 74.7%; p=0.003; Figure 1) and higher Cumulative incidence (CI) of non-cancer death (3-year CI 44.1% vs. 12.5%; p=0.02; Figure 2). Three-year Recurrence-Free Survival was lower in the frail group (34.2% vs. 62.2%; p=0.005), with three-year recurrence free rates, either within the area of the primary tumor or lobe, significantly lower for the frail group. There was a low incidence of treatment-related toxicities, all grade 3 or lower, with no significant differences between groups.

3.3 Univariate and Multivariate Analysis

On univariate analysis, significant adverse predictors for OS included frail status, male gender, and increased pack-years of smoking (Table 4). On multivariate analysis, both frailty [HR 2.25; (1.14-4.44); p=0.02] and smoking remained associated with OS.

A secondary analysis for competing risks (Table 5) showed frailty as significantly associated with increased non-cancer mortality (lung cancer death as a competing risk) [HR for mFI ≥2; 2.66 (1.15-6.14); p=0.02]. On a competing risk, univariate analyses for lung cancer-specific survival (with death from other causes as a competing event), only pack-years of smoking was significant [HR 1.01; (1.00-1.02); p=0.02].

4. Discussion

In this study of early stage NSCLC patients treated with SBRT, we found that frailty, defined by an mFI ≥2, was significantly associated with a lower OS and higher risk of non-cancer death. However, the fact that frail patients in this study had a 3-year OS of ~40%, median survival >2.5 years, and three year local failure of 21%, compared to the 3-year OS of 34% and three year local failure of 40% found by Qiao et al., prior to SBRT, suggests that this treatment modality may still be beneficial for patients who are too frail for surgery, chemotherapy, or other modalities.[23] Additionally, the significant difference in outcomes seen between frail and non-frail patients found in our study highlights the important role that frailty can play in stratifying overall risk-benefit ratios within the heterogeneous aging population.

To our knowledge, the use of the mFI to predict outcomes has never been reported in radiation oncology, and the impact of frailty in patients treated with RT is poorly understood. The advantages of applying the mFI to understand prognosis and life expectancy in patients under evaluation for RT include: 1) simple interpretation with a binary question of whether a patient has more than one component of the mFI; 2) ease of obtaining this information from the patient and/or medical record. The use of the mFI in Radiation Oncology can meaningfully enhance the discussion between the patient and provider when discussing expectations and predicted outcomes. Importantly, the mFI considers performance status, assigning one point for performance status ≥2, a variable which is not considered by the Charlson Comorbidity Index (CCI), but has been found to be a significant, independent prognostic factor in NSCLC.[24] The mFI also considers recent respiratory and cardiac events, ≤ 6 months, whereas the CCI does not account for the timeline of recent events, which can decrease a patient's physiological reserve to adequately recover from additional stressors, and have been found to be important in determining outcomes for NSCLC patients treated with SBRT.[25] While it was not the focus of our paper to do a comparison between the use of the CCI and mFI in predicting outcomes, a secondary analysis incorporating both indices in the final model showed frailty continued to be a significant predictor of overall survival whereas CCI lost significance after accounting for all other covariables. Further studies will be necessary to fully elucidate the role that

both frailty and comorbidities play in predicting outcomes for this aging population, but this finding underscores the importance of considering novel metrics, such as frailty, to inform shared decision making in the aging population.

Our study also highlights the potential usefulness of the mFI as a risk stratification tool that can be utilized by surgeons and radiation oncologists in multidisciplinary teams to identify optimal local therapy for high-risk patients. The mFI has been used in surgical series as a tool for predicting morbidity and mortality in thoracic surgery and the findings of the current study show it may also be a valuable predictive tool in radiation oncology.[26] and [27] Results of the current study also illustrate the survival benefits of SBRT for high risk patients, and the potential impact this may have on screening guidelines which currently exclude patients unable or unwilling to have curative surgery.[19] One other important finding that highlights the need to stratify results of SBRT outcomes by frailty status is seen when comparing the current findings to those seen in the Indiana Study (RTOG 0236), a prospective Phase II trial for SBRT in medically inoperable patients with a current 50 month follow time.[17] In the Indiana study the OS at 3-years was reported to be 42.7%, similar to that seen at our institution 46.2%. Yet, when this overall survival is further stratified into non-frail and frail patients we see that there is a striking difference between groups with 3-year OS of non-frail at 74.7% compared to 37.3% in the frail population ($p=0.003$). Therefore, a better understanding of frailty status, even within this high-risk lung cancer population, has the potential to improve patient risk stratification, and is critical to better identify cancer patients that are likely to benefit from, and tolerate, more aggressive treatments, helping reduce the underutilization of cancer screening and treatments in older patients.[28] and [29]

Given the prevalence of smoking in medically inoperable NSCLC patients, it is also important to understand the interaction between mFI and smoking status. In the Canadian Study of Health and Aging, heavy smokers (>20 pack-years) had a significantly higher frailty index, even when eliminating deficits consistently associated with smoking such as hypertension and cough. They also had higher mortality, due to any cause, than never smokers. Their study provided evidence that the associated inferior health status related to smoking could be captured through the frailty index.[30] Our current study also found a strong association between mFI and pack-year history ($p=0.013$), which is not surprising given the known correlation of smoking with components of the mFI such as cardiovascular conditions, COPD, and diabetes. Yet, frailty continued to be significant in predicting OS even after adjusting for pack-years ($p=0.02$) and showed a trend toward significance for non-cancer specific mortality ($p=0.07$).

These results should be interpreted in the context of the study design. Limitations to this study include weaknesses intrinsic to retrospective data collection and a relatively small sample size, such as incomplete data and follow-up. Additionally, the low incidence of severe toxicity and lack of patient-

reported outcomes does not allow us to adequately model the association between frailty and SBRT-toxicity. Another limitation is the fact that we were not powered to look for patients who were extremely frail. The highest frailty score in our dataset was 6, even though the frailty score is designed to go up to a value of 11. This is an important direction for future studies as it is possible that there is a point where a patient is too frail, even for a non-invasive procedure such as SBRT. Additionally, a sub analysis of the components of the modified frailty index most predictive of the outcomes of interest for SBRT could allow for the development of an even more targeted prediction model. Future analyses validating a more targeted index model with larger data sets and prospective data acquisition will be necessary to better characterize the impact of frailty on this patient population.

As frailty continues to become an emerging public health priority, our current study, and similar studies will play a pivotal role in describing the impact of frailty on outcomes after oncologic therapies.[31] Our findings suggest that assessment of frailty, through a simple clinical tool, has the potential to help predict overall survival, identify patients most at risk for death of non-cancer causes, improve patient care in lung cancer and add valuable information for an informed dialogue between patients and providers.

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Figure 1: Kaplan-Meier curves of overall survival for frail and non-frail patients with Stage I/II NSCLC treated with SBRT

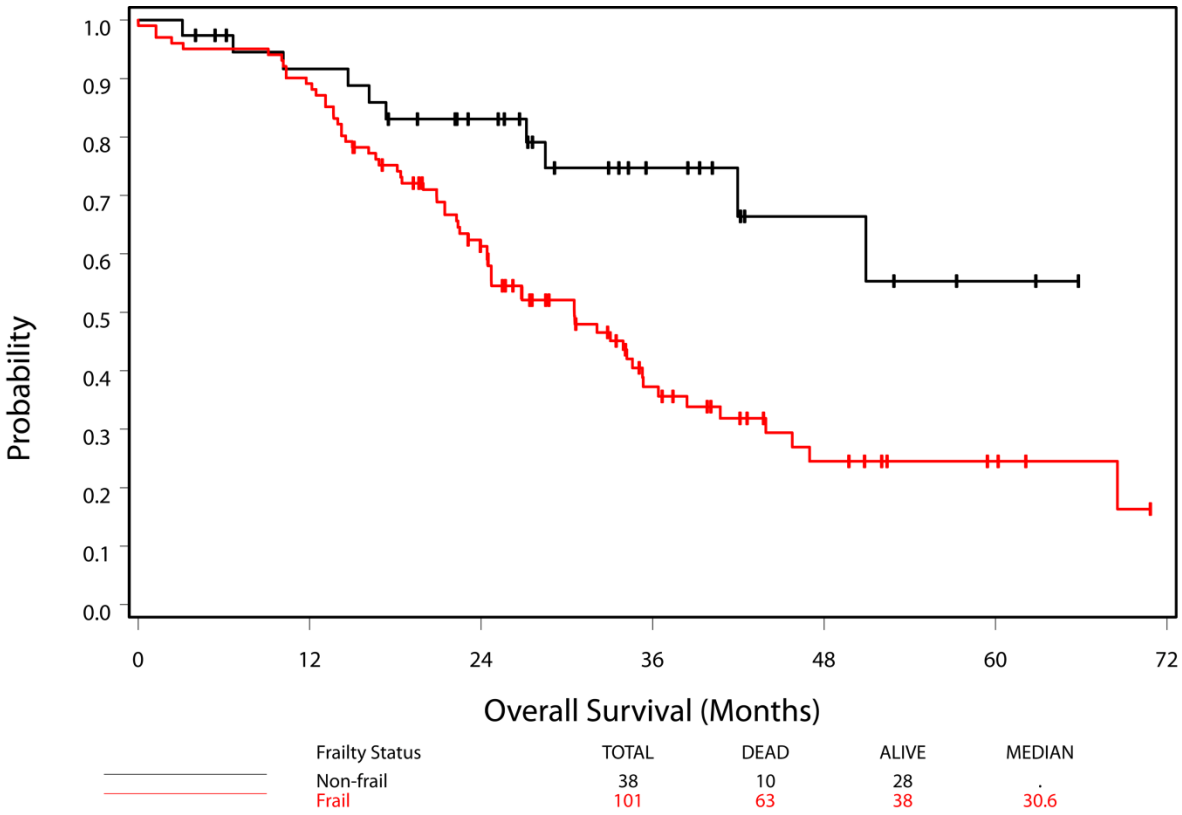

Figure 2: Cumulative incidence of non-cancer deaths by frailty status for patients with Stage I/II NSCLC treated with SBRT

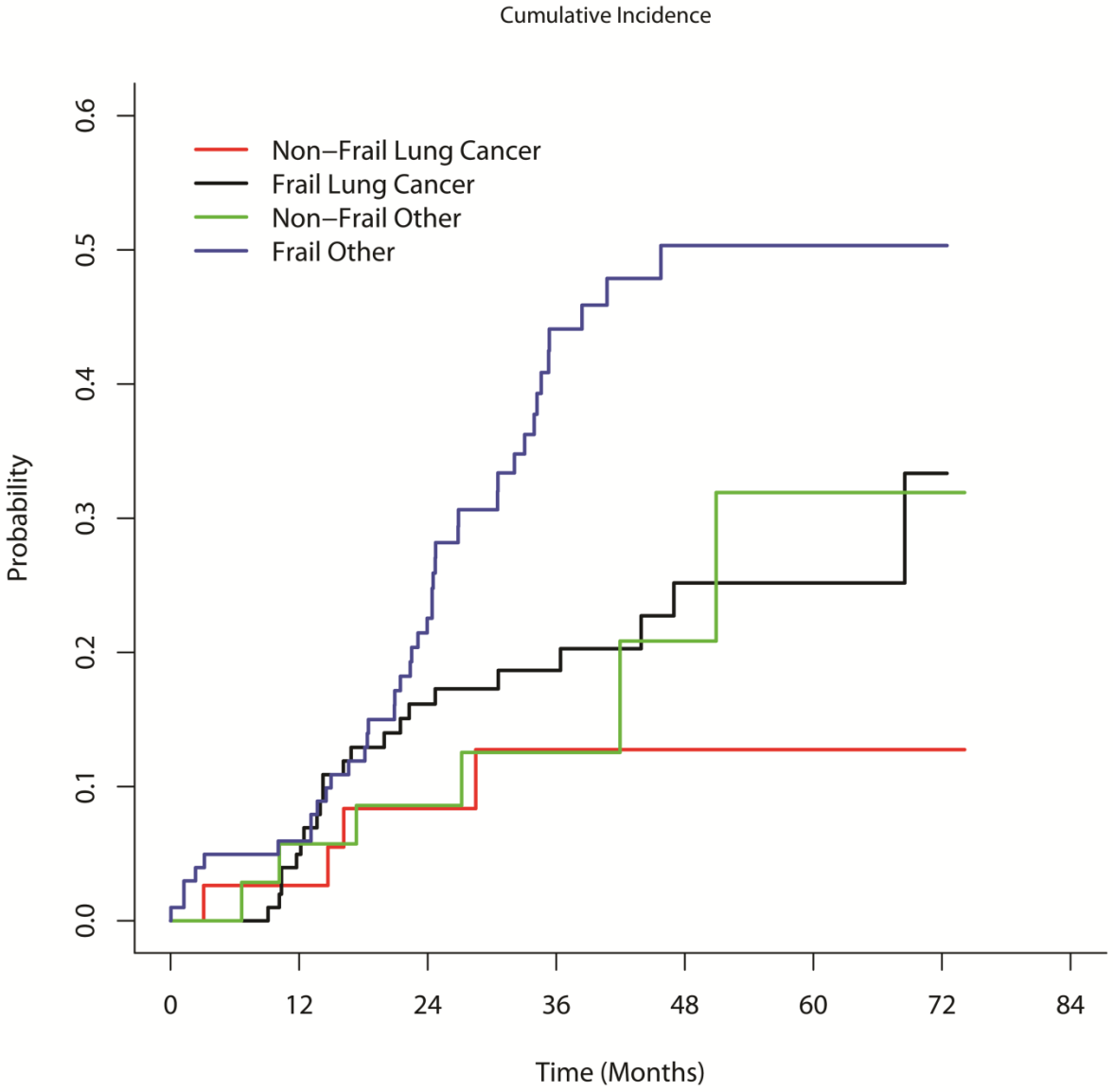

Table 1. Patient and Tumor Characteristics for patients with early stage NSCLC treated with SBRT with Comparisons by Frailty Status

	All Patients	Non-Frail Patients (mFI<2)	Frail Patients (mFI≥2)	p-value
N	139	38	101	
Age (years)				
≤74	71 (51.1%)	25 (65.8%)	46 (45.5%)	
>74	68 (48.9%)	13 (34.2%)	55 (54.5%)	0.04
Gender				
Female	72 (51.8%)	25 (65.8%)	47 (46.5%)	
Male	67 (48.2%)	13 (34.2%)	54 (53.5%)	0.06
Pack-years[a]	46	40	50	
Median [interquartile range]	[30,65]	[20,54]	[35,70]	0.013
BMI (kg/m^2)	25.7	24.5	26.3	
Median [interquartile range]	[22.4,30.5]	[21.5, 28.3]	[22.8,31.3]	0.07
Previous cancer diagnosis	85 (61.2%)	33 (86.8%)	52 (51.5%)	0.0002
Histology				
Adenocarcinoma	60 (43.2%)	21 (55.3%)	39 (38.6%)	
Squamous Cell Carcinoma	35 (25.2%)	6 (15.8%)	29 (28.7%)	
Other NSCLC	18 (12.2%)	3 (7.9%)	15 (14.9%)	
Clinical Diagnosis	26 (18.7%)	8 (21.1%)	18 (17.8%)	0.29
Stage				
IA	120 (86.3%)	35 (92.1%)	85 (84.2%)	
IB/ IIA	19 (13.7%)	3 (7.9%)	16 (15.8%)	0.28
Clinical T Stage (AJCC 7th edition)				
T1	118 (84.9%)	34 (84.4%)	84 (83.2%)	
T2	21 (15.1%)	4 (10.5%)	17 (16.8%)	0.36

[a]n=138

Table 2. Components of Modified Frailty Index

	All patients (n=139)	Non-frail patients (MFI <2/11; n=38)	Frail Patients (MFI ≥2/11; n=101)	p-value comparing non-frail to frail patients
Performance Status ≥ 2 (partially or totally dependent)	52 (37.4%)	2 (5.3%)	50 (49.5%)	<0.0001
Impaired Sensorium (history of cognitive impairment and delirium/clouding)	5 (3.6%)	1 (2.6%)	4 (4.0%)	1.00
Diabetes Mellitus	38 (27.3%)	1 (2.6%)	37 (36.6%)	<0.0001
Chronic or acute lung disease (History of Chronic Obstructive Lung Disease or Pneumonia ≤ 6 months).	67 (48.2%)	6 (15.8%)	61 (60.4%)	<0.0001
Myocardial Infarction ≤ 6 months	5 (3.6%)	0 (0.0%)	5 (5.0%)	0.3227
History of congestive heart failure ≤ 6 months	1 (0.7%)	0 (0.0%)	1 (1.0%)	1.00
History of coronary or cardiac disease	56 (40.3%)	2 (5.3%)	54 (53.5%)	<0.0001
Hypertension on medications	89 (64.0%)	13 (34.2%)	76 (75.3%)	<0.0001
History of Transient Ischemic Attack	17 (12.2%)	0 (0.0%)	17 (16.8%)	0.0036
History of Cerebrovascular Accident/ Stroke with neurologic deficit	8 (5.8%)	1 (2.6%)	7 (6.9%)	0.4462
History of Peripheral Vascular Disease	28 (20.1%)	1 (2.6%)	27 (26.7%)	0.0008

Table 3. Death, Recurrence, and Toxicity by Frailty Status

	All patients (n=139)	Non-frail patients (mFI <2; n=38)	Frail Patients (mFI ≥2; n=101)	p-value
Three-Year Survival Estimates				
Overall Survival	46.2%	74.7%	37.3%	0.004
Cumulative incidence of lung cancer-specific death	17.1%	12.8%	18.7%	0.24
Cumulative incidence of non-cancer death	36.7%	12.5%	44.1%	0.02
Three-Year Recurrence-Free Rates				
Primary Tumor	90.6%	100.0%	86.8%	0.05
Lobar	84.9%	100.0%	79.0%	0.01
Local/regional	74.8%	84.7%	70.8%	0.06
Distant Metastasis	71.6%	80.6%	67.4%	0.12
Recurrence-Free Survival at three years	41.5%	62.2%	34.2%	0.005
Toxicity				
Highest Grade Esophagitis on CTCAE 4.0				
Grade 1	1 (0.7%)	0 (0.0%)	1 (1.0%)	
Grade 2	1 (0.7%)	0 (0.0%)	1 (1.0%)	
Grade3	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.00
Highest Grade Pneumonitis on CTCAE 4.0				
Grade 1	5 (3.6%)	1 (2.6%)	4 (4.0%)	
Grade 2	3 (2.2%)	2 (5.3%)	1 (1.0%)	
Grade 3	1 (0.7%)	0 (0.0%)	1 (1.0%)	0.48
Highest Grade Chest Wall Pain on CTCAE 4.0				
Grade 1	6 (4.3%)	2 (5.3%)	4 (4.0%)	
Grade 2	3 (2.2%)	1 (2.6%)	2 (2.0%)	
Grade 3	1 (0.7%)	1 (2.6%)	0 (0.0%)	0.39
Rib Fracture	4 (2.9%)	1 (2.6%)	3 (3.0%)	1.00

Table 4: Univariate and Multivariate Cox Proportional Hazards Survival Analysis for patients with Stage I/II NSCLC treated with SBRT

	Univariate Analysis[a]		Multivariate Analysis	
Variable	Hazards Ratio (95% CI)	p-value	Adjusted Hazards Ratio (95% CI)	p-value
Frail (mFI≥2/11)	2.68 (1.37-5.23)	0.004	2.25 (1.14-4.44)	0.02
Age >74	1.04 (0.65-1.64)	0.88		
Female	0.51 (0.32-0.82)	0.005	0.63 (0.38-1.05)	0.07
Pack-years of smoking	1.01 (1.01-1.02)	0.0002	1.01 (1.00-1.02)	0.003
BMI	1.03 (0.99-1.07)	0.16		
Previous Cancer Diagnosis	0.75 (0.48-1.19)	0.23		
Clinical Diagnosis (No Pathology)	Ref			
Adenocarcinoma	0.83 (0.41-1.68)	0.61		
Squamous Cell Carcinoma	1.47 (0.71-3.04)	0.30		
Other NSCLC	1.38 (0.61-3.11)	0.44		
Overall Stage (IB/IIA vs. IA)	1.27 (0.68-2.35)	0.46		
Clinical T Stage (T2 vs. T1)	1.17 (0.63-2.17)	0.63		

[a]Univariate analysis represents a single variable Hazard Ratio analysis with Overall Survival (OS) as the outcome.

Table 5: Secondary Analysis Showing Competing Risk for Non-Cancer Death with Lung Cancer as the Competing Event

	Univariate Analysis[a]	
Variable	Hazards Ratio (95% CI)	p-value
Frail (mFI≥2/11)	2.66 (1.15-6.14)	0.02
Age > 74 (year)	1.21 (0.69-2.13)	0.52
Female	0.38 (0.21-0.69)	0.002
Pack-years of smoking	1.01 (0.998-1.02)	0.12
BMI	1.01 (0.96-1.06)	0.72
Previous Cancer Diagnosis	0.86 (0.49-1.52)	0.61
Clinical Diagnosis (No Pathology) Adenocarcinoma Squamous Cell Carcinoma Other NSCLC	1.00 0.99 (0.40-2.43) 2.10 (0.84-5.25) 1.76 (0.65-4.80)	 0.98 0.11 0.27
Overall Stage (IB/IIA vs. IA)	1.06 (0.50-2.24)	0.88
Clinical T Stage (T2 vs. T1)	0.99 (0.46-2.10)	0.97

[a]Univariate analysis represents a single variable Hazard Ratio analysis of Cumulative Incidence of non-cancer death, with death from lung cancer as a competing risk.