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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

Objectives: 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).
Materials and Methods: Medical records for all patients with Stage I/II NSCLC treated at our institution with SBRT from 2009 to 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%; $p = 0.003$) 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 older 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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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 [1,2,3,4].

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 older populations. Multiple studies have shown the mFI to accurately stratify patients at increased risk of postoperative delirium, institutionalization, readmission, and increased length of stay [8,9,10,11]. This mFI, created by mapping 11 variables available in the American College of Surgeons National Surgical Quality

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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 patients with early stage NSCLC undergoing lobectomy [12,13].

Historically, conventional radiotherapy or watchful waiting were the only options available for non-surgical candidates [14,15]. 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 overall survival (OS) of 34% [16]. Outcomes significantly improved with the development of Stereotactic Body Radiation Therapy (SBRT), with prospective studies demonstrating a high primary tumor control, low risk of severe toxicity, improved quality of life and decreased treatment times when compared to conventional radiotherapy [17,18,19], 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 patients with high-risk NSCLC, 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 [20]. 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 patients with cancer 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 patients with Stage I/II (N0M0) NSCLC 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 to 2014 were reviewed. NSCLC Stage I/II (N0M0) was defined per the American Joint Committee on Cancer (AJCC 7th edition) [21], with the highest classification as Stage IIA [T2b N0 M0]: tumor more than 5 cm but 7 cm or less in greatest dimension [T2b], no regional lymph node metastasis [N0], no distant metastasis [M0]. Patient, tumor, treatment characteristics, biologically effective dose (BED), 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 [22]. 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 unknown causes of death were combined and compared to death from lung cancer.

Data on recurrence was categorized as per Radiation Therapy Oncology Group (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 Common Terminology Criteria for Adverse Events (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. As of 2010, our institution began treating patients with early stage NSCLC with a risk-adapted SBRT fractionation approach based on chest wall dosimetry (V30). This was shown by Coroller et al. to result in a chest wall toxicity of 8.3% [23]. In this manner, patients in our study were treated with 18 Gy $\times$ 3 fractions (54 Gy) for peripheral tumors with minimal chest wall contact and CW V30 $\leq$30 ml, and 10–12 Gy $\times$ 5 fractions (50–60 Gy) for central tumors or peripheral tumors with broad chest wall contact and CW V30 $>$ 30 ml, irrespective of subjective assessment of potential patient frailty. Follow-up occurred every three to four months after treatment for the first two years with a chest CT, then every six months for the next three years, and annually thereafter.

2.4. Modified Frailty Index

The validated mFI score, consisting of eleven variables, was calculated by assigning one point for each of the following: performance status $\geq$2, impaired sensorium, diabetes mellitus, chronic/acute lung disease, myocardial infarction in past $\leq$6 months, hospitalization for congestive heart failure in past $\leq$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 $\geq$ 2), as previously described in the literature [9,10].

2.5. Statistical Analyses

Descriptive statistics were used to characterize patients at baseline. Differences in distributions of categorical variables and continuous variables between groups by frailty status were evaluated using Fisher's exact test [24] and Wilcoxon Rank-Sum test [25], respectively. Time-to-event outcomes were analyzed using the Kaplan-Meier method [26] and log-rank test [27].Cox Proportional Hazards model [28] was used to quantify the prognostic value of baseline frailty status on overall survival with adjustment for important patient characteristics via stepwise selection of the variables from the univariate analysis, with $p = 0.10$ as the inclusion and removal criteria. Gray's method [29] was used to compare the cumulative incidence functions between groups by frailty. A secondary analysis, the risk of non-cancer death, was analyzed by frailty status using Fine-Gray's method [30] with death from lung cancer as a competing event.

Study data were collected and managed using REDCap electronic data capture tools hosted at our institution [31]. 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).

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