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Age-not Charlson Co-morbidity Index-predicts for mortality after stereotactic ablative radiotherapy for medically inoperable stage I non-small cell lung cancer

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ABSTRACT

Purpose: In this single institution retrospective study of patients with stage I medically inoperable non-small cell lung cancer (NSCLC) treated with stereotactic ablative radiotherapy (SABR) we attempt to model overall survival (OS) using initial prognostic variables with specific attention on the Charlson co-morbidity index (CCI).

Methods: Between 2008 and 2013, 335 patients with medically inoperable stage I NSCLC were treated with SABR or hypofractionated radiotherapy (50–60 Gy in at least 5 Gy or 4 Gy fractions respectively) at our institution. Medical comorbidities and Charlson scores were determined by individual chart review. Patients were stratified into 3 groups based on the CCI score (0–1, 2–3, 4–9) and again based on the age-adjusted Charlson Comorbidity score (aCCI). Cumulative survival for each stratum was determined using the Kaplan-Meier method. Non-significant and confounding variables were identified and discounted from survival modeling. 3 sex stratified Cox regression models were tested: (1) aCCI with age and comorbidity combined; (2) age and CCI; (3) age alone, comorbidity removed.

Results: The median survival was 4.4 years and the median follow up 4.7 years. The median CCI and aCCI scores were 2 and 5 respectively. Patients with aCCI 7–12 had an increased hazard of death on univariate analysis HR 2.45 (1.15–5.22 95%CI, $p = 0.02$) and -excluding age as a competing variable- on multivariate analysis HR 2.25 (1.04–4.84 95%CI, $p = 0.04$). Patients with CCI 4-9 had an increased hazard of death on univariate analysis HR 1.57(1.30–2.90) but not on multivariate analysis. On formalized testing – with either continuous or categorical variables- all three survival models yielded similar coefficients of effect.

Conclusion: We identify male gender, weight loss greater than 10% and age as independent prognostic factors for patients treated with medically inoperable NSCLC treated with SABR or hypofractionated radiotherapy. Based on our survival models, age alone can be used interchangeably with aCCI or CCI plus age with the same prognostic value. Age is more reliably recorded, less prone to error and therefore a more useful metric than Charlson score in this group of patients.

Introduction

Worldwide, lung cancer is the second most common cancer (13% of all cancers) and the leading cause of cancer deaths (19.4% of cancer deaths) [1]. Stage I (T1-2a, N0) accounts for 18% of lung cancer cases [2]. For patients with stage I non-small cell lung cancer (NSCLC), surgical resection is the standard of care [3]. However, up to 25% of patients with early stage NSCLC are medically inoperable due to co-morbidities such as heart disease, emphysema and advanced age [4]. Stereotactic ablative radiotherapy (SABR) is an excellent alternative to surgery in those patients. The local control rates for SABR approach those of lobectomy (88–92% at 3 years) [5–7]. On the other hand, the reported long term survival rates vary widely and are generally inferior to surgical outcomes for the same stage patient [5]. There is a spectrum of comorbidity in medically inoperable patients that may account for

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variations in survival. How can we predict treatment outcomes in a group of patients with widely varying medical constitution?

The Charlson Comorbidity Index (CCI) was designed as a measure of risk of mortality (based on comorbidity) in longitudinal studies [8]. It is a weighted index that takes into account the number and the seriousness of comorbid diseases by assigning points for certain illnesses. The CCI score is the sum of the points for each disease. The goal is to create a categorical variable (CCI) where the score is proportional to the burden of disease. The age adjusted score (aCCI) assigns an additional point for each decade above the fourth: The higher the score the older and "sicker" the patient. It is not always clear whether studies using the "Charlson Comorbidity" score are referencing aCCI or CCI.

The aCCI has been applied to various clinical scenarios, including other domains of lung cancer. It is tempting to use given its simplicity. We attempt to correlate both aCCI and CCI to outcome with retrospective analysis in medically inoperable stage I NSCLC. Our objective is to further define prognostic factors that can be used to select patients who benefit from aggressive management and possibly those who may avoid it altogether.

Methods

Study population

A single institution ethics approved database for medically inoperable early stage 1 NSCLC treated with radiotherapy at our institution, records outcomes for patients treated between November 1994 and December 2013. The database was created for the purpose of observing patterns of failure post radiotherapy. Patients from the database were deemed eligible for *the present analysis* if they met the following criteria: (1) Pathologic confirmation of NSCLC; (2) clinical stage I lung cancer according to the American Joint Committee in Cancer (AJCC) 7th edition staging manual; (3) treatment with curative intent and with SABR or hypofractionated radiotherapy alone (we define SABR as 50 to 60 Gy delivered in at least 5 Gy fractions and hypofractionated radiotherapy as 50 – 60 Gy in at least 4 Gy fractions). Patients who had received previous thoracic radiation, had a synchronous malignancy more than stage I, or metastatic disease were excluded. 335 patients satisfied these criteria (210 were excluded). After completing their treatment, the patients were followed as per our institution's usual protocol with chest imaging (CT or X-ray) every 3 months for the first year and then every 6 months until the end of 5 years. Overall survival (OS) is defined as the time between biopsy and death of any cause.

Statistical analysis

The aCCI was calculated for each patient based on the age and medical conditions recorded in the health record at the time of diagnosis. The patients were stratified into three groups based on the aCCI score (1–4, 5–6 and 7–12). In an effort to further separate the impact of comorbidity from age, the CCI was similarly calculated for all patients based on the conditions recorded in the health record. Likewise they were stratified into three groups based on the CCI score (0–1, 2–3, 4–9). Cumulative survival for each stratum was determined using the Kaplan–Meier method. The log-rank test was used to compare OS between aCCI groups and between CCI groups.

With special attention to the Charlson comorbidity score, the variables listed in Table 1 were used to generate a series of statistical models to predict OS in this patient group. The selection of variables begins with a univariate analysis followed by evaluation of the proportional hazards assumption and a purposeful selection of variables in the model [17]. Variables with *p*-values greater than 0.2 on univariate analysis were not included in subsequent multivariate analyses. In the variable selection process we used the Wald test from logistic regression and a *p*-value cut-off point of 0.1 to remove the non-significant and confounding variables. After this step, the model is left with variables significant at the 0.05 level and not confounders.

3 sex stratified Cox regression models were tested: (1) aCCI with age and comorbidity combined; (2) Age and CCI; (3) Age alone, comorbidity removed. Models were created using age, CCI and aCCI as continuous or categorized (age dichotomized at median [<75 vs.>75], CCI and aCCI as tercile and quartile). The models were compared using Harrell's C concordance index, Akaike information criterion (AIC) and Bayesian information criterion (BIC). We used Stata version 13.1.

Table 1
Patient characteristics.

Variable		% (n = 335)
Age		74.7
Sex		
	Female	201(60)
	Male	134(40)
Smoking Status		
	Never Smoker	13(4)
	Ex-Smoker	130(39)
	Current Smoker	190(57)
	Unknown	2(1)
Weight Loss		
	<5%	262(78)
	5–10%	27(8.1)
	>10%	34(10)
	Unknown	12(4)
aCCI		
	1–4	135(40)
	5–6	136(41)
	7–12	64(19)
CCI		
	0–1	127(38)
	2–3	148(44)
	4–9	60(18)
Histology		
	Adenocarcinoma	163(49)
	Squamous	82(24)
	Other	90(27)
Performance Status		
	ECOG 0	139(41)
	ECOG 1	112(33)
	ECOG $\geq$ 2	84(25)
Radiation Dose		
	$EQD2_{10} \leq 80$ Gy	16(5)
	80 Gy < $EQD2_{10}$<100 Gy	108(32)
	100 Gy $\leq EQD2_{10} \leq$110 Gy	143(43)
	$EQD2_{10}$ > 110	68(20)
T - Stage		
	T1a	153(46)
	T1 b	112(33)
	T2a	70(21)

Results

Out of 545 patients treated with SABR or hypofractionated RT between January 2008 and December 2013, 335 were included for analysis. 210 patients were excluded from the study: 74 patients with NSCLC > Stage 1; 25 patients with no pathologic confirmation of malignancy; 14 patients with pathology other than NSCLC; 35 patients with other synchronous malignancy; the remaining 64 patients were treated surgically, palliatively, for oligometastatic disease, received up front chemo, were treated at another centre or received no treatment at all.