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Defining Optimal Comorbidity Measures for Patients With Early-Stage Non-Small Cell Lung Cancer Treated With Stereotactic Body Radiation Therapy

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Abstract

Purpose: Comparison of overall survival (OS) between stereotactic body radiation therapy (SBRT) and other treatments for early-stage non-small cell lung cancer is confounded by differences in age, performance status, and medical comorbidity. We sought to define the most robust measurement for this population among 5 indices: age, Eastern Cooperative Oncology Group performance status, Adult Comorbidity Evaluation 27, Charlson Comorbidity Index (CCI), and age-adjusted CCI (CCIA).

Methods and Materials: A total of 548 patients with stage I non-small cell lung cancer treated with SBRT were analyzed. Patients were divided into high- and low-risk groups for OS for each index using the log-rank test. Continuous and dichotomized models were compared via Akaike information criterion and the Vuong test. Multivariate Cox regression modeling was used with demographic information to determine the independent prognostic value of the continuous and dichotomized versions of the indices. The best was used to stratify the patients into as many significantly different cohorts as possible.

Results: Optimal cut-points between high-risk and low-risk OS groups for age, Eastern Cooperative Oncology Group status, Adult Comorbidity Evaluation 27, CCI, and CCIA were 75 years, 1, 3, 3, and 6 with hazard ratios for death of 1.23 (95% confidence interval, 1.00–1.50), 1.66 (1.28–2.15), 1.37 (1.12–1.67), 1.43 (1.17–1.76), and 1.47 (1.20–1.80), respectively. Dichotomizing did not result in a significant loss of prognostic power. Although there was no significant difference in prognostic power among the indices, CCIA best predicted OS. CCIA divided the patients into 3 cohorts with median OS of 42 months, 33 months, and 23 months for scores of 5, 6 to 7, and 8, respectively.

Conclusions: CCIA was the best indicator of OS in every model employed with no loss of prognostic power with dichotomization. Dichotomization of CCIA (6) could be implemented in

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future comparisons of SBRT with OS. No cohort could be identified with a median survival of less than a year, for which treatment could be deemed futile.

Introduction

Non-small cell lung cancer (NSCLC) is one of the most common causes of cancer death worldwide, and the number of patients with early-stage disease is expected to rise as a result of increasing use of computed tomography screening.¹ Comparisons between stereotactic body radiation therapy (SBRT) and other treatments for early-stage NSCLC, such as surgery and radiofrequency ablation, are confounded by differences in patient selection. Those selected for these more invasive interventions are typically younger and healthier, with fewer chronic illnesses and medical conditions or comorbidities. Comparisons of overall survival among different treatment modalities and SBRT, and even among different SBRT trials, remain difficult given these inherent differences in comorbidities.

We sought to define the most robust measure of comorbidity for patients treated with SBRT among age alone, Eastern Cooperative Oncology Group (ECOG) performance status, and 3 commonly employed comorbidity indices. The Adult Comorbidity Evaluation 27 (ACE-27) is a modification of the Kaplan-Feinstein Comorbidity Index, which grades specific coexisting diseases and conditions from 1 (mild) to 3 (severe) in 27 disease systems and gives an overall score of 0 to 3.² Its original oncologic validation was conducted in a large registry of patients with malignancies of all stages, including NSCLC.³ The Charlson Comorbidity Index (CCI) was designed to predict 10-year mortality of patients admitted to a medical service.⁴ Twenty comorbidities are weighted with different point values ranging from 1 to 6, and each comorbidity is scored simply on its presence but not its severity. The total score can range from 0 to 37. The CCI can be further adjusted by age (CCIa) by adding 1 point for each decade of life beyond the age of 50 years. The use of this score has been validated in several surgical series of early-stage NSCLC,^{5–7} but not yet for early-stage NSCLC treated with SBRT. The difficulty with these comorbidity indices is that they all result in a continuous score, which complicates comparisons of different patient populations. The most prognostic comorbidity index and a simpler cut-point to identify patients with low-versus high-risk early-stage NSCLC has yet to be defined. Our goal was to identify the optimal comorbidity index and cut-point to stratify future prospective trials, inform treatment decisions, and enable better comparisons across trials and treatment modalities.

Methods and Materials

Patients

All patients in this study signed an informed consent for enrollment in a prospective database approved by an institutional review board. All were treated with curative-intent SBRT for early-stage NSCLC from June 2004 to June 2015 at the Washington University in St. Louis School of Medicine. Medical records were reviewed by the senior physician author (MCR) for comorbid conditions at the time of initial consultation. ACE-27, CCI, and CCIa were then calculated. Notably, CCI and CCIa assign 2 points to any patient with a solid malignancy. The lung cancer being treated with SBRT was not included for calculation purposes.

Details of our SBRT treatment planning and delivery have been described previously.⁸ The prescribed dose was 45 to 60 Gy in 3 to 5 fractions. Patients with peripheral tumors more than 2 cm away from the central airways were generally treated to a total dose of 54 Gy total in 3 fractions regardless of proximity to the chest wall, whereas those with more central tumors generally treated to 50 or 55 Gy total in 5 fractions. Normal tissue doses were limited according to those applied in Radiation Therapy Oncology Group 0236 for 3 fractions and Radiation Therapy Oncology Group 0813 for 5 fractions. After completion of SBRT, patients were generally followed with computed tomography imaging every 3 months for the first 2 years, then biannually. Patient survival was confirmed from clinic notes, online obituaries, and queries of the Social Security Death Index. Overall survival was calculated from the time of last SBRT fraction to the latter of either death or last clinic follow-up.

Statistics

Initial univariate Cox regression modeling was performed to determine the prognostic value of age, ECOG, ACE-27, CCI, and CCIa comorbidity measures in predicting overall survival (OS). After concluding that the continuous versions of these covariates provided significant value via the likelihood ratio test, the measures were dichotomized into high-risk and low-risk groups via an outcome-oriented approach based on log-rank test statistics developed by Contal and O'Quigley.⁹ Kaplan-Meier estimates were used to create survival curves. Univariate cox models using both continuous and dichotomized versions of these measures were then compared via Akaike information criterion (AIC) to determine whether the use of the risk groups resulted in a change in prognostic value. To determine whether there were significant differences in the predictive power of the 5 continuous metrics on 1-, 2-, and 3-year survival, univariate logistic regression models were calculated and compared with the Vuong test¹⁰ for nonnested models based on the Kullback-Leibler information criterion. This methodology allows for identifying the best nonnested model and obtaining a test statistic and *P*value comparing models. Multivariate Cox regression was used with stepwise selection methodology to build multivariate models. Comparisons between models were made via AIC to determine which index performed the best when all other confounders were taken into account. Once the optimal index was determined, we used the previously described cut-point methodology in a sequential manner by iteratively separating the data based on statistically significant cut-points. We then reran the cut-point analysis until there was no longer a statistically significant cut-point. All statistical analysis was performed using SAS Version 9.4 (SAS Institute Inc, Cary, NC), tests were all 2-sided unless otherwise noted, and a *P*value .05 was determined as statistically significant.

Results

Patient characteristics

A total of 548 patients with medically inoperable stage I NSCLC (418 American Joint Committee on Cancer stage cT1 or ≤ 3 cm, 130 T2a or 3–5 cm) were treated with curative-intent SBRT from June 2004 to June 2015. Patients who had prior thoracic surgery, synchronous early-stage lung malignancies, or treatment for thoracic oligometastases were excluded. Most (61.5%) received an SBRT dose of 54 Gy in 3 fractions, with most of the remaining receiving 50 Gy in 5 fractions (20.6%). Median follow-up was 27.7 months

(range, 0.1–140) for all patients and 36.4 months (range, 0.1–140) for living patients. Median (range) age, ECOG, ACE-27, CCI, and CCIa were 74 years (31–93), 1 (0–3), 2 (0–3), 3 (0–11), and 5 (2–14), respectively. Additional characteristics are presented in Table 1.

Survival comparison

Univariate Cox regression showed that ECOG, ACE-27, CCI, and CCIa were all significantly associated with OS, with *P* values of <.001, .016, <.001, and <.001, respectively. Age as a continuous variable by decade was not significant (*P*=.23). To see if any of the indices performed better as a prognostic factor for OS, we first compared the AIC for univariate models. By looking at the AIC and ranking from lowest to highest (or most information explained to least), the most variability can be explained by ECOG, then CCIa, CCI, and finally ACE-27 (Table 2). Although AIC is a valuable metric in assessing model fit, it does not allow for statistical testing for nonnested models as used here. To obtain statistical tests, 3 different survival endpoints were calculated at 1, 2, and 3 years with respective OS rates of 81.8%, 64.2%, and 51.6%. Further time points were not analyzed because they were past the median follow-up for survivors. At each of these periods, univariate logistic regression was calculated for each index with the outcome death at each period. Once the model was run, predicted values for each patient were obtained and compared among nonnested models using the Vuong test (Table 3). This allowed both for ordering of the comorbidity indices based on the Kullback-Leibler information criterion and for performing tests of significance between nonnested models. Although none of the models were statistically significantly different from each other at 1 and 2 years after treatment, age was inferior to CCI and CCIa at 3 years. At all time points, CCIa had the best prognostic power.

Comorbidity index dichotomization

Next, high-risk and low-risk groups were created for each of the indices. Using Contal and O'Quigley's methodology, high-risk groups were found to be patients with age ≥ 75 years, ECOG ≥ 1, ACE-27 ≥ 3, CCI ≥ 3, and CCIa ≥ 6. Cox univariate regression for each of these groups yielded hazard ratios for death and corresponding 95% confidence intervals of 1.23 (1.00–1.50), 1.66 (1.28–2.15), 1.37 (1.12–1.67), 1.43 (1.17–1.76), and 1.47 (1.20–1.80) for age, ECOG, ACE-27, CCI, and CCIa, respectively. To determine whether using risk groups instead of the continuous version was detrimental to the prognostic power, AIC for each univariate model was compared (Table 4). The comparison among models was made by looking at the percent change in AIC from the raw/unmodeled AIC to the resulting AIC from each univariate model using either the continuous or dichotomized comorbidity index. The resulting AIC indicated that both CCI and CCIa were slightly less powerful from the risk grouping, whereas the AIC for age and ACE-27 were slightly improved. The AIC for ECOG was unchanged. However, there was less than a 0.3% change in AIC between each of the dichotomous and continuous versions for each index. Thus risk groups provide meaningful clinical information without loss of any significant prognostic power.

OS model

Patient demographic variables were included in the multivariate model to determine whether the 5 tested indices were independently predictive of OS given demographic information.

Univariate Cox analysis on patient demographics in Table 5 shows that male sex, clinical T stage 2 versus T stage 1, age ≥ 75 years at the start of radiation therapy, and ECOG ≥ 1 resulted in inferior OS, whereas operability, higher percentage of predicted forced expiratory volume in 1 second, and body mass index (BMI) ≥ 23.3 resulted in superior OS. These covariates were then entered into a stepwise selection regression to obtain the best prognostic model based on patient demographic characteristics. This resulted in a model with male, T2 versus T1, ECOG ≥ 1 , and BMI ≥ 23.3 characteristics. Age was not significant on multivariate analysis.

We then included each of the continuous comorbidity indices and their associated dichotomized covariate in this multivariate model of sex, stage, ECOG, and BMI to create 6 other models with each individual comorbidity covariate. Table 6 shows their model fit via AIC and significance, which was used to assess which covariate yielded the best model. Similar to previous results, the AIC for the dichotomized models were slightly worse for CCI and CCIa and slightly better for ACE-27; however, the maximum amount was less than 0.2% of the raw/unmodeled AIC. Comparing across the different metrics, models with ACE-27 performed the worst, whereas models using CCIa performed the best, with the maximum difference being about a 1% difference in AIC.

Because CCIa was the best index modeled, it next was used to stratify the patients into as many significantly different cohorts as possible. Three cohorts were found, with median survivals of 42 months, 33 months, and 23 months for CCIa scores of ≥ 5 , 6 to 7, and ≥ 8 , respectively (Fig. 1). Further divisions were not statistically significant. No cohort could be identified with a median survival of less than a year, wherein treatment would be deemed futile.

Discussion

Comorbid illnesses are common in patients with lung cancer because of associations of this diagnosis with increasing age and tobacco smoking. The effect of comorbidity on survival in patients with lung cancer is greatest for those with localized or early-stage disease and thus the greatest chance of cancer control.^{11–13} After a patient has been diagnosed with early-stage NSCLC, clinicians have to first determine the utility of any treatment^{14–16} and then select the most appropriate therapy, both of which continue to be debated.^{17,18} To determine the optimal treatment among different patient populations, a quantifiable means of comparing patients is needed in addition to stage and performance status.¹⁹

This is the first study to suggest the prognostic superiority of CCIa over other measures of comorbidity for patients with early-stage NSCLC treated with SBRT. This finding of the superiority of CCIa over CCI and other indices agrees with a recent population-based study of patients with operable lung cancer²⁰ that also found CCIa was the best predictor of OS. Several studies^{5–7} of patients with operable disease have reported that the CCI is a better predictor of immediate postoperative outcomes and long-term survival than the more commonly measured performance status. These studies invariably found CCI scores lower than the median of 5 in our SBRT cohort, however. Eguchi et al²¹ found that age had a significant impact on cause-specific mortality and morbidity in patients who underwent

resection, and Holmes et al²² found that age but not CCI predicted for mortality after SBRT for medically inoperable stage I NSCLC. In contrast, we found that age was the least useful index for OS in our population, which mostly had inoperable disease.

In this single-institution experience, we evaluated several measures of comorbidity and organ dysfunction in patients with early-stage lung cancer treated with SBRT. Our series found a prevalence of moderate comorbidity (ACE-27 of 2) in approximately 21% patients and severe comorbidity (ACE-27 of 3) in 48% patients. Our median CCI score was 3, which others consider a high level of comorbidity for patients with lung cancer.^{23–25} Our median CCIa score was 5, which is the same median as in another study of SBRT²⁶ that looked at the impact of comorbidity on outcomes. They too found that CCIa was a significant predictor of OS on both univariate and multivariate analysis but did not look at other comorbidity indices.

Although studies in other treatment modalities such as surgery^{5–7} and radiofrequency ablation²⁷ have shown that the CCI is an independent prognostic factor, ours is the first to identify optimal cut-points dividing low- and high-risk patients treated with SBRT for early-stage NSCLC. Notably, these cut-points do not cause a significant loss of information and, by dichotomizing groups, allow for simpler comparisons. Patients with a CCIa score of 3 or less in the lung SBRT study by Kopek et al²⁶ had a median survival of 41 months versus only 11 months for those scoring 6 or more. Our study identified CCIa of 6 as the best cut-point of all 3 measures of comorbidity, with those scoring 6 or more having a hazard ratio of death of 1.47. Our CCI cut-point was 3, which was the same as that of Luchtenborg et al²⁵ in their surgical patient study.

Importantly, we were not able to identify a cohort of patients with a median OS of less than a year, wherein diagnosis and treatment could be argued to be futile. This is in agreement with Klement et al,¹⁵ who concluded that SBRT should be offered to everyone. Unlike Klement et al¹⁵ and Louie et al,²⁸ however, we found CCIa and CCI to be more prognostic than ECOG and did not find operability to be significant for OS on multivariate analysis. Kopek et al²⁶ were able to use CCIa to divide their cohort into 4 groups of patients with a median OS of just 11 months in the highest risk group. We were able to use CCIa to divide the patients into 3 groups, and our highest risk group had a median OS of 23 months, where a short, noninvasive treatment like SBRT seems warranted.

Limitations of this study center on its retrospective nature. Comorbidities could not be assessed in real time by either the patient in a self-reported questionnaire or by the treating clinician. Instead, comorbidities were extracted from medical records after treatment, which could reduce the accuracy of the indices presented here. However, ACE and CCI scores were taken from an institutional registry, and registries have been proven to have the most accurate comorbidity scores in patients with lung cancer.²⁹ This study was also conducted in a single institution, and SBRT techniques and patient selection vary among institutions. It should be noted that this study was not designed to predict outcomes based on treatment modality selection but instead provides prognostic information to patients and physicians treating early-stage NSCLC with SBRT.

Conclusions

The Charlson comorbidity index, especially with adjustment for age, is superior to age, ECOG, and ACE-27 when quantifying comorbidities and predicting OS in patients with early-stage NSCLC treated with SBRT. It allows for significant division between patients at low and high risk for death after treatment with SBRT, and the use of such cut-points does not cause a significant loss of information. This provides a simple tool to stratify patients in future prospective trials and to better compare patients in both multi-institutional and multimodality studies of SBRT.

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Fig. 1. Kaplan-Meier overall survival curves of statistically significant cut-points of age-adjusted Charlson comorbidity index. Patients can be divided into 3 groups with age-adjusted Charlson Comorbidity Index 5, 6 to 7, and 8.

Table 1

Patient characteristics

Characteristic	Number (Percent) or Mean (range)
Age, mean (range), y	73.7 (31–93)
Age groups, y	
30s	1 (0.2%)
40s	4 (0.7%)
50s	30 (5.5%)
60s	147 (26.7%)
70s	219 (39.8%)
80s	144 (26.2%)
90s	5 (0.9%)
Male sex	284 (51.6%)
Central target location	170 (30.9%)
Stage	
T1a	223 (40.7%)
T1b	195 (35.6%)
T2a	130 (23.7%)
Current smoker	181 (33.0%)
Pack years	
<30	113 (20.6%)
30–59	220 (40.0%)
60–89	130 (23.6%)
>90	87 (15.8%)
Medically inoperable	495 (90.1%)
FEV1 percent of predicted, mean (range)	56% (14–133%)
BMI, mean (range)	26.8 (14.2–66.6)
BMI	
<18.5	45 (8.6%)
18.5 to <25	173 (33.1%)
25 to <30	167 (31.9%)
30	138 (26.4%)
ECOG performance status	
0	132 (25.1%)
1	286 (54.4%)
2	100 (19.0%)
3	8 (1.5%)
ACE-27	
0	16 (2.9%)
1	151 (27.5%)
2	118 (21.5%)
3	265 (48.2%)

Characteristic	Number (Percent) or Mean (range)
CCI, mean (range)	2.71 (0–11)
CCI 3	281 (51.1%)
CCla, mean (range)	5.67 (1–14)
CCla 6	272 (49.9%)

Abbreviations: ACE-27 = Adult Comorbidity Evaluation 27; BMI = body mass index; CCI = Charlson Comorbidity Index; CCIa = age-adjusted CCI; ECOG = Eastern Cooperative Oncology Group; FEV1 = forced expiratory volume in 1 second.

Table 2

Results of univariate Cox model based on the continuous indices with model fit statistics based on the Akaike information criterion

Comorbidity covariate	HR (95% CI)	Akaike information criterion
Age (per 10 years)	1.07 (0.96–1.20)	4130
ECOG	1.32 (1.15–1.51)	3922
ACE 27	1.15 (1.03–1.30)	4124
CCI	1.14 (1.07–1.20)	4115
CCla	1.15 (1.09–1.21)	4056

Abbreviations: ACE-27 = Adult Comorbidity Evaluation 27; CCI = Charlson Comorbidity Index; CCla = age-adjusted CCI; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio.

Table 3

Results of Vuong's test for overall survival at 1, 2, and 3 years

Time of analysis	Significantly different models	Best model parameter	Second-best vs best
1 y	NA	CCla	CCI ($P = .13$)
2 y	NA	CCla	CCI ($P = .83$)
3 y	CCI vs. Age ($P = .023$) CCIa vs Age ($P = .015$)	CCla	CCI ($P = .47$)

Abbreviations: CCI = Charlson Comorbidity Index; CCIa = age-adjusted CCI; NA = None.

Models with significantly different prognostic power are given with appropriate P -values. The most prognostic covariate among all models is given along with the corresponding P -value when compared to the second most prognostic model. A P -value $< .05$ means the listed covariate is significantly better at predicting overall survival at that time point than its counterpart.

Table 4

Results of univariate Cox model based on the dichotomized comorbidity metrics with model fit statistics based on the Akaike information criterion

Dichotomized comorbidity covariate	HR (95% CI)	Akaike information criterion
Age ≥75 vs age <75 y	1.23 (1.00–1.50)	4128
ECOG ≥1	1.66 (1.28–2.15)	3922
ACE-27 ≥3	1.37 (1.12–1.67)	4122
CCI ≥3	1.43 (1.17–1.76)	4119
CCla ≥6	1.47 (1.20–1.80)	4068

Abbreviations: ACE-27 = Adult Comorbidity Evaluation 27; CCI = Charlson Comorbidity Index; CCla = age-adjusted CCI; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio.

Table 5

Univariate and multivariate Cox regression models for overall survival using patient characteristics

Patient characteristic covariate	Univariate hazard ratio (95% CI)	Multivariate hazard ratio (95% CI)
Male sex	1.28 (1.05–1.57) *	1.30 (1.05–1.62) *
Stage T2 vs T1	1.50 (1.19–1.88) *	1.40 (1.10–1.79) *
Current smoker	1.18 (0.95–1.46)	NS
Central target location	1.16 (0.94–1.45)	NS
Age ≥75 vs age <75 y	1.23 (1.00–1.50) *	NS
ECOG ≥1	1.66 (1.28–2.15) *	1.60 (1.23–2.09) *
Pack years	1.00 (0.997–1.003)	NS
BMI ≥23.3 vs BMI <23.3	0.71 (0.57–0.88) *	0.68 (0.54–0.84) *
FEV1 percent of predicted	0.994 (0.994–0.999) *	NS
Operability	0.66 (0.46–0.95) *	NS

Abbreviations: BMI = body mass index; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; FEV1 = forced expiratory volume in 1 second

NS implies that the variable was not significant on multivariate regression and excluded from the model.

* $P < .05$.

Table 6

Results of multivariate Cox regression models for different comorbidity indices and their dichotomized versions

Comorbidity covariate	Multivariate HR (95% CI)	Multivariate P-value	Akaike information criterion
ACE-27	1.11 (0.98–1.26)	.09	3672
ACE-27 3	1.30 (1.05–1.61)	.02	3669
CCI	1.13 (1.06–1.20)	.0002	3662
CCI 3	1.30 (1.05–1.61)	.02	3669
CCla	1.12 (1.06–1.19)	<.0001	3635
CCla 6	1.38 (1.11–1.71)	.004	3642

Abbreviations: ACE-27 = Adult Comorbidity Evaluation 27; CCI = Charlson Comorbidity Index; CCIa = age-adjusted CCI; CI = confidence interval; HR = hazard ratio.

HRs and associated model statistics are for multivariate models controlling for male sex, T stage 2, ECOG 1, and body mass index 23.3.