Original Study

Predictors of Early Hospice or Death in Patients With Inoperable Lung Cancer Treated With Curative Intent

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Abstract

Stage II to III non-small-cell lung cancer(NSCLC) treatment involves chemo-radiotherapy(CRT). We present a model-including age, ECOG, planning target volume, heart dose, lack of energy, and cough-prognosticating early poor outcomes. The area under the ROC curve was 0.71, with NPV 95%, specificity 97%, PPV 23%, sensitivity 16% at a risk threshold of 20%. This multivariate model may identify patients at risk for early poor outcomes.

Introduction: Treatment for inoperable stage II to III non-small cell lung cancer (NSCLC) involves chemo-radiotherapy (CRT). However, some patients transition to hospice or die early during their treatment course. We present a model to prognosticate early poor outcomes in NSCLC patients treated with curative-intent CRT. **Methods and Materials:** Across a statewide consortium, data was prospectively collected on stage II to III NSCLC patients who received CRT between 2012 and 2019. Early poor outcomes included hospice enrollment or death within 3 months of completing CRT. Logistic regression models were used to assess predictors in prognostic models. LASSO regression with multiple imputation were used to build a final multivariate model, accounting for missing covariates. **Results:** Of the 2267 included patients, 128 experienced early poor outcomes. Mean age was 71 years and 59% received concurrent chemotherapy. The best predictive model, created parsimoniously from statistically significant univariate predictors, included age, ECOG, planning target volume (PTV), mean heart dose, pretreatment lack of energy, and cough. The estimated area under the ROC curve for this multivariable model was 0.71, with a negative predictive value of 95%, specificity of 97%, positive predictive value of 23%, and sensitivity of 16% at a predicted risk threshold of 20%. **Conclusions:** This multivariate model identified a combination of clinical variables and patient reported factors that may identify individuals with inoperable NSCLC undergoing curative intent chemo-radiotherapy who are at higher risk for early poor outcomes.

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Introduction

The landmark trial by Temel et al.[1] demonstrated that patients with non-small cell lung cancer (NSCLC) who received early palliative care had improved overall survival. Notably however, this trial was in the setting of patients with metastatic disease. Considerably less is known about the combination of palliative care services with definitive treatment in patients with locally advanced, nonmetastatic NSCLC. One of the difficulties in understanding the implications of combined treatment in this patient population stems from the lack of prognostic models to identify which patients may have poorer outcomes.[2]

The standard of care for patients with locally advanced, inoperable NSCLC is chemoradiation (CRT).[3] A large systematic review

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of randomized control trials demonstrated that concurrent CRT conferred statistically significant survival benefits, and decreased relapse rates.[4] Importantly, patients receiving concurrent CRT had a 32% reduction in locoregional recurrence. Due to the increased risk of side effects with concurrent CRT, another meta-analysis addressed the question of whether concurrent CRT held any significant advantages over sequential CRT. Assessing survival over 6-years, this review found that patients treated with concurrent CRT had a 16% reduction in mortality rate, and a 23% reduction in rate of locoregional recurrence, consistent with the findings of the landmark clinical trial RTOG 9410.[5-6]

While in recent years the integration of immunotherapy into the treatment paradigm has improved outcomes for many patients, the aggressive nature and side effect profile of CRT combined with immunotherapy necessitates a significant risk-benefit consideration.[7] Generally, it would be most appropriate for clinicians to personalize care such that most aggressive treatment strategies are used for patients who are more likely to experience positive clinical improvements rather than patients who are at a higher risk for adverse treatment outcomes. If oncologists could identify patients who may be predisposed to poorer treatment outcomes a priori, they could individualize sequencing of therapies or offer supportive and palliative care services earlier to optimize care.

Considering the importance of appropriately allocating healthcare resources, it is essential to identify cases where CRT may pose more harm than benefit. Brownlee et al.[8] quantified the paradoxical overuse of unnecessary medical services and underuse of palliative care services at the end-of-life and found that, in western countries especially, therapeutic procedures were more likely to be employed in futile situations. When applied to radiation oncology, there have also been reports of radiation overuse at the end-of-life, despite findings that such treatment is unlikely to provide significant palliative or survival benefits.[9–11]

In the era of personalized medicine where clinicians are able to offer directed therapy to patients based on tumor genome sequencing, the decision to treat with CRT and immunotherapy must be made in the context of patient expectations. Consideration should be given to the optimization of treatment by maximizing patient response while curtailing the unnecessary use of aggressive treatment. Central to this process is the need to develop accurate models to predict patient response to treatment. Although the oncologic "gestalt" for estimating prognosis may be imperfect, there are clinical factors that may provide significant guidance when prognosticating patient outcomes. Therefore, the goal of this study was to develop a predictive model to identify patients with locally advanced lung cancer who experienced early poor outcomes defined as early hospice enrollment or early death.

Methods and Materials

Patients who received radiation therapy for locally advanced (AJCC 7th ed. Stage II-III) non-small cell lung cancer between April 2012 and November 2019 were included in this study. Patient information was collected prospectively as part of a statewide consortium, the Michigan Radiation Oncology Quality Consortium (MROQC). MROQC is a multicenter collaboration that is funded by Blue Cross and Blue Shield of Michigan and Blue Care Network to collect clinical, sociodemographic, treatment, dosimetric, patient reported ouctomes (PRO) and clinical outcomes data for patients receiving radiation therapy in Michigan. Data was collected on all eligible patients in MROQC practices, regardless of insurance type. All data analyses were performed independently of the funding agency. For this study, data from 27 academic and community clinics was available, and as the data was provided in a deidentified format consent was not required.

Information in the MROQC databases consisted of patient demographics, smoking status, tumor stage, location, histology, and treatment data including treatment plans, dose-volume histograms (DVHs), and indicators for chemotherapy usage. Each institution also provided prescription dosages separate from the DVH data.[12] Prior to beginning radiation therapy, patients completed the Physical Well-Being, Functional Well-Being, and Lung Cancer Symptoms subscales of the Functional Assessment of Cancer Therapy – Lung (FACT-L) quality of life instrument.[13] Patient responses to individual FACT-L items were utilized in the predictive modeling process. During radiation treatment, patients were evaluated on a weekly basis by the treating radiation oncologist. Long term follow-up with the treating radiation oncologist was done at 1, 3, and 6-month visits after the completion of radiation therapy. Means and proportions were compared to evaluate for statistically significant differences between the 2 groups.

Early death or hospice enrollment were determined by analyzing patients who had early termination of MROQC participation. After initiation of radiotherapy, all patients were scheduled to follow-up with an MROQC site manager for at least 6 months unless they terminated follow-up early. Site managers compiled reasons for early termination of follow-up, and patients were counted as having the outcome of interest if the reason for termination included death or transitioning to hospice or palliative care, and the termination occurred within than 5 months after the date of first RT fraction, in all cases corresponding to within 3 months after completion of RT.

Univariable Models

Several explanatory variables including patient demographics (age, gender, smoking status, and marital status), patient reported outcomes (FACT-L quality of life instrument, and Eastern Cooperative Oncology Group performance status [ECOG]), disease characteristics (forced expiratory volume , clinical stage, PTV, and incidence of concurrent chemotherapy), and treatment variables (dose to esophagus, heart, and lung, dose constraint for proportion of lung receiving 5 Gy and 20 Gy Lung [Lung V5 and V20 respectively], and treatment location) were assessed for potential relationships with early poor outcomes. To evaluate the association between these variables and the primary outcome of early death or hospice care, a series of univariable logistic regression models were fitted. The odds ratio (OR) associated with each predictor as well as the Akaike information criteria and area under the receiver operating characteristic (ROC) area under the curve (AUC) were also calculated for each model.

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Multivariable Models and Multiple Imputation

Multivariable regression models were also fit to assess whether incorporation of multiple patient factors could lead to improved identification of patients at high risk for early death or early hospice enrollment. To account for missing covariate values for some patients, a multiple imputation approach was used to generate 25 complete imputed data sets. Least absolute shrinkage and selection operator (LASSO) regularized logistic regression was utilized as it performs variable selection and leads to parsimonious models. Only variables that were selected by LASSO in ≥80% of the 25 imputed datasets were utilized in the final iteration of the multivariate regression model. These variables included: Age, ECOG) Performance Status, PTV, patient-reported lack of energy, patient-reported cough, and mean heart dose. One generalized linear model including the variables selected via LASSO regression was fit for each of the 25 imputed data sets. Rubin's Rule was utilized to summarize the modeling results across imputed datasets. OR estimates with corresponding 95% confidence intervals and *P*-values (pooled across all 25 models) were determined for each predictor. The predicted risk of early death or hospice was computed by averaging across imputed data sets. An AUC estimate averaged across all 25 models was also calculated. The predictive performance of our final, multivariable model was further evaluated by calculating the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for 4 different risk thresholds (10%, 15%, 20%, and 30%) that were used to determine which patients were at the highest risk of negative outcomes within 3 months of completing radiation therapy.

Patients were treated according to ASCO guidelines regarding chemotherapeutics for patients with stages II and III NSCLC, however the list of and timing of medical therapy was not available for ad-hoc analysis.[14] Patients who did not receive concurrent CRT were felt to be high-risk candidates and thus received sequential CRT due to the lower risk of side-effects. Similarly, stage II patients who did not receive surgery were deemed ineligible surgical candidates due to comorbid risk factors.

Results

Clinical and outcomes data were available for 3189 lung cancer patients. Patients were excluded if they had stage I disease (N = 653) or were treated with surgery (N = 269), yielding a final sample size of 2267 patients. Of these patients, 128 terminated MROQC within 3 months of completing radiation therapy due to death or entry into hospice care.

There were no differences between the early poor outcomes cohort and the nonearly poor outcomes cohort with respect to age, sex, marital status, smoking status, utilization of concurrent chemotherapy, mean esophagus and lung doses, lung V5, lung V20, and treatment location (academic vs. nonacademic). Over 70% of patients across both groups were treated at a nonacademic center, and 61% of patients received concurrent chemotherapy. Across both cohorts, the majority of patients had stage III lung cancer and pretreatment ECOG performance statuses between 0 and 1. The early poor outcomes cohort had a lower proportion of patients with an ECOG performance status between 0 and 1 (58.6% vs. 69.1%) and a higher proportion of patients with an ECOG performance status of 2 (14.8% vs. 6.5%). The early poor outcomes cohort also had a lower proportion of patients with stage IIB malignancy (2.3% vs. 7.8%), a higher mean PTV (528cc vs. 444cc), and a higher mean dose to the heart (15.3Gy vs. 12.7Gy) (Table 1).

Among patients with early poor outcomes (death or hospice within 3 months of completing radiation therapy), most patients experienced these outcomes after radiation treatment was completed. Early poor outcomes most commonly occurred between 1 month prior to and 1 month following completion of radiation therapy (Figure 1**a**). Using our cutoff value of death or admission to hospice care within 3 months of completing radiation therapy, the average time to death or hospice care in the early poor outcomes cohort was 83 ± 41 days.

Table 2 shows the results for univariate logistic regression models predicting early death or hospice. Among patient characteristics, age was significantly associated with early death or hospice care. For every 1-year increase in age, the odds of an early poor outcome after chemoradiation increase by 4% (OR = 1.04, $P < .001$). Better pretreatment scores on the Physical Well-Being, Functional Well-Being, and Lung Cancer Symptoms subscales of the FACT-L quality of life instrument were significantly associated with lower odds of death or hospice care within 3 months of completing CRT (OR = 0.964, 0.944, and 0.92, and $P = .033$, .003, and < .001, respectively). Similar associations were also found for many individual items of the FACT-L. stage IIIB malignancy was found to increase odds of early poor outcomes by over 250% compared to stage IIA cancer (OR = 2.59, $P = .048$). Larger PTV were also found to increase the risk of early poor outcomes, although the size of this effect was marginal (OR = 1.001, $P = .024$). Finally, increased mean dose to the heart increased the odds of experiencing early poor outcomes by nearly 3% for each additional Gy of radiation (OR = 1.027, $P = .015$). Importantly, smoking status was not identified as a statistically significant predictor of early poor outcomes.

Table 3 shows the ORs, 95% confidence intervals, and *P*-values for the 7 predictors that were selected through LASSO which were age, ECOG performance status, PTV, patient-reported lack of energy (PROs energy), patient-reported cough (PROs cough), and mean heart dose (MHD). In this multivariate model, age, ECOG status, and insurance status remained significant predictors in the presence of other covariates. Holding other covariates constant, every 1-year increase in age increases the odds of an early poor outcome by 4% (OR=1.04, 95% CI: [1.02, 1.06], $P < .001$). A1-point increase in ECOG performance status increases the odds of an early poor outcome by 40% after controlling for other covariates (OR=1.40, 95% CI: [1.12, 1.76], $P = .003$). Compared to insured patients, uninsured patients have 4.82 times the odds of early death or hospice care, after controlling for other covariates (95% CI: [1.28, 18.08], $P = .020$). The AUC estimate (pooled across all 25 fitted models) was 0.71.

Figure 1**b** shows the average predicted risk of early death or hospice for the 2267 patients included in this analysis. While most patients had a low predicted risk of early death or hospice, 12% of patients had an average predicted risk above 10% and 1.37% of patients had an average predicted risk above 20%. There

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Table 1 Patient Characteristics

Variable	Early Death/Hospice (n=128)	No Early Poor Outcome (n = 2139)	Overall (n = 2267)
Age (y)			
Mean (SD)	71 (10)	67 (10)	68 (10)
Median [min, max]	72 [48, 92]	67 [34, 100]	67 [34, 100]
Sex			
Female	58 (45.3%)	1031 (48.2%)	1089 (48.0%)
Male	70 (54.7%)	1108 (51.8%)	1178 (52.0%)
Marital status			
Unmarried	65 (50.8%)	1035 (48.4%)	1100 (48.5%)
Married	63 (49.2%)	1104 (51.6%)	1167 (51.5%)
ECOG performance status			
0-1	75 (58.6%)	**1479 (69.1%)**[a]	1554 (68.5%)
2	**19 (14.8%)**[a]	139 (6.5%)	158 (7.0%)
3	6 (4.7%)	47 (2.2%)	53 (2.3%)
4	0 (0%)	4 (0.2%)	4 (0.2%)
Missing	28 (21.9%)	470 (22.0%)	498 (22.0%)
Stage			
IIA	5 (3.9%)	179 (8.4%)	184 (8.1%)
IIB	3 (2.3%)	**166 (7.8%)**[a]	169 (7.5%)
IIIA	77 (60.2%)	1199 (56.1%)	1276 (56.3%)
IIIB	43 (33.6%)	595 (27.8%)	638 (28.1%)
PTV (cc)			
Mean (SD)	**528 (439)**[a]	444 (325)	448 (332)
Median [Min, Max]	408 [18.4, 2170]	361 [3.80, 2220]	365 [3.80, 2220]
Concurrent chemotherapy			
No	52 (40.6%)	833 (38.9%)	885 (39.0%)
Yes	76 (59.4%)	1306 (61.1%)	1382 (61.0%)
Mean esophagus dose (Gy)			
Mean (SD)	50.6 (17.1)	52.0 (15.1)	52.0 (15.2)
Median [Min, Max]	59.1 [0.480, 69.3]	57.7 [0.548, 76.9]	57.7 [0.480, 76.9]
Mean lung dose (Gy)			
Mean (SD)	15.1 (4.98)	14.9 (4.43)	14.9 (4.46)
Median [Min, Max]	16.0 [0.114, 26.7]	15.2 [0.135, 69.1]	15.2 [0.114, 69.1]
Mean heart dose (Gy)			
Mean (SD)	**15.3 (9.39)**[a]	12.7 (9.46)	12.9 (9.47)
Median [Min, Max]	14.1 [0.051, 38.5]	11.3 [0.098, 58.0]	11.5 [0.051, 58.0]
Lung V5 (%)			
Mean (SD)	56.9 (20.9)	54.2 (18.8)	54.4 (18.9)
Median [Min, Max]	57.7 [0.000176, 95.4]	54.9 [1.34e-05, 100]	55.1 [1.34e-05, 100]
Lung V20 (%)			
Mean (SD)	25.7 (10.9)	25.4 (9.64)	25.4 (9.71)
Median [Min, Max]	27.4 [0.000176, 51.3]	25.8 [1.34e-05, 100]	25.8 [1.34e-05, 100]
Treatment Center Type			
Academic	36 (28.1%)	583 (27.3%)	619 (27.3%)
Nonacademic	92 (71.9%)	1556 (72.7%)	1648 (72.7%)

[a] denotes the group with a significantly higher proportion/mean at a 0.05% significance level. Reported variables include those in which imputation was required in < 10% of cases across both cohorts.

were 7 patients who had an average predicted risk of above 30%. Table 4 presents the PPV, NPV, sensitivity, and specificity for the 4 risk thresholds under consideration: 10%, 15%, 20%, and 30%. NPV and specificity are above 94% and 89%, respectively, for all risk thresholds. The sensitivity decreases as the risk threshold increases and achieves a maximum of 35.6% using the 10% threshold. The PPV reaches a maximum of 35.5% using the 20% risk threshold.

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Table 2 Univariate Logistic Model Results

Predictor Category	Predictor	OR	*P*-value	AUC
Patient characteristics	Age	1.04	**< .001**	0.61
	Male Sex (reference is female sex)	1.123	.526	-
	Married (reference is unmarried)	0.909	.599	-
	Current smoker (reference is never smoker)	0.95	.916	-
	Former smoker (reference is never smoker)	1.06	.899	-
Patient reported outcomes[b]	Functional Well-Being Scale[a]	0.964	**.033**	0.57
	Physical Well-Being Scale[a]	0.944	**.003**	0.62
	Lung Cancer Symptoms Scale[a]	0.921	**< .001**	0.63
	"I have accepted my illness"	1.017	.812	0.5
	"I have lack of energy"	1.516	**< .001**	0.65
	"I am forced to spend time in bed"	1.226	**.029**	0.56
	"I am enjoying the things I usually do for fun"	0.927	.301	0.53
	"My work (including work at home) is fulfilling"	0.841	**.020**	0.57
	"I have a good appetite"	0.884	.093	0.45
	"I have been coughing"	1.293	**.001**	0.6
	"I have been short of breath"	1.341	**< .001**	0.61
	"I feel tightness in my chest"	1.162	.097	0.55
	"Breathing is easy for me"	0.893	.136	0.45
	"I am bothered by side effects of treatment"	1.055	.665	0.5
	"Because of my physical condition, I have trouble meeting the needs of my family"	1.174	.050	0.56
	"I am bothered by hair loss"	0.965	.729	0.49
	"I feel ill"	1.323	**.004**	0.57
	"I am able to enjoy life"	0.936	.369	0.47
	"I have nausea"	1.155	.223	0.53
	"I have pain"	1.076	.349	0.52
	"I am content with the quality of my life right now"	0.889	.118	0.45
	"I am sleeping well"	1.058	.456	0.52
	"My thinking is clear"	1.075	.316	0.53
	"I am losing weight"	1.208	**.017**	0.56
	"I am able to work"	0.844	**.035**	0.56
	ECOG Performance Status	1.610	**< .001**	0.62
Disease characteristics	FEV1	0.819	.270	0.54
	Stage (reference is IIA)			-
	Stage IIB	0.645	.555	-
	Stage IIIA	2.299	.076	-
	Stage IIIB	2.587	**.048**	-
Treatment variables	PTV Volume	1.001	**.024**	0.54
	Concurrent Chemotherapy (reference is none)	0.932	.705	-
	Mean Esophagus Dose	0.994	.394	0.49
	Mean Lung Dose	1.009	.717	0.54
	Mean Heart Dose	1.027	**.015**	0.59
	Lung V5	1.008	.196	0.55
	Lung V20	1.003	.798	0.53
	Academic Center (reference is non-academic center)	1.04	.83	-

Bolded values indicate statistical significance.
[a] Subscale from baseline (before RT), higher scores indicate better symptoms.
[b] All subcategories of "Patient Reported Outcomes" reflect pretreatment data.

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Figure 1 (a) Time to early death or hospice care for patients with poor outcomes, with the time to death or hospice in terms of months from the start of RT (radiation therapy) shown on the X-axis and the number of patients shown on the Y-axis. The median time to death or hospice care was 2.82 months (85 days) after starting RT. (b) Predicted risk of early death or hospice care, averaged across all 25 imputed data sets, where predicted risk is shown on the X-axis and the percentage of patients is on the Y-axis.

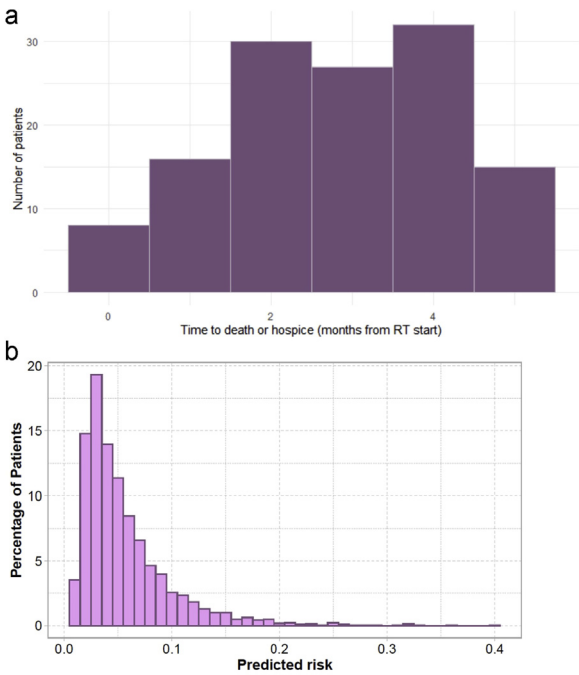

Table 3 Multivariable Model Results

Predictor	OR	95% Confidence Interval	*P*-value
Age (y)	1.04	[1.02, 1.06]	**< .001**
ECOG performance status	1.40	[1.12, 1.76]	**.003**
PTV (per 10 cc)	1.00	[0.99, 1.00]	.188
PROs energy[a]	1.33	[1.12, 1.76]	**.004**
PROs cough[a]	1.10	[0.93, 1.31]	.282
Mean heart dose (Gy)	1.01	[0.99, 1.03]	.232
Uninsured (vs. Insured)	4.82	[1.28, 18.08]	**.020**
Model AUC		**0.71**	

[a] Patient reported outcomes (PROs) are on a 0-4 scale on (0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, 4 = very much).

Table 4 Predicted Risk of Early Hospice Care or Death Model Characteristics

Risk Threshold	PPV	NPV	Sensitivity	Specificity
30%	28.6%	94.4%	1.6%	99.8%
20%	35.5%	94.8%	8.6%	99.1%
15%	23.3%	95.0%	15.6%	96.9%
10%	16.9%	95.9%	35.6%	89.4%

Discussion

Predicting prognoses for patients with stage II-III lung cancer is notoriously difficult but has critical implications for the selection of appropriate therapy and the delivery of anticipatory guidance to patients and family members. To address this issue, we developed a predictive model that identifies patients with early poor outcomes receiving curative intent CRT for locally advanced non-small cell lung cancer. This model includes a combination of demographic descriptors, clinical variables and patient-reported symptoms that

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may help identify patients with inoperable NSCLC undergoing curative intent CRT who are at a higher risk of early hospice enrollment or early death.

A systematic review by Walls et al[15]. concluded that there are no published, validated predictive tools for estimating the risk of recurrence or toxicity after radical (definitive) radiation for NSCLC patients, effectively identifying a significant gap in the existing literature.This study thus lends important insights as a first step towards developing a comprehensive predictive tool to identify patients at risk for poor outcomes, and hence requires further substantiation. Other studies have quantified the risk of hospitalization for patients with lung cancer receiving definitive radiotherapy, which is independently associated with increased mortality.[16] However, to our knowledge, this study is the first of its kind to propose a predictive model for identifying lung cancer patients who may be predisposed to early poor outcomes.

Expectedly, younger age and better ECOG performance scores were negatively correlated with incidence of early poor outcomes. Intuitively, such patients have fewer medical comorbidities and are often more amenable candidates to CRT. As is true across several cancer subtypes, including lung cancer, these patients experienced a lower rate of poor outcomes following CRT.[17,18]

Several variables were also not found to be statistically significant predictors of early death or hospice after CRT. Consistent with results from published literature, patient gender did not have an impact of the likelihood of early poor outcomes.[19] Scant research exists on the subject of a potential impact of facility type on radiation treatment outcomes. One study notes a potential benefit for lung cancer patients treated at very high volume facilities, although our results do not support this finding.[20] While patient reported dyspnea was not a statistically significant predictor, 1 potential explanation is that the inclusion of ECOG acted as a surrogate for this variable. Similarly, the mechanism of fatigue in patients with underlying malignancy is inherently multifactorial and is therefore unlikely to contribute to risk of early death or hospice.[21] It was unexpected to observe that clinical stage was not a statistically significant predictor of early poor outcomes. However, this can potentially be explained by the fact that the 2 groups were relatively homogenous with respect to the proportion of patients with each clinical stage; while the early poor outcomes group had a lower proportion of patients with stage IIA lung cancer, the majority of patients across both groups had III malignancy, and this difference was therefore unlikely to be a contributory factor. An unanticipated finding from this analysis was that concurrent chemotherapy was not associated with early poor outcomes. Potentially, the lack of statistical significance might be due to the similar proportion of patients who received concurrent chemotherapy between both groups. However, this result may potentially change in future analyses with larger samples. Finally, mean lung dose was also not a statistically significant predictor of early poor outcomes; again, patients across both groups did not receive a statistically different mean dose of radiation, potentially explaining the lack of statistical significance.

Our model also demonstrated that higher PTV and mean radiation dose to the heart were independent predictors of early poor outcomes but did not remain significant in the multivariable model. As with SBRT for other solid organ malignancies, higher PTV may portend a higher rate of side effects.[22] A larger PTV results in a larger volume of radiation being delivered to native tissue, and a higher likelihood of radiation being administered to critical adjacent structures.[23] However, this specific association has not been clearly established in the literature, supporting our findings. Various sources have also placed the risk of cardiovascular death over 70% for patients receiving radiation.[24] However, the mean heart dose for patients who experienced early poor outcomes was 15.3 Gy, significantly less than the threshold dose for cardiovascular complications of 30 Gy, and the lack of statistical significance for mean heart dose is therefore concordant with the published literature.[25]

This study has several notable strengths and limitations. The robust statistical analyses, multivariable modeling of prospectively identified clinical variables, the inclusion of a detailed number of patient-reported outcomes, and evaluation of the efficacy of this model over multiple risk strata certainly support the merit of this study. However, 1 limitation of this study is the small number of deaths or hospice admissions within 3 months of completing CRT, which may limit the broader applicability of the model. Another limitation is the amount of missing data for certain variables, such as ECOG performance status for which over 20% of patients had missing data. Despite the level of missing data for this variable, ECOG performance status was still a significant predictor for early poor outcomes in the multivariable model. However, this finding remains concordant with clinical expectations and published literature, determining that worse ECOG performance status is indeed associated with poor outcomes.[26,27]

Additionally, the low PPV and sensitivity impose limitations on the generalizability of this model. Considering the prognostic nature of the model, the low values for these metrics impedes the ability to reliably predict outcomes on the individual level. Although sensitivity and PPV are expected to be low when modeling a rare event, the statistical significance of the correlation between pretreatment variables and the incidence of early death or early hospice enrollments remains an important finding. Considering that this study is providing a baseline for the development of a comprehensive model, it is also conceivable that the predictive value of the model may improve as more data is gathered. Additionally, the proportion of patients with an average predicted risk of at least 20% account for only 1.4% of our data, possibly contributing to the low PPV and sensitivity. Moreover, the goal of this study is not to separate patients who ought to receive palliative care or to argue merits of triaging care. On the contrary, the aim of this study is to inform patients regarding their potential likelihood for poor outcomes after initiating CRT. Similarly, the presentation of an insurance variable is not to suggest the stratification of patients based on economic rationale. Instead, we believe this variable reinforces the importance of considering the impact of sociodemographic factors in the treatment of a diverse patient population.

On a more granular level, the manner in which the FACT-L questionnaire is utilized in this model may present a further point of contention. While the composite FACT-L score is a thoroughly tested metric, there is a paucity of data to support the reliability or unreliability of individual items from the FACT-L questionnaire. Due to our inclusion of individual items from the FACT-L questionnaire, we felt it was important to highlight this distinction.

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Conclusions

In summary, this predictive model helps identify locally advanced non-small cell lung cancer patients who may be at increased risk of developing an early poor outcome, defined as hospice enrollment or death within 3 months of completing curative-intent chemo-radiation treatment. These preliminary results are encouraging and warrant further evaluation in a larger cohort of patients.

Clinical Practice Points

- Treatment for stage II-III non-small cell lung cancer (NSCLC) involves chemo-radiotherapy (CRT). A large systematic review of randomized control trials demonstrated that concurrent CRT conferred statistically significant survival benefits, and decreased relapse rates.[4] However, some patients transition to hospice or die early during their treatment course. One of the difficulties in understanding the implications of combined treatment in this patient population stems from the lack of prognostic models to identify which patients may have poorer outcomes.[2]
- Of the 2,267 included patients in our study, 128 experienced early poor outcomes. Mean age was 71 years (range 48-91) and 59% received concurrent chemotherapy. The best predictive model included age, ECOG, PTV, mean heart dose, pretreatment lack of energy, and pretreatment cough. The area under the ROC curve for this multivariable model was 0.71, with a NPV of 95%, specificity of 97%, positive predictive value of 23%, and sensitivity of 16% at a predicted risk threshold of 20%.
- Predicting prognoses for patients with stage II-III lung cancer is notoriously difficult but has critical implications for the selection of appropriate therapy and the delivery of anticipatory guidance to patients and family members. A systematic review concluded that there are no published, validated predictive tools for estimating the risk of toxicity after definitive radiation for NSCLC patients.[15] This predictive model helps identify locally advanced non-small cell lung cancer patients at increased risk of developing an early poor outcome. These preliminary results are encouraging and warrant further evaluation in a larger cohort of patients.

Disclosure

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CRediT authorship contribution statement

Siddharth Ramanathan: Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Kimberly A. Hochstedler:** Data curation, Formal analysis. **Anna M. Laucis:** Investigation, Writing – original draft. **Benjamin Movsas:** Writing – review & editing. **Craig W. Stevens:** Writing – review & editing. **Larry L. Kestin:** Writing – review & editing. **Michael M. Dominello:** Writing – review & editing. **Inga S. Grills:** Writing – review & editing. **Martha Matuszak:** Writing – review & editing. **James Hayman:** Writing – review & editing. **Peter A. Paximadis:** Writing – review & editing. **Matthew J. Schipper:** Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Shruti Jolly:** Conceptualization, Writing – original draft, Writing – review & editing. **Thomas P. Boike:** Conceptualization, Writing – original draft, Writing – review & editing.

Data Sharing Statement

We are not authorized to share MROQC data. The data is individually owned by the member institutions of MROQC.

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