ORIGINAL ARTICLE

Prediction of Early Death in Patients with Early-Stage NSCLC—Can We Select Patients without a Potential Benefit of SBRT as a Curative Treatment Approach?

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ABSTRACT

Introduction: Stereotactic body radiotherapy (SBRT) is the guideline-recommended treatment for medically inoperable patients with peripheral stage I non–small cell lung cancer (NSCLC). This study analyzed whether short-term (<6 months) death can be predicted reliably to select a subgroup of patients who will not have a benefit from SBRT.

Methods: A total of 779 patients with early-stage NSCLC who had been treated with cone beam computed tomography–guided SBRT in five institutes and for whom information on overall survival during the first 6 months after treatment was available were included in this analysis. The probability of dying within 6 months after treatment was defined as the end point "early death" and modeled by multivariate logistic regression. Model fitting was performed using the least absolute shrinkage and selection operator method, and model test performance was estimated using double 10-fold cross validation. The variables age, sex, Eastern Cooperative Oncology Group performance status, operability, forced expiratory volume in 1 second, and Charlson comorbidity index were considered for model building.

Results: Eastern Cooperative Oncology Group performance status and (to a lesser extent) operability were the most important predictors of early death, whereas the Charlson comorbidity index was associated only with the overall survival time. On the basis of the best expected test performance (area under the curve = 0.699), the risk for early death would be 8.8% (range 8.2%–13.7%) and 4.1% (3.0%–4.3%) for the 10% of patients with the highest and lowest risk, respectively. Overall, predictive performance was too low for clinical application.

Conclusions: SBRT should be offered to all patients irrespective of their comorbidities, unless the performance status of the patients and the comorbidities prevent accurate SBRT planning and delivery.

Keywords: Stereotactic body radiotherapy; Non–small cell lung cancer; LASSO method; Logistic regression; Overall survival

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Introduction

Stereotactic body radiotherapy (SBRT) has become the guideline-recommended treatment of choice for patients with peripheral stage I non–small cell lung cancer (NSCLC) if they are medically inoperable or do not accept the risk of surgery.[1] There are different mechanisms through which SBRT improved the outcome in stage I NSCLC, and they apply to different patient populations. First, SBRT allowed the safe delivery of highly escalated irradiation doses with improved local tumor control and, consequently, improved overall survival (OS).[2,3] Therefore, SBRT replaced conventionally fractionated radiotherapy as the standard of care in a patient population.

The second mechanism is associated with the methodology of SBRT: the combination of being a safe and effective treatment with practice in an outpatient setting, being noninvasive, and most often being finished in only 1 week makes SBRT a highly attractive option for referring clinicians and for patients themselves. This may not be of highest relevance for patients previously treated with other curative treatment options. However, it might be of high relevance for elderly patients and patients with severe comorbidities who were not offered any curative treatment at all but instead were referred to best supportive care. Studies from the Netherlands focusing on the elderly population (>75 years old) reported increased treatment practice with curative intent compared with use of best supportive care only after the introduction of SBRT, which was associated with improved OS on a patient population level.[4,5] Simultaneously, experiences from many centers and countries report a promising outcome after SBRT for elderly patients[6,7] and patients suffering from very severe comorbidities.[8,9] Consequently, the practice of SBRT expanded to a high-risk patient population, offering them a curative option.

However, some of these high-risk patients might not encounter any benefit of SBRT-induced cancer control because their life expectancy is too short. It was therefore the aim of this study to evaluate whether the risk for very early death in patients referred to SBRT can be estimated and modeled. A patient at high risk for early death (in <6 months) could potentially be spared from SBRT as from any other cancer treatment with curative intent.

Materials and Methods

This study was performed on a database of 904 SBRT treatments for early-stage NSCLC at five international institutions, all of which are members of the Elekta Lung SBRT Research Consortium. Treatments were performed between February 1, 2007, and December 31, 2010. Ethical approval was available at all participating institutions.

The primary end point of this analysis was death from any cause other than lung cancer within 6 months after the start of SBRT; this interval was chosen because death due to early-stage NSCLC within 6 months after diagnosis is a rare event. For 782 patients with 816 SBRT treatments, sufficient follow-up for 6 months was available. In the case of multiple treatments of one patient (with multiple primary NSCLCs treated with SBRT) the date of the first treatment was used for calculation of OS; two patients who died within 6 months from cancer progression and one patient with grade 5 pneumonitis were also excluded. This resulted in 779 patients and SBRT treatments included into this analysis. A summary of treatment and tumor characteristics for these patients is provided in Table 1.

The probability of early death was modeled by multivariate logistic regression:

$$y_i = \exp\left(\beta_0 + \sum_{j=1}^{p} \beta_j x_j\right) \div \left[1 + \exp\left(\beta_0 + \sum_{i=1}^{p} \beta_j x_j\right)\right]$$

Here $i = 1, \ldots, N$ denotes patient i, $y_i = 1$ if early death occurred for patient i, and x_j is one of p predictors and the β_j are their regression coefficients. Because the goal is to predict whether a patient is likely to die independently from receiving radiation treatment, the variables of interest were restricted to patient characteristics; treatment characteristics were not included

Table 1. Treatment and Tumor Characteristics of the 779 Patients Included in the Analysis

Variable	Value	n
No. fractions	3 (1-10)	775
PTV min dose, Gy	46.2 (5.1-68.1)	747
GTV dose, Gy	66.0 (23.3-97.2)	748
GTV mean BED_{10}, Gy_{10}	188.8 (58.5-360.1)	748
Clinical stage		760
Stage I	34.3	
Stage IA	39.3	
Stage IB	16.7	
Stage II	8.8	
Stage IV	0.1	
Local recurrence	0.7	
Histologic classification		560
Adenocarcinoma	42.9	
Squamous cell carcinoma	25.4	
Large cell carcinoma	9.3	
Unknown	12.9	
Other	9.5	
Maximum tumor diameter, cm	2.3 (0.6-8.5)	773
Tumor location		771
Central	10.6	
Peripheral	89.4	

Note: For continuos variables, the median and range are given; for categorical variables percentages are given.
PTV, planning target volume; GTV, gross tumor volume, BED_{10}, biologically effective dose with alpha/beta=10 Gy.

in the analysis. The patient-specific variables available in our data were as follows (Table 2): age, sex, weight, Eastern Cooperative Oncology Group (ECOG) performance status, operability as judged by the responsible interdisciplinary tumor board (yes/no), smoking status, absolute and predicted forced expiratory volume in 1 second (FEV_1), diffusing capacity of the lung for carbon monoxide, and the Charlson comorbidity index (CCI [defined in Charlson et al.[10]]).

Multivariate model fitting was performed using the least absolute shrinkage and selection operator (LASSO) method.[11] LASSO is a form of feature selection in which regression coefficients of less important (so-called noise) variables get shrunk to zero by constraining the sum of absolute values of the regression coefficients so that the quantity

$$\sum_{i=1}^{N}\left(y_i-\beta_0-\sum_{j=1}^{p}\beta_j x_j\right)^2+\lambda\sum_{j=1}^{p}|\beta_j|$$

is minimized. The optimal value of the tuning parameter λ can be found from a grid of possible λ values by using cross validation (CV).[11] In general, the LASSO method is preferable over backward or forward feature selection for determining variables that are related to the response, also called "signal" variables. Its superiority over forward feature selection in model building has been demonstrated by Xu et al.[12] in a case of modeling the occurrence of xerostomia after radiation treatment of patients with head and neck cancer.

To validate the logistic regression model we followed the approach of Xu et al.[13] and used double k-fold CV. Briefly, double k-fold CV involves programming an outer loop that predicts each patient's probability for the outcome of interest and an inner loop in which the prediction model is optimized. In the outer loop, the data set is split into k distinct parts, one of which is used as a test set and the others of which are combined to be used for k-1 fold CV in the inner loop to determine the optimal value of λ and thus fit the model according to the LASSO method.[13] The fitted model is then applied to the test set and the predictions for each patient are stored. This procedure is repeated k times such that each of the k folds serves as a test set once. The stored model predictions for each patient provide an estimate of the test performance, which is the performance the model would achieve on an independent data set. We used stratified k-fold CV for the outer loop, so that the proportion of cases ($y = 1$) was roughly equal in all k folds. For the inner loop, we used the function cv.glmnet contained within the R package glmnet, which also standardizes all predictor variables to zero mean and unit variance before fitting the model.[14] Model performance was evaluated on the basis of the area under the receiver operating curve computed using the R package pROC.[15]

Table 2. Potential Patient-Specific Predictor Variables and Tumor Location

Variable	Value	n	Dead within 6 mo (n = 50)	Alive >6 mo (n = 729)	*p* Value
Age, y	76 (42-93)	778	76 (57-89)	75 (42-93)	0.33[a]
Sex		778			
Male	50.9		60.0	50.2	0.19[b]
Female	49.1				
Weight, kg	68.5 (32.9-130.5)	393	71.2 (38.5-103.0)	68.4 (32.9-130.5)	0.97[a]
ECOG PS		754			
0	26.5		17.0	27.2	0.003[b]
1	45.8		31.9	46.7	
2	25.2		44.7	23.9	
3	2.5		6.4	2.3	
Smoking status		445			
No	6.1		4.3	6.2	1[b]
Yes	93.9				
FEV_1, L	1.44 (0.43-4.4)	660	1.40 (0.50-2.88)	1.44 (0.43-4.40)	0.54[a]
DLCO (predicted), %	54 (6-129)	538	51 (19-111)	54 (6-129)	0.43[a]
CCI	3 (0-11)	779	2 (0-6)	3 (0-11)	0.08[a]
Operable		770			
No	87.8		98.0	87.1	0.02[b]
Yes	12.2				

Note: The full sample size was 779. Continuous variables are given as median and range, while categorical variables are given as percentages.
[a]The Mann-Whitney *U* test has been used to compute *p* values for continuous variables.
[b]Fisher's exact test has been used to compute *p* values for categorical variables.
mo, month; ECOG PS, Eastern Cooperative Oncology Group performance status; FEV_1, forced expiratory volume in 1 second; DLCO, diffusing capacity of the lung for carbon monoxide; CCI, Charlson comorbidity index.

Because the test performance estimate from k-fold CV depends somewhat on the splitting of the data set, the aforementioned steps were repeated multiple times to derive the variability of the model performance and variable selection.[13] We chose to repeat the model fitting and classification 100 times, obtaining a total of $k \times 100$ models because a single run of double k-fold CV yields k individual models that might differ in the variables included.

In general, double 10-fold CV was used. As a compromise between including as many patients as possible and examining as many variables as possible, only the variables age, sex, ECOG performance status, operability, FEV_1, and CCI were considered for model building. Finally, the LASSO method with double 10-fold CV was also used to identify signal predictors of OS in the Cox proportional hazards model.[16]

Results

Patient characteristics are provided in Table 2. A total of 50 patients died within 6 months after SBRT with no local, regional, or distant progression. Median follow-up for all 729 patients who lived longer than 6 months was 24.4 months (range 6.0–101.8). OS rates at 2 and 3 years were 65.6 ± 1.8% and 54.3 ± 2.1%, respectively (Fig. 1). Median OS was 40. 8 months (95% confidence interval: 36.5–49.3).

The LASSO method identified the variables age (selected into 99.9% of models), operability (100%), CCI (100%), and ECOG performance status (100%) as signal predictors in the Cox proportional hazards model. Inserting these variables into a multivariate Cox model indicated that ECOG performance status was the most significant predictor of OS, followed by operability and CCI (Table 3).

To determine whether these or other variables would also predict early death, patients who lived longer than 6 months and patients who died early (within 6 months) after SBRT were first compared using univariate analysis (see Table 2). Patients who died early had a significantly worse ECOG performance status, and a larger percentage were nonoperable. No significant difference in any other variable was observed—only (paradoxically) a trend toward a higher risk for early death in patients with a lower CCI. For multivariate analysis, logistic regression models were built using different combinations of the patient characteristics according to the LASSO method and their performance in predicting early death (within 6 months) was evaluated. Performance parameters were area under the curve (AUC), accuracy, sensitivity, and specificity.

Different combinations of the variables considered for model building resulted in different sample sizes and model performances that are summarized in Table 4. The mean AUC was 0.654 for the models selecting from age, sex, ECOG performance status, operability, FEV_1, and CCI. ECOG performance status was the most important prognostic factor for early death (within 6 months), and most frequently the only variable selected into a model. Accordingly, models selecting only from age, sex, and CCI had a significantly worse performance (AUC = 0.546, $p < 2.2 \times 10^{-16}$ according to the t test). On the basis of the 10 models that produced the highest AUC value in double 10-fold CV (AUC = 0.699), the risk for early death was 8.8% (range 8.2%–13.7%) and 4.1% (3.0%–4.3%) for 10% of the patients with the highest and lowest risk, respectively. Nine of these 10 models selected only the ECOG performance status, whereas one selected ECOG performance status and operability. The pooled regression coefficients of these models were $\beta_0 = -3.06 \pm 0.05$ (intercept), $\beta_{ECOG} = 0.29 \pm 0.04$, and $\beta_{operability} = -0.03 \pm 0.03$.

An example of the results of the variable selection procedure is shown graphically in Figure 2, in which the

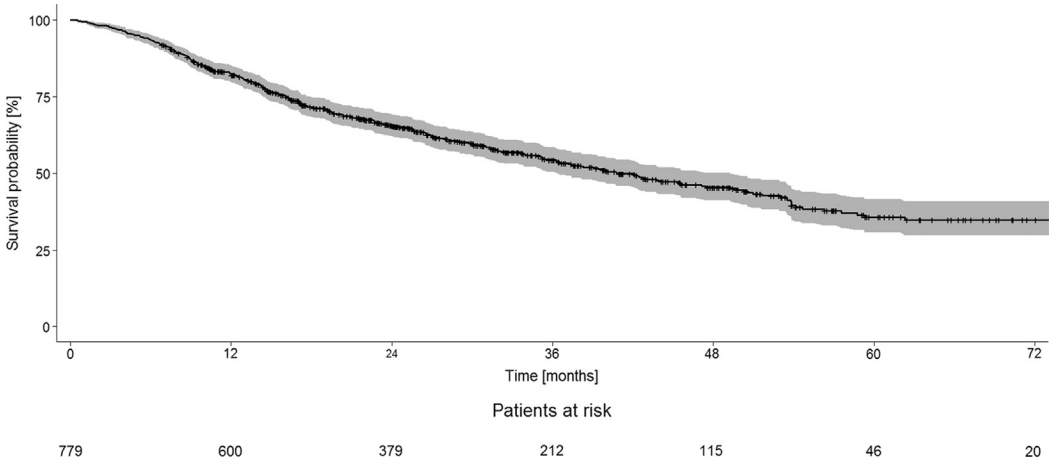

Figure 1. Kaplan-Meier curve showing the overall survival of the 779 patients used for analysis. Note the exclusion of censored observations within the first 6 months after treatment. The shaded area indicates the 95% confidence interval.

Table 3. Signal Predictors of OS in the Cox Proportional Hazards Model

Variable	Regression Coefficient	SE	*p* Value
ECOG PS	0.32	0.07	1.9×10^{-6}
Operability	-0.56	0.21	0.007
CCI	0.07	0.03	0.02
Age	0.01	0.006	0.07

Note: Higher values of ECOG performance status, CCI, age, and inoperability are associated with shorter survival times.
OS, overall survival; SE, standard error; ECOG PS, Eastern Cooperative Oncology Group performance status; CCI, Charlson comorbidity index.

left panel displays the number of models into which each variable has been selected and the right panel shows the relative frequency of the number of variables that were selected into an individual model. After ECOG performance status, operability and CCI were the second and third most frequently selected variables and gained importance as the number of other variables considered for model building decreased. Interestingly, higher CCI values were associated with a greater chance of surviving 6 months.

Adopting double 20-fold or 5-fold CV yielded similar results concerning the dominance of the ECOG performance status and model performance measures (results not shown). ECOG performance status and, subsequently, operability and CCI remained the most important variables when missing variable values were imputed using multiple imputation by chained equations with the R package mice,[17] so that all 779 patients could be used for analysis. Finally, ECOG performance status dominated all other variables when death within 9 months was considered instead of within 6 months after SBRT.

Discussion

In this study, we have identified ECOG performance status as the dominant predictor of early death (within 6 months after SBRT) for stage I NSCLC. However, in our study, neither models based on the ECOG performance status alone nor models based on the combination with the patient characteristics sex, operability, CCI, and age achieved sufficient accuracy of predicting early death after SBRT for early lung cancer. None of the models in our study achieved an AUC value greater than 0.699. Such low model performance is insufficient in clinical practice, with unacceptable risks of both overtreatment and especially undertreatment. The patient characteristics analyzed in this study and predictive models based on them should therefore not be used to select a patient cohort for best supportive care instead of SBRT with curative intent. In other words, SBRT should be offered to all patients unless the patients' performance status (mental or physical) and comorbidities prevent accurate SBRT planning and delivery.

We have chosen early death (within 6 months) after SBRT as the primary end point of our study. This is based on the expectation of a low risk for NSCLC-caused death within 6 months if no treatment with curative intent is given. Very few studies reported the natural course of stage I NSCLC after best supportive care or observation only. McGarry et al. reported OS after observation only for 49 patients with stage I NSCLC, with most of the patients (53%) dying of lung cancer: the

Table 4. Results of the Model-Fitting Procedure

Characteristic	Variables		
	Age, Sex, ECOG PS, Operability, FEV_1, CCI	Age, Sex, ECOG PS, Operability, CCI	Age, Sex, CCI
Sample size	642	749	778
No. cases	39	47	50
Mean AUC	0.654 ± 0.002	0.612 ± 0.002	0.546 ± 0.003
Mean accuracy, %	65.3 ± 0.1	61.7 ± 0.1	56.8 ± 0.2
Mean sensitivity, %	57.9 ± 0.5	53.4 ± 0.7	76.7 ± 1.2
Mean specificity, %	72.7 ± 0.4	70.1 ± 0.6	36.8 ± 1.4
Variables selected into >20% of models	ECOG PS: 100%	ECOG PS: 100% Operability: 54.9% CCI: 37.7% Age: 33.2% Sex: 30.5% (see Fig. 2)	CCI: 98.4% Sex: 83.9% Age: 75.3%
No. of variables selected into >20% of models	1: 84.4%	1: 45.1% 5: 29.7%	3: 80.5%

Note: Models were fit separately to three subsamples of the data containing different variables that have been considered for model building and thus different sample sizes because some variables were missing for some patients (see Table 1).
ECOG PS, Eastern Cooperative Oncology Group performance status; FEV_1, forced expiratory volume in 1 second; CCI, Charlson comorbidity index; AUC, area under the ROC curve; No., number.

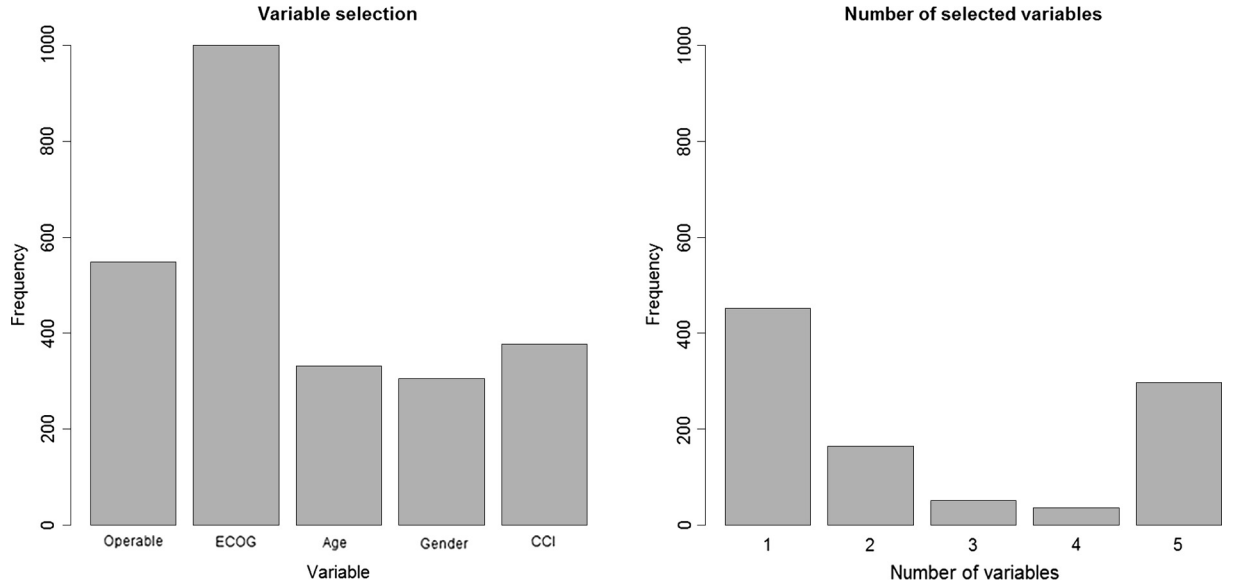

Figure 2. Results of the variable selection by the least absolute shrinkage and selection operator method for all data containing the variables operability, Eastern Cooperative Oncology Group (ECOG) performance status, age, sex, and Charlson comorbidity index (CCI) on the basis of 100 double 10-fold cross validation runs, resulting in a total of 1000 individual models. (*Left*) Frequency with which a variable was selected into a model. (*Right*) Frequency distribution of the number of variables that were selected into a model.

median OS of 14.2 months suggests few NSCLC-caused deaths within 6 months.[18] Raz et al. performed an analysis of the California Cancer Center Registry and identified 1432 patients who were not treated with surgery, chemotherapy, or radiotherapy for stage I NSCLC.[19] The median lung cancer–specific survival times were 26 months and 10 months for patients with cT1 and cT2 tumors, respectively, which again supports the hypothesis of low cancer-related deaths within 6 months after diagnosis and observation only.

Most of the patients in this cohort were treated with SBRT because of medical inoperability (87.8%); consequently, this is a patient population with reduced overall life expectancy and increased risk for early death. Severe chronic obstructive pulmonary disease (COPD) is known as the most frequent reason for referral to SBRT,[20] and severe COPD is associated with a high risk for early death: elderly patients (>65 years old) admitted to the hospital because of chronic COPD have 90-day and 1-year death rates of 14.5% and 27.7%, respectively.[21] In our overall patient cohort, 53 of 782 patients (6.8%) died within 6 months after SBRT and the cause of death was unrelated to their cancer in 94% of cases. Grade V toxicity was reported in only one patient (0.1%).

ECOG performance status, CCI, and operability were associated with OS in the multivariate analysis (see Table 3); all are well established prognostic factors. However, there was a discrepancy between parameters predicting OS and early death: ECOG performance status was the only factor significantly correlated with early death within 6 months after SBRT.

The ECOG performance status describes patients' level of functioning in terms of their ability to care for themselves, daily activity, and physical ability. It is included in every baseline patient assessment in clinical trials as well as in daily clinical practice. The relevance of the ECOG performance status lies in the fact that it is known as a global predictor for survival, which is true in SBRT for stage I NSCLC as well.[22,23] Therefore, the identification of ECOG performance status as a prognostic factor for both OS and early death confirms the validity of this study.

Although there are consensus definitions for being operable—both for being suitable for anesthesia and a major surgical procedure and for being suitable for lobectomy—it is not surprising that their interpretation and the referral to SBRT varies between institutions and health care systems.[9] Nevertheless, inoperability as captured in this multi-institutional database was significantly associated with early death and OS.

The CCI is a well-established tool for estimating OS,[10] and several studies have evaluated the CCI in patients treated with SBRT for stage I NSCLC. Kopek et al. reported a median OS of 41 months for patients with an age-adjusted CCI of 3 or lower compared with only 11 months for patients with a score of 6 or higher ($n = 23$).[24] Early death within 6 months was not reported, but visual analysis of the Kaplan Meier curve suggests a death rate of approximately 15% for the cohort with the

worst CCI. The Free University Amsterdam established a prognostic model to predict OS after SBRT for stage I NSCLC.[22] Age of at least 75 years and CCI of 3 or higher are the patient-specific factors of this model, which is complemented by a tumor diameter of 2 cm or larger. The 1-year OS rates were 87.1% and 81% for classes 1 and 2 in the training set and 92.5% and 77.8% in the validation set, respectively. Although the model clearly separated cohorts with different OS rates, the large absolute differences between the training and validation sets indicate the uncertainties of this model.

The CCI has been identified as an important prognostic factor not only in patients treated with SBRT but also in patients treated with surgery for stage I NSCLC. Consequently, all matched pair analyses or studies using propensity score matching to compare SBRT and surgery included the CCI into the matching process.[25–28] These studies consistently showed higher CCI scores for patients treated with SBRT than for patients treated with surgery, and as a consequence, OS was better for the surgical cohorts. This OS difference consistently disappeared after propensity score matching and accounting for this and other imbalances.

Despite the fact that CCI is clearly correlated with OS, this score was insufficient to predict the risk for early death. This is known in the fields of palliative care and geriatric care, disciplines that overlap with the target population of this study. Versteeg et al. performed a systematic review of prognostic parameters in elderly patients with solid malignancy[29]: comorbidity was associated with worse OS, but poor nutritional status and functionality were the most frequent reasons for adapting the treatment plan.

Consequently, future studies should evaluate different factors regarding their suitability predicting the risk for early death. The comprehensive geriatric assessment is a multidimensional, multidisciplinary diagnostic instrument in geriatrics, which differs from a standard medical evaluation in three general ways: (1) it focuses on elderly individuals with complex problems, (2) it emphasizes functional status and quality of life, and (3) it frequently takes advantage of an interdisciplinary team. This tool is slowly making its way into cancer care and lung cancer treatment specifically.[30,31] In patients with inoperable or metastatic solid cancer (lung cancer 16%), the 6-month death rate was higher than 50% for patients with severe multidimensional prognostic index values.[32] To gather more data, we need randomized studies that examine the impact of such a geriatric assessment on the treatment decision in patients with stage I NSCLC that are medically inoperable.

Besides objective scores, it is well known that estimates by physicians frequently overestimate OS. In palliative care, the "surprise" question Would I be surprised if this patient died in the next year? has been demonstrated to improve the selection of patients with a very high risk for early death. In a cohort of 853 consecutive patients with breast, lung, or colon cancer, physicians answered no in 16% of cases, and the answer to the surprise question was the strongest predictor of OS, stronger than stage of cancer.[33]

Besides the potential assessments adopted from geriatrics and palliative care, more in-depth description of the underlying comorbidities might be useful in predicting the risk for early death. Especially younger patients with a single and dominant comorbidity as opposed to elderly patients with polymorbidity might benefit from such an approach.

In summary, we were unable to generate an accurate model predicting a high risk for early death after SBRT in patients with early-stage lung cancer; it is important to keep in mind that these patients had already been selected for SBRT by good clinical judgment (in the form of multidisciplinary team meetings). Consequently, besides comorbidities and physical or mental conditions making SBRT with the required technical accuracy infeasible, no further contraindications for SBRT can be recommended.

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