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Original article

Co-morbidity index predicts for mortality after stereotactic body radiotherapy for medically inoperable early-stage non-small cell lung cancer

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ABSTRACT

Purpose: To determine the prognostic role of co-morbidity in medically inoperable early-stage non-small cell lung cancer (NSCLC) treated with stereotactic body radiotherapy (SBRT).
Methods and materials: Between 2000 and 2007, 88 consecutive early-stage medically inoperable NSCLC patients were treated by linac-based SBRT. The dose was either 45 Gy or 67.5 Gy in three fractions prescribed to the isocenter. Baseline co-morbidities were retrospectively retrieved by consultation of a formal electronic registry of diagnoses as well as patients' charts. The age-adjusted Charlson Co-morbidity Index (CCI) was scored for each patient and subjected to univariate and multivariate analysis.
Results: With a median follow-up of 44 months, the actuarial local control rate at 4 years was 89% while the median overall survival was 22 months. The median age-adjusted CCI score was 5. The age-adjusted CCI was a significant predictor of overall survival on both univariate ($p = 0.002$) and multivariate analysis ($p = 0.011$). Patients with an age-adjusted CCI score of 3 or less had a median survival of 41 months versus only 11 months for those scoring 6 or more.
Conclusion: The number and seriousness of co-morbidities predict overall survival in medically inoperable early-stage NSCLC treated with SBRT. Because the determination of medical operability is frequently based on both objective measures and subjective clinical judgment, it is recommended that co-morbidity be formally indexed in all studies examining the outcomes of SBRT.
 Radiotherapy and Oncology xxx (2009) xxx–xxx

Lobectomy remains the standard of care for early-stage non-small cell lung cancer (NSCLC) with reported 5-year local control rates between 60% and 80% [1–3]. In stark contrast, local control for stage I NSCLC treated with 60 to 66 Gy of conventionally fractionated radiotherapy ranges from 30% to 50% [1–3]. Among the strategies to improve control rates is stereotactic body radiotherapy (SBRT), a technique which permits precise delivery of extremely high doses per fraction. Numerous reports have indicated extremely good local control after SBRT [4–17]. Toxicity has been very favourable with only a few severe adverse events reported in association with centrally located tumours [18].

Despite these encouraging results, the reported overall survival rates after SBRT for early-stage NSCLC tend to lag behind the improved local control [6,11,15,17–19]. This has frequently been attributed to competing co-morbidities. There has not, however, been a rigorous assessment of the prognostic role of baseline co-morbidity in the SBRT lung population which has largely consisted of patients deemed medically inoperable. The determination of medical inoperability, although guided by objective measures relating to lung and cardiac function, is often based on overall clinical judgment. Consequently there may be considerable variability in the number and seriousness of co-morbidities affecting those patients considered "medically inoperable." The present report of long-term outcomes of SBRT in the treatment of early-stage NSCLC investigates the impact of number and seriousness of baseline co-morbidities upon overall survival.

Materials and methods

Eighty-eight consecutive medically inoperable early-stage NSCLC patients were treated with SBRT at the Aarhus University Hospital between January 2000 and December 2007. Forty-one of these patients were treated under protocol, either a Danish phase II ($n = 32$) [20] or a multicenter Nordic phase II study ($n = 9$) [21]. The selection criteria for both studies were histologically proven NSCLC, stage T1-2N0M0 (UICC 1997), tumour diameter < 6 cm, medically unfit for surgery, and World Health Organisation (WHO) performance status of 0–2. Staging of tumour and distant metastasis was based on computed tomography (CT) scan. Regional lymph node metastasis was preferentially assessed by mediastinoscopy ($n = 49$), otherwise by CT alone. Six patients with suspicious lymph nodes on CT but who did not undergo mediastinoscopy had a positron

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emission tomography (PET) scan. PET scan was the only verification of malignancy for one patient with a solitary nodule who could not undergo histological verification of the tumour due to severe pulmonary insufficiency.

The study was approved by the Ethics Committee of Aarhus County. Informed consent was obtained from all patients and the study was carried out in accordance with the Helsinki Declaration II.

Immobilization was achieved using a customized vacuum pillow and stereotactic body frame (SBF; Elekta, Stockholm, Sweden). Respiratory motion was minimized for all patients by means of diaphragmatic compression [22]. All patients were CT simulated using spiral CT performed with a 5 mm slice thickness (8 mm/s) and reconstructed with a 4 mm interslice distance.

Treatment planning was done using the Helax-TMS (MDS-Nordion, Freiburg, Germany) or CadPlan Plus/Eclipse (Varian Medical Systems, Palo Alto, CA) treatment planning systems. The gross tumour volume (GTV) was contoured under pulmonary windows by a radiation oncologist assisted by a radiologist. The clinical target volume (CTV) was identical to the GTV. The planning target volume (PTV) was formed by expanding the CTV by 5 mm in the radial direction and by 10 mm in the cranial–caudal direction. A typical treatment plan consisted of five to eight static coplanar or non-coplanar beams formed by a multileaf collimator with a leaf width of 5 or 10 mm at the isocenter. The prescription dose (45 Gy or 67.5 Gy in three fractions) was delivered to the isocenter. The CTV was encompassed by the 95% isodose surface while the PTV was completely covered by the 67% isodose surface. This corresponds to a minimum dose to the PTV of 30 Gy or 45 Gy in three fractions, depending on the central prescribed dose. Only peripheral lesions were treated to a centrally prescribed dose of 67.5 Gy ($n = 26$). Dosimetric calculation was conducted using a pencil beam algorithm with heterogeneity correction.

A CT scan was carried out on the first treatment day to confirm the position of the isocenter. Patient positioning for the subsequent two fractions was controlled with portal film imaging by matching to the vertebral column. Treatment was given without respiratory gating on either a Siemens Primus (Siemens Medical Solutions, Concord, CA) or a Varian Clinac 2100/2300 using 6 or 8 MV beam energies. The overall treatment time was 5–8 days.

Control CT imaging occurred at 3, 6, 9, 12, 18 and 24 months after the last treatment fraction and then annually. Tumour response was evaluated according to the WHO criteria [23]. The clinical follow-up schedule was the same as for radiographic control imaging. Protocol patients were also seen in follow-up at 2 weeks and 2 months post-treatment. Performance status and analgesia use were scored according to the WHO criteria. The National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (CTCAEv.3) was used for all other parameters.

Co-morbidity was rated using the Charlson Co-morbidity Index (CCI), a well-defined and validated scale that has been used in numerous clinical studies with reliable results [24–26]. The CCI has been correlated with mortality in many studies and has good interrater reliability. The scale was developed in 1987 [24] based on the 1-year mortality of patients admitted to a medical hospital service for a variety of problems and validated against a cohort of breast cancer patients. A weighted index of co-morbidity for 19 clinical conditions was developed on the basis of the relative risk of death that reflects both number and seriousness of co-morbid disease. In the validation phase of the CCI, age was also found to be an independent risk factor for death from a co-morbid condition. A combined age–co-morbidity scale was subsequently validated which accounts for the effects of increasing age by adding one point to the index score for each decade of life over 50 [27]. It is this combined index which has been used in the present analysis. Although the CCI attributes two points for "any tumour", we have not regarded a patient's primary lung tumour as a co-morbidity and, therefore, the primary tumour was not scored in the tabulation of the age-adjusted CCI. In the present study, co-morbidity data were retrieved from a centralised electronic database of diagnoses formally coded and registered for each patient, as well as by review of all medical and surgical consultation notes in patients' hospital charts.

Sufficient pulmonary function data were available for 40 chronic obstructive pulmonary disease (COPD) patients to permit grading of airflow limitation using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification [28,29]. This classification system is based on two objective parameters, the ratio of forced expiratory volume in 1 s over the forced vital capacity (FEV1/FVC) and FEV1 as a percentage of predicted values (FEV1%). FEV1/FVC is reduced to less than 70% for GOLD classes 1–4. The severity of air flow limitation is indicated by the FEV1%, ranging from $\geqslant$80% (class I, mild) to <30% (class 4, very severe).

Statistics

Actuarial analysis of outcomes was conducted using the Kaplan–Meier method and calculated from the date of first SBRT treatment. Local control was defined as the absence of radiologically and/or cytologically proven progression. Freedom-from-failure was defined as the time to local and/or distant failure. Overall survival was defined as the time to death from any cause. To calculate cancer-specific survival, the cause of death was determined based on the presence of pathological and/or clinical evidence of disease progression in conjunction with a careful review of all medical documentation at the time of death. If patients were admitted to external medical facilities at the time of their death, documentation from these centers was requested for review.

Log rank statistics were used to test for differences in outcomes when stratifying by relevant tumour, patient and treatment factors. Cox regression analysis using the forward selection method was used to assess for the effect of multiple prognostic factors. Dichotomization of continuous variables was based on the median value ($\leqslant$median versus >median). Univariate analysis of the age-adjusted CCI was conducted for both the absolute score as well as by dichotomizing the variable above and below the median score for the entire cohort. Since there was only 1 patient with an age-adjusted CCI score of less than 3, and 7 patients with an age-adjusted CCI score of 7 or 8, these patients were grouped with those scoring 3 and 6, respectively. Statistical computation was done with SPSS 13.0 software and a significance level of 5%, two-tailed, was used for univariate and multivariate analysis.

Results

The median follow-up time was 44 months (range 1.6–96.5 months) calculated from the date of first treatment. Baseline patient and tumour characteristics are given in Table 1. The median age-adjusted CCI score was 5 with 16 (18.2%), 24 (27.3%), 25 (28.4%) and 23 (26.1%) patients scoring $\leqslant$3, 4, 5 and $\geqslant$6, respectively. COPD was the most frequently registered co-morbidity ($n = 63$) followed by cardiac disease ($n = 31$). Seventeen patients were GOLD class 1 or 2, and 23 patients were GOLD class 3 or 4.

There were 79 patients with follow-up radiographic imaging evaluable for tumour response. Complete response was observed in 6 patients; 19 patients had a partial response, and a further 49 patients demonstrated stable disease. Altogether 26 patients had recurrent disease: 5 local (2 isolated and 3 in conjunction with distant metastases), 5 mediastinal nodal all of which were in conjunction with distant failure; and a further 16 isolated distant failures. Local failures occurred between 2.4 and 16 months after the start of treatment.

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Table 1
Baseline patient characteristics.

Characteristic	Value
Patients (*n*)	88
Gender	
Male	45 (51)
Female	43 (49)
Age	
Median	72.8 years
Range	47.1–88.5 years
WHO performance status	
0	15 (17)
1	51 (58)
2	19 (21.2)
3	2 (2.3)
Age-adjusted Charlson Co-morbidity score	
⩽3	16 (18.2)
4	24 (27.3)
5	25 (28.4)
⩾6	23 (26.1)
Median	5
FEV1	
Mean	1.06 L
Range	0.25–2.60 L
Histology	
Adenocarcinoma	30 (34.1)
Squamous	34 (38.6)
Other	24 (27.2)
Tumour and node stage	
T1	51 (58)
T2	36(40.9)
T3	1 (1.1)
N+	0 (0)
Tumour diameter	
Median	30 mm
Range	10–80 mm

Abbreviations: WHO = World Health Organisation; FEV1 = forced expiratory volume in 1 s. Values are *n* (%).

At 4 years the actuarial local control (LC) and freedom-from-failure (FFF) were 89% and 36%, respectively (Fig. 1). The 1, 2, 3, 4 and 5 year overall survival was 67%, 49%, 36%, 24% and 21%, respectively. The median cancer-specific (CSS) and overall survival (OS) were 61 months and 21.8 months, respectively (Fig. 2).

Univariate and multivariate analysis

Table 2 presents the variables and results of the univariate analysis for overall survival. T-stage, tumour size, and age-adjusted CCI were statistically significant. Patients with an absolute age-adjusted CCI score of 3 or less had a median survival of 41 months versus 11 months for those scoring 6 or more (Fig. 3). Multivariate analysis included the variables gender, histology, WHO performance status, age-adjusted CCI, total dose and T-stage. Both age-adjusted CCI > 5 (relative risk [RR] 2.14, 95% confidence interval [CI] 1.19–3.84, $p = 0.011$) and T2 tumours (RR 2.57, 95% CI 1.51–4.39, $p = 0.001$) were observed to be independently associated with inferior overall survival.

Toxicity

A frequency table of the most severe grade registered by each patient for each toxicity parameter is presented in Table 3. Only deteriorations from baseline were registered as adverse events. For most parameters, therefore, the majority of patients experienced no change from baseline. The grade of adverse events presented in Table 3 has not been corrected for the baseline score in order to provide a sense of the overall burden of grade 3/4 symptomatology experienced by this cohort after SBRT, regardless of their status at baseline. Overall, there were relatively few grade 3 or 4 adverse events. The majority of these represented deteriorations in performance status, analgesia use and dyspnea. When baseline grade is taken into account, only four patients had deterioration in performance status by ⩾3 grade points, 7 patients had a ⩾3 grade point worsening in analgesia use and only 1 patient had a 3 grade point deterioration in dyspnea. Finally, 7 cases of rib fracture were observed, all of which occurred between 9 and 24 months post-treatment.

Discussion

The present study, in addition to reporting some of the most mature SBRT data for lung cancer published to date, provides a quantitative assessment of the impact of number and seriousness

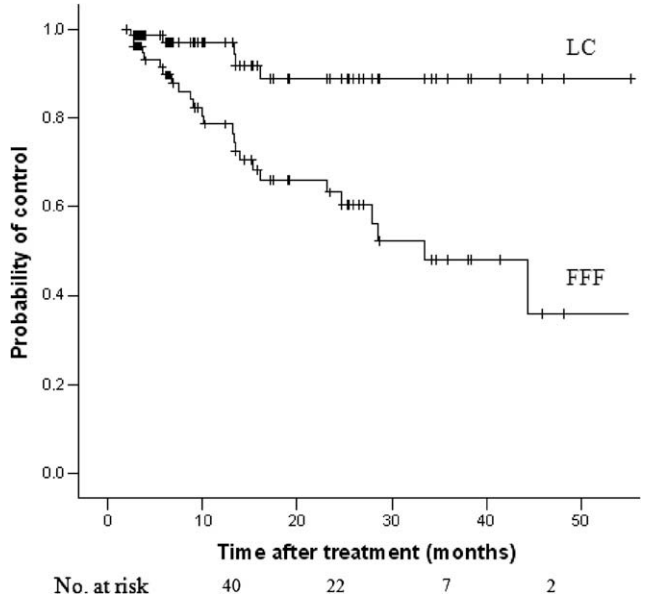

Fig. 1. Local control (LC) and freedom-from-failure (FFF) in 79 medically inoperable patients with early-stage NSCLC treated with SBRT.

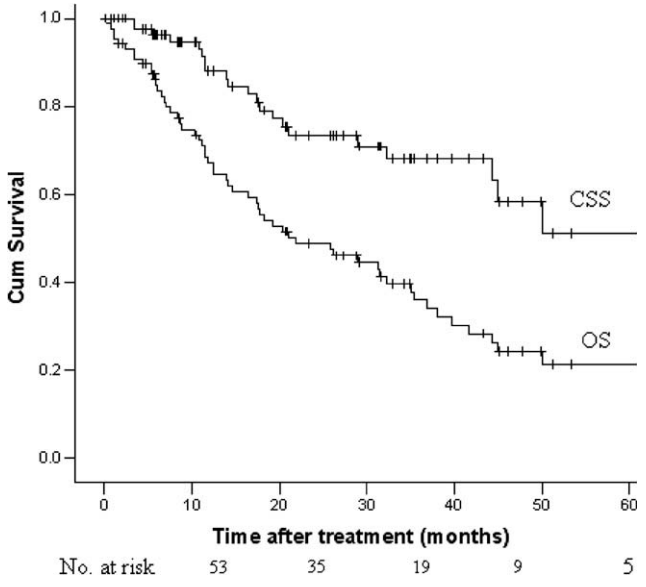

Fig. 2. Cancer-specific survival (CSS) and overall survival (OS) of 88 patients with medically inoperable early-stage NSCLC treated with SBRT.

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Table 2
Summary of univariate analysis for overall survival.

Variable	Categories (*n*)	Median OS in months (95% CI)	Log rank *p*-value
Tumour diameter	⩽30 mm (51)	35.1 (26.5–43.7)	<0.001
	>30 mm (37)	10.8 (7.3–14.2)	
T- stage	T1 (51)	35.1 (26.5–43.7)	<0.001
	T2 (36)	10.8 (6.7–14.9)	
Histology	Adenocarcinoma (30)	26.1 (5.7–46.6)	0.546
	Squamous (34)	17.5 (10.8–24.2)	
	Other (23)	21.8 (14.5–29.2)	
Gender	Male (45)	21.0 (11.7–30.3)	0.296
	Female (43)	29.0 (3.0–55.0)	
Age (median 73 years)	⩽73 (46)	26.1 (12.9–39.4)	0.403
	>73 (42)	17.5 (0.0–35.8)	
Performance status[a]	0–1 (67)	29.0 (17.2–40.7)	0.115
	2–3 (21)	17.7 (4.4–31)	
GOLD classification[b]	0, 1 or 2 (42)	19.3 (3.7–34.9)	0.676
	3 or 4 (23)	26.1 (9.7–42.5)	
Age-adjusted Charlson Co-morbidity	⩽5 (65)	32.3 (21.9–42.7)	0.002
	>5 (23)	10.8 (6.4–15.2)	
FEV1 (median 1.05 L)	⩽1.05 L (26)	17.5 (7.9–27.1)	0.954
	>1.05 L (30)	19.2 (2.6–36.0)	
Total dose	45 Gy (62)	19.3 (8.3–30.3)	0.636
	67.5 Gy (26)	21.8 (9.0–34.6)	

[a] World Health Organisation (WHO) performance status.
[b] Global Initiative for Chronic Obstructive Lung Disease (GOLD).

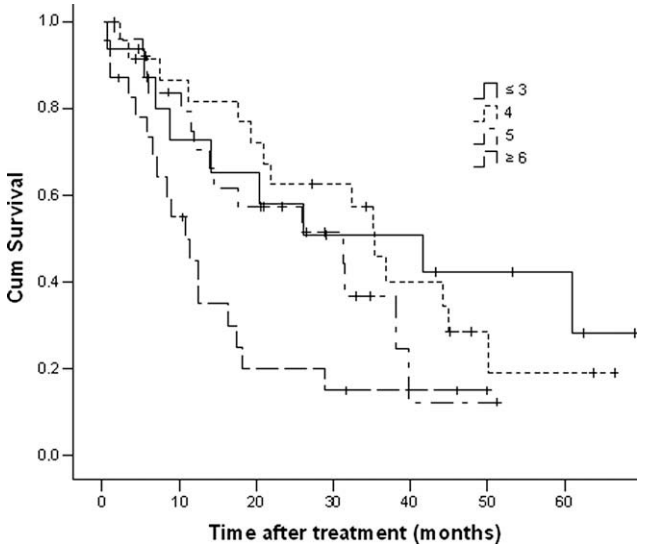

Fig. 3. Overall survival of 88 medically inoperable NSCLC patients treated with SBRT stratified by the age-adjusted Charlson Co-morbidity score. (Log rank $p = 0.015$).

of baseline co-morbidities on the overall survival of primary early-stage NSCLC treated by SBRT. As in the previous reports of SBRT for early-stage NSCLC, excellent local control was observed and the toxicity profile was favourable. Actuarial 5-year overall survival, however, was only 21%. Although disappointingly low, this rate is consistent with the few other studies that have reported long-term survival rates for SBRT which ranges from 18% to 30% at 5 years [11,15].

A more encouraging cancer-specific survival was observed. In the present study care was taken to verify the cause of death by reviewing all medical documentation at the time of death, including reports from external facilities when necessary. In this cohort there were no patients with documented disseminated disease whose death was attributed to causes other than their cancer. Nonetheless, cause-specific survival must always be interpreted with caution. As in many other SBRT reports, pathological assessment of post-SBRT lung parenchyma changes was not systematically obtained in this study. This is reasonable since there is some morbidity associated with obtaining a lung biopsy, the biopsy is subject to sampling error due to the surrounding normal lung tissue changes, and further treatment options for medically inoperable patients are usually limited. However, this also renders cancer-specific survival an imprecise means of accounting for co-morbidity in the assessment of the survival outcomes after SBRT.

Table 3
Adverse events (CTCAEv.3) registered as worst grade above baseline over the entire follow-up period.

Parameter	1	2	3	4	Any grade
Performance status[a]	6	15	13	3	37
Pain MSK	5	2	1	0	8
Pain PULM	10	7	1	0	18
Analgesia[a]	6	5	5	4	20
Dyspnea	12	9	11	0	32
Pulmonary fibrosis	52	2	0	0	54
Pneumonitis/infiltrates	48	1	0	0	49
Atelectasis	31	0	0	0	31
Pleural effusion	4	2	0	0	6
Cough	1	0	1	0	2
Skin erythema	1	1	0	0	2
Skin fibrosis	2	0	0	0	2
Skin hyperpigmentation	0	2	0	0	2
Esophagitis	0	1	0	0	1
Other (fatigue × 2, dysphagia × 1)	2	1	0	0	3
Total	180	48	32	7	267

Abbreviations: CTCAEv.3 = Common Terminology Criteria Adverse Events version 3.0; MSK = musculoskeletal; PULM = pulmonary.
[a] World Health Organisation scoring criteria.

More convincing data suggesting that advanced age and competing co-morbidities are largely responsible for the poor overall survival post-SBRT comes from subgroup analysis of patients who were deemed medically operable but who opted for SBRT as the primary treatment modality. These medically operable patients had a much higher overall survival [12,14,19]. Firat et al. [30], in their retrospective analysis of prognostic factors for stage I NSCLC patients treated with surgery or conventionally fractionated radiotherapy, have observed statistically significant differences in Karnofsky performance status (KPS) and co-morbidity index scores between the surgery and radiotherapy groups. On the whole, therefore, it is reasonable to assume that, compared to medically operable patients, patients who are deemed medically inoperable and consequently offered a non-surgical treatment approach for their NSCLC suffer from a greater number and severity of co-morbidities which may compromise their overall survival.

There can, however, be a range in the co-morbidity burden within both medically operable and inoperable patients. The study of Firat et al. [30], in addition to observing a significant difference in co-morbidity scores between surgical and radiotherapy patients, also observed a range of KPS and co-morbidity index scores within the respective treatment modality groups which was of prognostic significance for overall survival. Moreover, they observed that for patients with a KPS < 70 and Cumulative Illness Rating Scale for Geriatrics (CIRS-G) score of 4 (severe co-morbidity), the mortality between the surgically treated and radiotherapy treated patients was similar. The importance of co-morbidity upon overall mortality rates within surgically treated stage I NSCLC has been documented by others, notably Battafarano et al. [31] who observed statistically significant differences in 3-year mortality as a function of co-morbidity prospectively scored by the Kaplan–Feinstein index.

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The Charlson Co-morbidity Index was used in this study to assess the prognostic significance of co-morbidity. The CCI is a well established and widely used co-morbidity index but it may not be sufficiently sensitive to appreciate significant differences in co-morbidity burden in all populations. Extermann et al. [25] have urged some caution with respect to the CCI because of its tendency to give co-morbidity scores that are lower than those observed with other indices. Firat et al. [30] applied the Charlson index as well as the CIRS-G to both the surgical and radiotherapy patients of their study. While the CIRS-G index was significant within both treatment groups, the CCI was significant only for the radiotherapy group which consisted primarily of patients considered medically inoperable. The CCI may not, therefore, be the optimal index to use to control for co-morbidity in studies assessing SBRT in medically operable patients where the overall co-morbidity burden and patient age are expected to be lower.

The results of our analysis, in addition to demonstrating the prognostic importance of co-morbidity in the SBRT lung population, provide some reassurance that it is indeed advanced age coupled with competing baseline co-morbidity rather than overlooked treatment-related mortality which is largely responsible for the low overall survival rate post-SBRT. It is possible that there may be an interaction between treatment toxicity and patient co-morbidities, such that treatment-induced toxicity may exacerbate and potentially hasten death due to pre-existing comorbid conditions. This is most conceivable with respect to lung toxicity since lung parenchymal changes (pneumonitis/fibrosis) are very frequently documented post-SBRT and the most frequently encountered co-morbidity in the SBRT lung population is COPD. The physiological nature of this possible interaction, however, is not straightforward. One might speculate that patients with more severe baseline COPD would be more vulnerable to SBRT-induced pneumonitis by virtue of increased activation of inflammatory mechanisms. Alternatively one might imagine the risk of SBRT-induced lung toxicity to be less in patients with more severe baseline COPD by virtue of a decreased amount of remaining healthy lung parenchyma susceptible to treatment toxicity. Baumann et al. [32], in their recent analysis of SBRT lung toxicity using both subjective and objective measures did not observe any significant difference in crude rates of lung-related toxicity as a function of baseline GOLD classification. Moreover, GOLD classification was not observed in the present study or by Lagerwaard et al. [33] to be a significant prognostic factor for overall survival post-SBRT. Thus, with respect to pulmonary disease, if a treatment–co-morbidity interaction exists it does not appear to impact significantly upon overall survival.

Conclusion

The results of the present study indicate that SBRT is a well-tolerated treatment modality that appears to offer long-term tumour control. The advanced age and array of co-morbidities characterising this medically inoperable patient population is a major reason for the persistently low overall survival observed. However, the prognostic significance of co-morbidity observed in our analysis demonstrates the existence of a range in the number and seriousness of co-morbidities in the lung cancer patient population typically offered SBRT which is not adequately accounted for by the simple classification of medically "operable" versus "inoperable." To permit meaningful comparisons of SBRT results reported by different institutions and especially in analyses which directly compare SBRT against other treatment modalities, it is recommended that co-morbidity be formally indexed and controlled for in all studies examining survival outcomes after SBRT for NSCLC.

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