

## CLINICAL INVESTIGATION

# Heart rate recovery and survival in patients undergoing stereotactic body radiotherapy for treatment of early-stage lung cancer

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**Objectives:** Up to 25% of patients with stage I non-small cell lung cancer (NSCLC) are considered high-risk for surgery, due to severe medical comorbidity and/or poor pulmonary reserve. Many of these patients are treated with stereotactic body radiotherapy (SBRT). Prognosis in this subgroup of patients is difficult to determine. We investigated the association of impaired heart rate recovery (HRR) with survival in patients who received SBRT for treatment of early-stage lung cancer.

**Methods:** We collected data from consecutive patients who, between October 2009 and December 2012, received SBRT for treatment of lung cancer at the Cleveland Clinic, and had 6-minute walk test (6MWT) followed by HRR evaluation performed within six months of initiation of treatment. Impaired HRR was defined as a  $\leq 12$  beat decrease within the first minute following the 6MWT. Survival analyses were performed using Kaplan-Meier estimates and Cox proportional hazard ratios.

**Results:** Forty nine patients who received SBRT for treatment of early-stage lung cancer had HRR data available. Thirty two (65%) patients had impaired HRR following the 6MWT. In univariable and multivariable Cox regression analyses, impaired HRR was associated with poorer survival (HR: 11.0, 95% CI: 1.42 – 84.4,  $p = 0.004$ , and HR: 15.8, 95% CI: 1.96 – 128.0,  $p = 0.010$ , respectively). The 2-year overall survival rates were

52.6% for those with impaired HRR, and 94.1% for those with normal HRR.

**Conclusion:** Impaired HRR was associated with poorer survival in patients who received SBRT for treatment of early-stage lung cancer. HRR following the 6MWT can be one of the factors considered in patient selection for treatment with SBRT, along with other medical comorbidities.

**Keywords:** Stereotactic body radiotherapy, early-stage lung cancer, heart rate recovery, prognosis

## 1. INTRODUCTION

Surgery is the best curative treatment option for patients with early-stage lung cancer [1]. However, up to 25% of patients with stage I non-small cell lung cancer (NSCLC) are considered high-risk for lobectomy due to severe medical comorbidity and/or poor pulmonary reserve [2]. Stereotactic body radiotherapy (SBRT) is an effective alternative [3]. It involves a highly precise and accurate delivery of conformal radiation to small-volume targets and offers more aggressive

dose intensification than can be safely achieved with conventional fractionated radiation therapy [4]. SBRT is the recommended treatment for patients who cannot tolerate lobectomy or segmentectomy for treatment of stage I NSCLC [2]. Despite treatment, the prognosis of patients receiving SBRT is poorer than those receiving surgery for early-stage lung cancer, primarily attributed to co-existing medical conditions. The 5-year overall survival (OS) rate is 25-45%, compared to 65-80% for those receiving lobectomies for stage I NSCLC [2].

While the introduction of SBRT is associated with a decrease in the number of stage I NSCLC patients who receive no treatment and an improvement in OS in the population of patients receiving radiotherapy [5], the high rate of underlying comorbidities in this population is the prime driver for non-cancer mortality. Better stratification of the competing risks in this patient population could improve patient selection and allocation of resources, however is quite challenging on an individual patient basis. Previous investigations examining pulmonary function test criteria alone have not demonstrated a particular cut-off value to guide patient selection [6-8], with the patients with the worst pulmonary function actually having improved survival in the Indiana University and Cleveland Clinic series. This is likely a reflection on the complex nature of the comorbidities in this select patient population, in which patients without significant pulmonary comorbidities likely have been deemed medically inoperable for other causes.

Heart rate recovery (HRR) measures autonomic activity, and is traditionally thought to reflect one's physical fitness. It is obtained following a period of sustained activity, in this case the six-minute walk test (6MWT). In this present study, we investigated the association of HRR with survival. We hypothesized that a functional measurement such as HRR may be a better predictor of patient function than a less physiological measured variable such as pulmonary function testing alone, and that HRR may be a better tool to assist in pre-treatment patient selection and stratification.

## 2 METHODS

This study was approved by the Cleveland Clinic Institutional Review Board. We retrospectively reviewed consecutive patients who, between October 2009 and December 2012, received SBRT for treatment of early-stage lung cancer at the Cleveland Clinic, and had HRR evaluation following 6MWTs within 6 months of SBRT initiation. Data collected included variables previously shown to be associated with survival in patients with lung cancer: age [9], gender, smoking

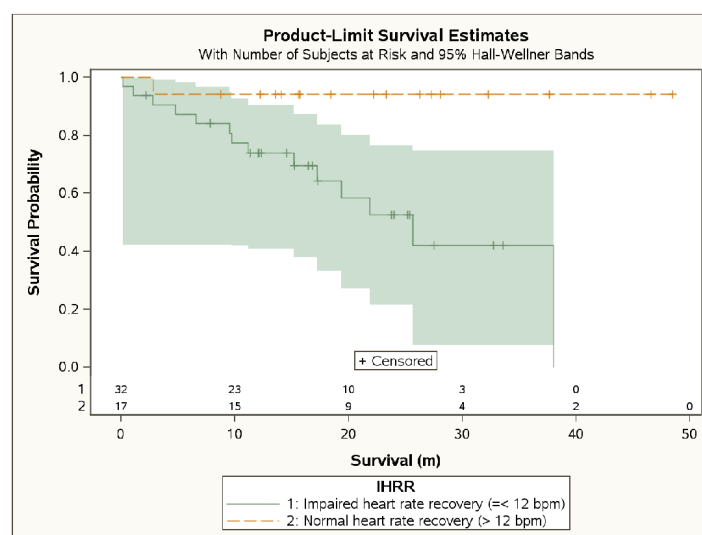
status [10], Karnofsky performance status (KPS) score [11], Charlson comorbidity index (CCI) [12], histologic subtype [13], and clinical stage. Tumor and treatment-related data included tumor size, location, positron emission tomography standardized uptake value (PET-SUV), and total radiation dose and number of fractions delivered. The primary outcome was OS.

Pretreatment pulmonary evaluation was performed according to the American College of Chest Physicians guideline for the physiologic evaluation of the lung cancer patient being considered for surgical resection [14], beginning with forced expiratory volume in 1 second (FEV<sub>1</sub>) and diffusion capacity of carbon monoxide (DL<sub>CO</sub>). In our practice, 6MWTs were frequently used in place of shuttle walk tests and stair climb test for patients being considered for curative treatment. All tests were done according to standards suggested by the American Thoracic Society Pulmonary Function Standards Committee [15], modified to include HRR evaluation. 6MWTs began after patients have been seated for 10 minutes. Pulse oximeters (Ohmeda Biox 3740 or Ohmeda 3900, Datex-Ohmeda Inc., Laurel, MD) with finger probes were used to obtain heart rates. HRR was defined as the difference between the heart rate at the end of the 6MWT and 1 minute after its completion, with the patient in the seated position. Impaired HRR was defined as a  $\leq 12$  beat decrease in heart rate as suggested by previous literature [16]. Other measurements obtained from the 6MWT included blood pressure (BP), distance walked during the 6MWT (6MWD), oxygen saturation, and Borg dyspnea score (BDS).

The decision to offer SBRT for early-stage lung cancer treatment was made by a multidisciplinary tumor board following appropriate clinical assessment. SBRT was performed according to the American Society for Therapeutic Radiology and Oncology and American College of Radiology practice guidelines [17]. Patients were treated on a Novalis (BrainLAB, Feldkirchen, Germany) platform with the ExacTrac (BrainLAB) stereotactic body system for image guidance at the time of delivery. SBRT was delivered in doses 30-60 Gy, in 1-5 fractions. Doses were selected by the treating radiation oncologist using a risk-adapted or a trial-based approach. Survival time was defined as the difference (in months) between the date of treatment initiation and either the date of death or date last-known alive, documented in notes from clinic visits or through telephone contact.

### 2.1 Statistical analysis

Descriptive statistics for all continuous variables were summarized as means and standard deviations, and for categorical variables, counts and percentages.



HRR = heart rate recovery; IHRR = impaired HRR; OS = overall survival

**Figure 1.** Kaplan-Meier estimates of HRR and OS

Student t-tests and Pearson's chi-squared tests were used to assess potential differences in prognostic variables between the study sample and other patients receiving SBRT within the same time period. The Kaplan-Meier method was used to estimate OS. Survival analyses were performed using univariable and multivariable Cox proportional hazards regressions. Variables were considered for multivariable analyses if they have a p value of  $< 0.1$  in univariable analyses. Correlation analyses were performed on all variables included in the multivariable analyses. Independent variables were retained in the model if their AICs were  $\leq 0.05$ .

All analyses were two-tailed. Statistical significance was defined as  $p < 0.05$ . Hazard ratios (HRs) and 95% confidence intervals (CIs) were used whenever appropriate. SAS 9.3 (SAS Institute, Cary, NC), R software, and JMP Pro (SAS Institute, Cary, NC) were used for analyses.

### 3 RESULTS

A total of 438 patients were treated with SBRT between October 2009 and December 2012. Forty nine patients underwent SBRT for treatment of early-stage lung cancer and had 6MWTs and HRR evaluation prior to treatment; compared to the other 389 patients who received SBRT in the same time frame, there was no difference in age, gender, race, tobacco exposure,

CCI, KPS, tumor size, tumor PET-SUV, histology, and clinical staging (E-Table 1).

Among the 49 patients, 48 (98%) patients were medically inoperable due to pulmonary (34 patients, 69%), cardiac (8 patients, 16%), or other co-morbidities (6 patients, 12%). One patient was medically operable but refused surgical treatment (2%). Patients had a mean age of 70 years, the majority of whom were current or former smokers (98%), with CCIs 0-2 (61%), and clinical stage I disease (92%); 4 patients (8%) had  $T_{2b}$  tumors (Table 1). The mean tumor size was 2.8 cm. The majority of patients were treated with 50 Gy in 5 fractions or 60 Gy in 3 fractions (74%).

A total of 32 (65%) patients had impaired HRR following the 6MWT (Table 2). Patients had a mean systolic blood pressure (SBP) of 134 mmHg and diastolic blood pressure (DBP) of 75 mmHg prior to 6MWT; their respective values after 6MWTs were 155 mmHg and 81 mmHg. Oxygen saturation decreased by 2.4% on average during the test. The mean 6MWD was 63% predicted and BDS was 3.1. Fifteen (31%) patients were deceased at the end of data collection. Of those who died, 14 (93%) had impaired HRR.

In univariable Cox regression analysis, impaired HRR was significantly associated with an increased risk of death (HR 11.0, CI 1.42 – 84.4,  $p = 0.004$ ) (Table 3, Figure 1). Among those with impaired HRR, the 2-year OS rate and median survival time (MST) were 52.6% and 21.8 months, respectively. Among those with normal HRR, the 2-year OS rate was 94.1%; only one patient died (the survival time was 2.8 months). For

**E-Table 1.** Comparison of prognostic variables\*

| Clinical variable              | Study cohort | Comparative cohort | p-value |
|--------------------------------|--------------|--------------------|---------|
| Age                            | 70.3 (8.7)   | 73.8 (9.7)         | 0.99    |
| Female, n (%)                  | 24 (49.0)    | 218 (56.0)         | 0.35    |
| Race, n (%)                    |              |                    | 0.77    |
| African American               | 9 (18.4)     | 44 (12.8)          |         |
| Caucasian                      | 39 (79.6)    | 305 (84.3)         |         |
| Pack-years                     | 50.0 (28.7)  | 56.3 (39.8)        | 0.23    |
| CCI, n (%)                     |              |                    | 0.69    |
| 0-2                            | 26 (60.5)    | 212 (54.3)         |         |
| 3-6                            | 17 (39.5)    | 177 (45.4)         |         |
| KPS                            | 81.2 (9.3)   | 78.1 (10.0)        | 0.06    |
| Tumor size, cm                 | 2.8 (1.4)    | 2.5 (1.3)          | 0.12    |
| SUV                            | 10.4 (7.3)   | 9.5 (6.8)          | 0.17    |
| FEV <sub>1</sub> , % predicted | 59.8 (20.0)  | 65.7 (56.8)        | 0.90    |
| DL <sub>CO</sub> , % predicted | 44.5 (18.3)  | 55.1 (19.8)        | 1.00    |
| Histology, n (%)               |              |                    | 0.27    |
| Adenocarcinoma                 | 17 (34.7)    | 96 (25.1)          |         |
| Squamous cell carcinoma        | 13 (26.5)    | 111 (29.0)         |         |
| Small cell carcinoma           | 2 (4.1)      | 7 (1.8)            |         |
| Non-diagnostic/never-biopsied  | 17 (34.7)    | 131 (34.2)         |         |
| Clinical stage                 |              |                    | 0.62    |
| Ia                             | 37 (75.5)    | 268 (68.9)         |         |
| Ib                             | 8 (16.3)     | 90 (23.1)          |         |
| IIa                            | 4 (8.2)      | 21 (5.4)           |         |

6MWD = 6-minute walk distance; 6MWT = 6-minute walk test; BDS = Borg dyspnea score; BMI = body-mass index; CCI = Charlson comorbidity index; DBP = diastolic blood pressure; DL<sub>CO</sub> = diffusion capacity of carbon monoxide; FEV<sub>1</sub> = forced expiratory volume within 1 second; HR = heart rate; HRR = heart rate recovery; KPS = Karnofsky performance status; LLL = left lower lobe; LUL = left upper lobe; RLL = right lower lobe; RML = right middle lobe; RUL = right upper lobe; SBP = systolic blood pressure; SUV = standardized uptake value

\*The 49 patients in the study cohort were compared to 389 other patients receiving SBRT within the same time period for early-stage lung cancer.

Values are expressed as means and standards of deviations, unless specified

the entire cohort, the 2-year OS rate was 67.3%, median follow-up 15.6 months, and MST 25.7 months. Other variables which had statistically significant associations with survival included smoking status ( $p = 0.005$ ), post-6MWT DBP ( $p = 0.014$ ), and BDS ( $p = 0.018$ ).

In multivariable analyses (MVA), which included all variables whose p-values were  $< 0.10$  from univariable analyses (additionally included tumor size, KPS, and clinical stage), impaired HRR was significantly associated with an increased risk of death (HR 15.8, CI 1.96 – 128.0,  $p = 0.010$ ). Post-6MWT DBPs and BDSs were also significantly associated with mortality (Table 4). No other variables were statistically significant in MVA.

## DISCUSSIONS

In this study, we investigated the association between HRR and survival in patients receiving SBRT for treatment of early-stage lung cancer. We found that impaired HRR was significantly associated with worse survival in this group. Our cohort of patients had similar age, tumor histology, and clinical stage compared to other series on patients with medically inoperable, early-stage lung cancer treated with SBRT [3, 18-21]. The MST of 26 months and 2-year OS rate of 67% were also comparable with outcomes from published series on SBRT patients.

**Table 1.** Patient demographics

| Patient characteristics        | Value       |
|--------------------------------|-------------|
| Age                            | 70.3 (8.7)  |
| Gender, n (%)                  | 24 (49.0)   |
| Female                         |             |
| Race, n (%)                    |             |
| African American               | 9 (18.4)    |
| Caucasian                      | 39 (79.6)   |
| BMI, kg/m <sup>2</sup>         | 26.7 (6.1)  |
| Smoking status, n (%)          |             |
| Current smoker                 | 15 (30.6)   |
| Former smoker                  | 33 (67.3)   |
| Pack-years                     | 50.0 (28.7) |
| CCI, n (%)                     |             |
| 0-2                            | 26 (60.5)   |
| 3-6                            | 17 (39.5)   |
| Tumor size, cm                 | 2.8 (1.4)   |
| SUV                            | 10.4 (7.3)  |
| FEV <sub>1</sub> , % predicted | 59.8 (20.0) |
| DL <sub>CO</sub> , % predicted | 44.5 (18.3) |
| Tumor location, n (%)          |             |
| RUL                            | 12 (26.1)   |
| RML                            | 3 (6.5)     |
| RLL                            | 6 (13.0)    |
| LUL                            | 21 (45.7)   |
| LLL                            | 4 (8.7)     |
| Central location, n (%)        | 14 (28.6)   |
| Cardiac involvement, n (%)     | 2 (4.1)     |
| Histology, n (%)               |             |
| Adenocarcinoma                 | 17 (34.7)   |
| Squamous cell carcinoma        | 13 (26.5)   |
| Small cell carcinoma           | 2 (4.1)     |
| Non-diagnostic/never-biopsied  | 17 (34.7)   |
| Clinical stage, n (%)          |             |
| IA                             | 37 (75.5)   |
| IB                             | 8 (16.3)    |
| IIA                            | 4 (8.2)     |
| KPS                            | 81.2 (9.3)  |
| Radiation dose, n (%)          |             |
| 30 Gy                          | 6 (12.2)    |
| 34 Gy                          | 3 (6.1)     |
| 48 Gy                          | 4 (8.2)     |
| 50 Gy                          | 24 (49.0)   |
| 60 Gy                          | 12 (24.5)   |

**Table 1.** Continued

| Fractions, n (%)     | Value     |
|----------------------|-----------|
| 1                    | 9 (18.8)  |
| 3                    | 7 (14.6)  |
| 4                    | 5 (10.4)  |
| 5                    | 27 (56.2) |
| Local failure, n (%) | 2 (4.1)   |

6MWD = 6-minute walk distance; 6MWT = 6-minute walk test; BDS = Borg dyspnea score; BMI = body-mass index; CCI = Charlson comorbidity index; DBP = diastolic blood pressure; DL<sub>CO</sub> = diffusion capacity of carbon monoxide; FEV<sub>1</sub> = forced expiratory volume within 1 second; HR = heart rate; HRR = heart rate recovery; KPS = Karnofsky performance status; LLL = left lower lobe; LUL = left upper lobe; RLL = right lower lobe; RML = right middle lobe; RUL = right upper lobe; SBP = systolic blood pressure; SUV = standardized uptake value

**Table 2.** 6MWT measurements

| Measurements          | Value         |
|-----------------------|---------------|
| Blood pressure, mmHg  |               |
| Pre-6MWT SBP          | 134.5 (19.2)  |
| Pre-6MWT DBP          | 74.9 (9.6)    |
| Post-6MWT SBP         | 155.4 (23.4)  |
| Post-6MWT DBP         | 81.2 (11.8)   |
| Change in SBP         | +21.0 (21.9)  |
| Change in DBP         | +6.3 (11.2)   |
| Oxygen saturation, %  |               |
| Pre-6MWT              | 95.3 (2.7)    |
| During 6MWT           | 92.9 (3.2)    |
| Post 6MWT             | 95.3 (3.6)    |
| Distance              |               |
| 6MWD, ft              | 963.6 (256.6) |
| 6MWD, % predicted     | 63.3 (18.7)   |
| BDS                   | 3.1 (1.9)     |
| Heart rate, beats/min |               |
| Resting HR            | 81.2 (14.4)   |
| 6MWT HR               | 105.4 (16.0)  |
| HR-1min               | 94.1 (15.6)   |
| HRR                   | -11.3 (8.7)   |
| Impaired HRR, n (%)   | 32 (65.3)     |

Values are expressed as means and standards of deviations, unless specified

**Table 3.** Univariable survival analyses

| Variable                       | HR (95% CI)          | p value |
|--------------------------------|----------------------|---------|
| Age                            | 1.02 (0.96, 1.08)    | 0.51    |
| Gender                         | 1.24 (0.44, 3.51)    | 0.69    |
| Female: male                   |                      |         |
| Race                           | 0.88 (0.25, 3.14)    | 0.85    |
| Not Caucasian: Caucasian       |                      |         |
| BMI                            | 0.91 (0.82, 1.02)    | 0.11    |
| Smoking status                 |                      | 0.005   |
| Former: current                | 1.53 (0.42, 5.58)    |         |
| Never: current                 | 21.0 (1.76, 251)     |         |
| Pack years                     | 0.99 (0.97, 1.01)    | 0.38    |
| CCI 3-6: CCI 0-2               | 1.28 (0.45, 3.60)    | 0.65    |
| Tumor size                     | 1.33 (0.99, 1.78)    | 0.050   |
| SUV                            | 0.98 (0.91, 1.07)    | 0.66    |
| FEV <sub>1</sub> , % predicted | 1.01 (0.99, 1.03)    | 0.37    |
| DL <sub>CO</sub> , % predicted | 0.98 (0.95, 1.02)    | 0.38    |
| Histology                      |                      | 0.95    |
| Squamous: adenocarcinoma       | 1.08 (0.29, 4.02)    |         |
| Small cell: adenocarcinoma     | 1.80 (0.21, 15.6)    |         |
| Clinical stage                 |                      | 0.093   |
| IB: IA                         | 1.19 (0.32, 4.45)    |         |
| IIA: IA                        | 3.93 (1.04, 14.8)    |         |
| KPS                            | 0.95 (0.91, 1.00)    | 0.055   |
| Local failure                  | 1.04 (0.12, 8.77)    | 0.97    |
| Total dose                     | 0.98 (0.93, 1.03)    | 0.47    |
| Fractions                      | 1.12 (0.83, 1.52)    | 0.45    |
| Pre-6MWT SBP                   | 1.00 (0.97, 1.02)    | 0.77    |
| Pre-6MWT DBP                   | 0.96 (0.91, 1.01)    | 0.15    |
| Post-6MWT SBP                  | 0.98 (0.95, 1.00)    | 0.10    |
| Post-6MWT DBP                  | 0.94 (0.90, 0.99)    | 0.014   |
| Resting HR                     | 0.98 (0.94, 1.02)    | 0.35    |
| 6MWD                           | 0.999 (0.997, 1.001) | 0.50    |
| 6MWD, % pred                   | 1.00 (0.97, 1.03)    | 0.88    |
| BDS                            | 1.33 (1.04, 1.69)    | 0.018   |
| HR during 6MWT                 | 0.98 (0.94, 1.01)    | 0.19    |
| HR-1 min after 6MWT            | 1.00 (0.96, 1.03)    | 0.85    |
| HRR                            | 1.08 (0.998, 1.16)   | 0.054   |
| Impaired HRR                   | 11.0 (1.42, 84.4)    | 0.004   |

CI = confidence interval; HR = hazard ratio; 6MWD = 6-minute walk distance; 6MWT = 6-minute walk test; BDS = Borg dyspnea score; BMI = body-mass index; CCI = Charlson comorbidity index; DBP = diastolic blood pressure; DL<sub>CO</sub> = diffusion capacity of carbon monoxide; FEV<sub>1</sub> = forced expiratory volume within 1 second; HR = heart rate; HRR = heart rate recovery; KPS = Karnofsky performance status; LLL = left lower lobe; LUL = left upper lobe; RLL = right lower lobe; RML = right middle lobe; RUL = right upper lobe; SBP = systolic blood pressure; SUV = standardized uptake value

**Table 4.** Statistically significant variables from multivariable survival analyses

| Variable      | HR (95% CI)        | p value |
|---------------|--------------------|---------|
| Post 6MWT DBP | 0.93 (0.88, 0.97)  | 0.002   |
| BDS           | 1.36 (1.07, 1.73)  | 0.013   |
| Impaired HRR  | 15.8 (1.96, 128.0) | 0.010   |

CI = confidence interval; HR = hazard ratio; 6MWD = 6-minute walk distance; 6MWT = 6-minute walk test; BDS = Borg dyspnea score; BMI = body-mass index; CCI = Charlson comorbidity index; DBP = diastolic blood pressure;  $DL_{CO}$  = diffusion capacity of carbon monoxide;  $FEV_1$  = forced expiratory volume within 1 second; HR = heart rate; HRR = heart rate recovery; KPS = Karnofsky performance status; LLL = left lower lobe; LUL = left upper lobe; RLL = right lower lobe; RML = right middle lobe; RUL = right upper lobe; SBP = systolic blood pressure; SUV = standardized uptake value

Heart rate recovery is traditionally thought to reflect an individual's physical fitness. Impaired HRR has previously been shown to be predictive of mortality independent of coronary artery disease [16, 22], in those with chronic heart failure [23], and in recent years, in those with idiopathic pulmonary fibrosis (IPF) [24]. To the best of our knowledge, our study is the first to describe an association between impaired HRR and mortality in patients with early-stage lung cancer receiving SBRT.

The decision to treat medically inoperable, early-stage lung cancer patients can be challenging. Patients who are too ill to benefit from aggressive treatment should be identified to avoid unnecessary treatment and treatment-related harms. It has been difficult to identify on an individual basis from the group of medically inoperable patients as a whole. There exist only a few prognostic variables in this select group of patients. HRR is a new variable with prognostic value that can be used for risk-stratification in this group of patients.

Impaired HRR, however, does not appear to portend a prognosis poor enough to withhold treatment. In our series, patients with impaired HRR has a MST of 22 months and 2-year OS rate of 53%, better than outcomes for untreated patients (the same rates for those with untreated stage I NSCLC are ~ 9-14 months and 20-30% [25], and among those  $\geq$  75 years of age, 15-20% [5]). This comparison should be made with caution as our patient cohort only included those who had thorough clinical evaluation, including staging, and deemed healthy enough to undergo curative treatment. While impaired HRR alone might not drive patient selection, it is possible that a more strict definition than  $\leq$  12 beats per minute might improve the predictive performance, or that HRR in combination with other predictive factors could lead to a more robust selection model.

The BDSs and post-6MWT DBPs were also associated with survival in our cohort of patients. Dyspnea, including as defined by the BDS, has been associated with mortality in patients with pulmonary disease in previous studies [26-28]. Results from our multivariable survival analysis suggested that for every 1 point increase in the BDS, there is a 36% increased relative risk of death. This variable, therefore, can also be useful in predicting mortality in this patient group. No previous studies, however, have reported post exercise BP as a predictor of mortality. Post exercise BP is partly modulated by parasympathetic activity, the same mechanism by which HRR is modulated. A higher post-6MWT DBP could therefore, theoretically increase the risk of death, through the same mechanism by which impaired HRR predicts mortality. Our results suggested that higher post-6MWT DBP is associated with a decreased risk of death (and not an increased risk as suggested by the proposed mechanism). Other BP measurements, including post-6MWT SBP and SBP, and changes in SBP and DBP following the 6MWT, did not predict mortality.

Other 6MWT variables which have been implicated with survival in patients with underlying pulmonary diseases include oxygen saturation/desaturation [29-31] and 6MWD [32-35]. These variables were not found to be associated with survival in our study, possibly due to the small sample size. Clinical variables previously known to be associated with survival in lung cancer patients include age, gender, KPS, CCI, and clinical stage. These variables did not have a statistically significant association with survival in our series, again, possibly due to our small sample size.

The 6MWT is a simple and relatively low-cost test in which HRR can be readily measured. Performance of a 6MWT is more common in many pulmonary function labs than those suggested by current guidelines (i.e. the shuttle walk test or formalized stair climbing test) [14]. We propose that the 6MWT, coupled with HRR evaluation, is another variable which can be incorporated into the physiologic evaluation of patients with lung cancer being considered for SBRT. We plan to develop a risk prediction model which incorporates HRR, other 6MWT variables, and previously identified clinical prognostic variables in a clinical algorithm to guide treatment decision-making. Such model can include patient-related factors (e.g. CCI), lung lesion characteristics (e.g. PET-SUV), and patient fitness (e.g. 6MWT variables).

Our study is limited by its retrospective nature. The small sample size makes it difficult to gauge the actual hazard ratio for impaired HRR and death. While helpful in predicting survival, we did not include quality of life, another important evaluation in the pretreatment assessment of patients with lung cancer. It is unclear if impaired HRR predicts mortality in other lung cancer patients, including those who are candidates for surgical

treatment, and those who are unable to undergo 6MWT due to poor fitness. Our study has several strengths. We included many of the variables previously known to be associated with survival in the lung cancer patient population, including in the population receiving SBRT. We tested for potential differences in prognostic variables between our patient cohort and other patients treated with SBRT in the same time period and found no difference in these variables, which allowed us to generalize our findings to other SBRT patients. Survival data were collected and maintained by our own department, and therefore, are highly accurate compared to data obtained from public databases such as the social security death index.

We conclude that impaired HRR is associated with worse survival in patients with early-stage lung cancer who are treated with SBRT.

## ABBREVIATIONS

6MWT = 6-minute walk test; 6MWD = 6-minute walk distance; AIC = Akaike Information Criterion; BDS = Borg dyspnea score; BP = blood pressure; CCI = Charlson comorbidity index; CI = confidence interval; DBP = diastolic blood pressure;  $DL_{CO}$  = diffusion capacity of carbon monoxide;  $FEV_1$  = forced expiratory volume in 1 second; HR = hazard ratio; HRR = heart rate recovery; IPF = idiopathic pulmonary fibrosis; KPS = Karnofsky performance status; MST = median survival time; MVA = multivariable analysis; NSCLC = non-small cell lung cancer; OS = overall survival; PET-SUV = positron emission tomography standardized uptake value; SBP = systolic blood pressure; SBRT = stereotactic body radiotherapy

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