



## ORIGINAL ARTICLE

# Validating impact of pretreatment tumor growth rate on outcome of early-stage lung cancer treated with stereotactic body radiation therapy

Soha Atallah<sup>1,2</sup> , Lisa W. Le<sup>3</sup>, Andrea Bezjak<sup>4,5</sup>, Robert MacRae<sup>1,2</sup>, Andrew J. Hope<sup>4,5</sup>  & Jason Pantarotto<sup>1,2</sup>

1 Radiation Medicine Program, The Ottawa Hospital Cancer Centre, Ottawa, Ontario, Canada

2 Department of Radiation Oncology, University of Ottawa, Ottawa, Ontario, Canada

3 Department of Biostatistics, Princess Margaret Cancer Centre, Toronto, Ontario, Canada

4 Radiation Medicine Program, Princess Margaret Hospital, Toronto, Ontario, Canada

5 Department of Radiation Oncology, University of Toronto, Toronto, Ontario, Canada

## Keywords

Growth rate; lung cancer; predictive model; SBRT.

## Correspondence

Andrew J. Hope, Radiation Medicine Program, Princess Margaret Hospital, 6th floor, 700 University Ave, Toronto, ON M5G 1X6, Canada.

Tel: +1 416 946 2124

Fax: +1 416 946 6566

Email: andrew.hope@rmp.uhn.ca

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## Abstract

**Background:** To assess correlation of pretreatment specific growth rate (SGR) value of  $0.43 \times 10^{-2}$  with overall and failure-free survival of patients with early-stage non-small cell lung cancer (NSCLC) treated with stereotactic body radiation therapy (SBRT).

**Methods:** A retrospective chart review of 160 patients with pathologically confirmed stage I NSCLC treated with SBRT between June 2010 and December 2012 in a large, tertiary cancer institute was undertaken. Both diagnostic and archived planning CT were uploaded to the treatment planning system to determine tumor volume at diagnosis (GTV1) and planning time (GTV2). The time (t) between both CTs was recorded. SGR was calculated using GTV1, GTV2, and t. The median SGR ( $0.43 \times 10^{-2}$ ) from our previous data was used to group patients into low and high SGR cohorts. Log-rank test was used to compare overall (OS) and failure-free survivals (FFS) of SGR groups.

**Results:** The median time interval between diagnostic and planning CT scans was 87 days. The median OS was 38 and 66 months for high and low SGR cohorts, respectively ( $P = 0.03$ ). The median FFS was 27 and 55 months for high and low SGR cohorts, respectively ( $P = 0.005$ ). High SGR ( $P < 0.05$ ), male gender ( $P = <0.01$ ), and GTV2 ( $P = <0.05$ ) were associated with poorer FFS.

**Conclusions:** High SGR was associated with poorer outcome in patients with early-stage NSCLC treated with SBRT. SGR can be used in conjunction with other well-known predictive factors to formulate a practical predictive model to identify subgroups of the patient at higher risk of recurrence after SBRT.

## Introduction

Lung cancer remains the leading cause of cancer death.<sup>1</sup> The five-year overall survival (OS) for localized disease is as low as 55%.<sup>2</sup> Stereotactic body radiotherapy (SBRT) is the standard of care for inoperable patients or those who refuse surgery. Patients at standard operative risk should not be considered for SBRT as a surgical alternative outside of clinical trial,<sup>3–5</sup> but SBRT options for operable patients are being explored.<sup>6,7</sup>

Early stage non-small cell lung cancer (NSCLC) are heterogeneous tumors even among the same histopathological subtype. Several prognostic factors for early stage NSCLC treated with SBRT have been identified including tumor size, SUVmax, and radiation dose.<sup>8</sup> Several efforts are ongoing to create predictive models for this patient group.<sup>9,10</sup> Tumor progression has been documented in the time between diagnostic and planning CT that sometimes results in upstaging<sup>11,12</sup> but also

provides an opportunity to measure tumor growth rates prior to treatment.

We have previously demonstrated that pretreatment tumor specific growth rate (SGR) is an independent prognostic factor for failure-free survival (FFS) and OS in early stage NSCLC. Patients treated with SBRT were divided into two groups (high and low SGR) where specific growth rate (SGR) was used as a metric for pretreatment tumor growth rate, and its median ( $0.43 \times 10^{-2}$ ) as a cutoff.<sup>13</sup> This SGR threshold, if validated at an outside institution, may be useful in predictive models to personalize treatment.

The aim of this study was to assess correlation of an early-stage non-small cell lung cancer (NSCLC) specific growth rate (SGR) value of  $0.43 \times 10^{-2}$  with overall and failure-free survival of patients treated with stereotactic body radiation therapy (SBRT).

## Methods

After local ethics board approval, a retrospective review of 160 patients with inoperable biopsy-proven stage I NSCLC treated with SBRT between June 2010 and December 2012 at a large, tertiary cancer institution was conducted. TRIPOD guidelines were used during this analysis and a TRIPOD statement has been included (Appendix A).<sup>14</sup>

Only patients with solitary lesions were analyzed. Replication of the previously reported method was performed at a different institution and independent dataset.<sup>13</sup> Similar sample size was used. Patients' demographic data, clinical parameters, the time interval between diagnostic CT and planning CT, and vital status were collected from the prospectively-kept database.

## Analysis of CT images

The selected diagnostic CT was the CT after which the decision to obtain a biopsy was made. Diagnostic CT images of 160 patients were imported into a Focal Treatment Planning System, v.4.70 (FTPS). GTV was contoured by one radiation oncologist, guided by the GTV2 contouring, on each slice on the lung window (1700, -300 HF) to generate the initial tumor volume (GTV1).

4DCT (Philips Brilliance Big Bore CT scanner) was used for all patients. The slice thickness was 3 mm. No intravenous contrast was administered. All the archived plans were restored to FTPS. The GTV volume from the original planning CT was recorded (GTV2). The time interval between diagnostic and planning CTs was calculated. The growth rate was quantified using the specific growth rate (SGR) equation, where "t" is the time interval between diagnostic and planning CT.<sup>15</sup>

$$SGR = \ln \left[ \frac{GTV2}{GTV1} \right] / t$$

The previously reported SGR median value of  $0.43 \times 10^{-2}$  was used to group patients into high and low SGR cohorts.

## Statistical analysis

The primary endpoint was OS. Secondary endpoints included: failure-free survival (FFS), local, regional and distant failure-free survival, and cumulative incidence rate of local, regional, and distant failures. OS time was calculated from the diagnosis date to the date of death or censored at the last follow-up date. FFS time was calculated from the diagnosis date to the first date of local, regional or distant failure, or the date of death, or censored at the last follow-up date. Local failure-free survival (LFFS), regional failure-free survival (RFFS) and distant failure-free survival (DFFS) time were calculated from the diagnosis date to the date of failure or death, otherwise censored at the last follow-up date.

Kaplan Meier method was used for OS, FFS, LFFS, RFFS, and DFFS. Log rank test was used to test the survival differences between groups. Cox proportional hazard model was used in the univariable and multivariable analysis to investigate the association between survival outcomes (OS and FFS) and clinical factors. A stepwise variable selection was carried out in the multivariable analysis retaining all predictors with a *P*-value <0.25 in the final model. The hazard ratio and its associated 95% CI was reported.

The cumulative incidence was calculated for local failure (LF), regional failure (RF), and distant failure (DF) using the competing risk approach, and was compared using Gray's test.

## Results

### Patients and tumor characteristics

A total of 160 patients with biopsy proven stage I NSCLC were included; 79% of the patients had T1 disease and PET scan was part of the staging work-up for all but four patients. The median duration between the PET scan and start of radiation treatment was 39 days and the interquartile range was 23–63.5 days. All patients were simulated using 4DCT (Philips Brilliance Big Bore CT scanner). Radiation doses were 54 Gy in three fractions for peripheral lesions, 60 Gy in five fractions if found to be abutting the chest wall and 60 Gy in eight fractions for central tumors. Patients and tumor characteristics are shown in

(Table 1). The median duration between reference pre-treatment diagnostic and planning CT was 87 days and the interquartile range was 63–118 days. The median SGR ( $\times 10^{-2}$ ) was 0.42 (range – 1.1– 23.2). Median GTV1 was 3.43 cc (range: 0.18–51.86 cc) and median GTV2 was 6 cc (range: 0.2–79.1 cc). The slice thickness for the diagnostic CT ranged from 1–6.5 mm. The maximum tumor dimension on diagnostic CT ranged from 0.7–6.1 cm (median 2.1 cm).

## Overall survival

Of 160 patients, 74 were dead and 86 alive at the last follow-up. The median follow-up time was 38 months

(range 5.1–90.4 months). The median OS was 59 months. Three- and five-year OS were 62% (95% CI: 54.9–70.5) and 48% (95% CI: 40.2–58.2), respectively (Fig 1).

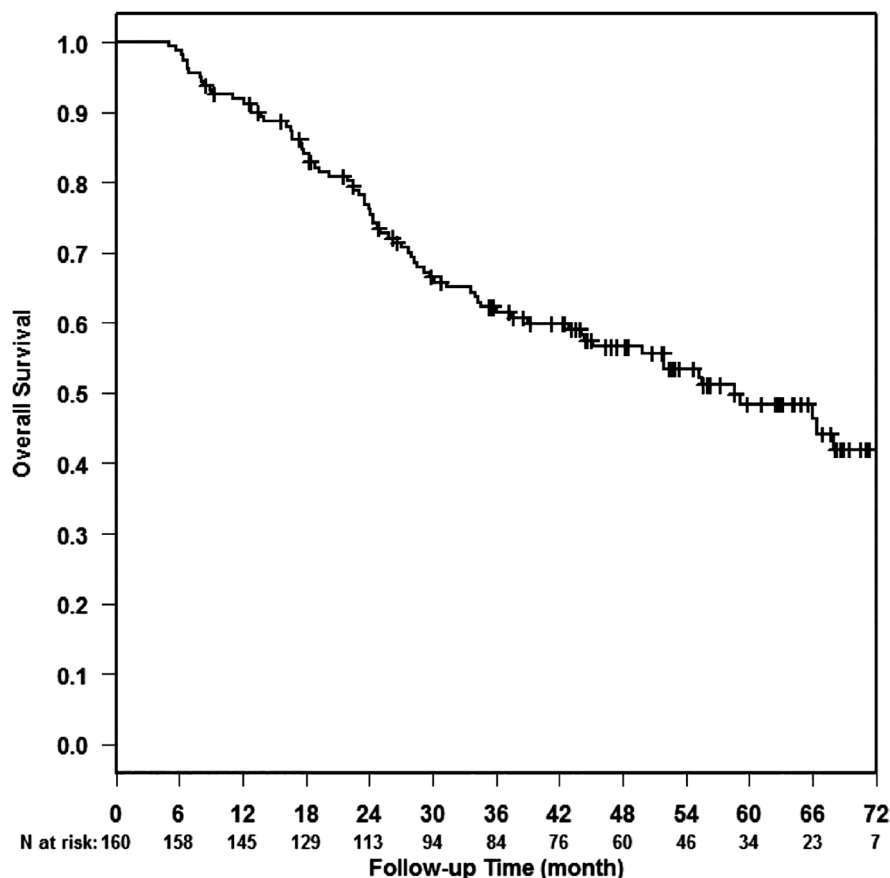
Patients were grouped into high and low SGR using previously reported median SGR as a cutoff ( $0.43 \times 10^{-2}$ ). The median survival was 38 months for high SGR and 66 months for low SGR. Five-year OS for patients with high SGR tumors was 46% (95% CI: 35.7–59.9) and 52% (95% CI: 40.7–66.1) for patients with low SGR tumors ( $P = 0.03$ , Fig 2).

High SGR, male gender, T2 disease, and GTV2 were all associated with worse OS on univariable analysis ( $P < 0.01$ ). Male gender and GTV2 remained independent

**Table 1** Patient and tumor characteristics (N = 160)

		Current study - n (%)	Development study - n (%)
Age (years)		Median: 76.0 Range: 54.0–95.2	Median: 74.1 Range: 48.0–90.2
Gender	F	96 (60.0)	81 (50.6)
PS (ECOG)	0	73 (45.6)	37 (23.3)
	1	45 (28.1)	82 (51.6)
	2	40 (25)	36 (22.6)
	3	2 (1.3)	4 (2.5)
	Unknown	0	1
Smoking	No (never smokers)	7 (4.5)	31 (19.5)
	Current	64 (40)	
	Ex	85 (53)	
	Unknown	4 (2.5)	
Histopathology	Adenocarcinoma	69 (43.1)	59 (36.9)
	Squamous cell carcinoma	33 (20.6)	25 (15.6)
	Large cell carcinoma	1 (0.6)	9 (5.6)
	NSCLC-NOS	40 (25)	23 (14.4)
	Others	17 (10.6%)	2 (1.2)
	No biopsy/not diagnostic	0	42 (26.25)
T stage (AJCC 7th)	T1	127 (79.4)	119 (74.4)
	T2	33 (20.6)	41 (25.6)
Primary site	LLL	16 (10.0)	24 (15)
	LUL (including lingual)	51 (31.9)	44 (27.5)
	RLL	35 (21.9)	34 (21.3)
	RML	9 (5.6)	8 (5.0)
	RUL	49 (30.6)	50 (31.3)
SGR ( $\times 10^{-2}$ )	Median:	0.42	0.43
	Range:	–1.12–23.2	–2.03–6.11
	IQR:	0.12–0.84	0.15–0.98
GTV1 ( $\text{cm}^3$ )	Median:	3.43	3.9
	Range:	0.18–51.86	0.2–56.9
	IQR:	1.7–8.5	1.4–10
GTV2 ( $\text{cm}^3$ )	Median:	6.09	6.0
	Range:	0.22–79.14	0.6–77.2
	IQR:	2.5–11.3	2.7–15.5
GTV2/GTV1 ratio	Median:	1.5	1.5
	Range:	0.5–7.4	0.3–14.4
	IQR:	1.1–1.8	1.2–2.1

GTV1, gross tumor volume on diagnostic CT; GTV2, gross tumor volume on planning CT; PS (ECOG), Eastern Cooperative Oncology Group Performance Status; SGR, specific growth rate.



**Figure 1** Overall survival for the whole cohort ( $n = 160$ ).

prognostic factors on multivariable analysis ( $P = 0.002$ ) (Table 2) while high SGR did not ( $P = 0.09$ ).

### Failure-free survival (FFS)

A total of 44 patients had local, regional or distant failure prior to death and 49 patients died without observed failure. The four patients who did not have a diagnostic PET scan, did not experience any failures at the time of analysis. Median FFS was 41 months. Three and five-year FFS were 54% (95% CI: 46.0–62.1) and 39% (95% CI: 31.4–48.7).

Median FFS was 27 months for patients with high SGR tumors and 55 months for patients with low SGR tumors. Five-year FFS were 35% and 43%, respectively ( $P = 0.005$ , Fig 3).

On Cox regression analysis, high SGR, male gender, and GTV2 were all associated with lower FFS ( $P < 0.05$ ).

### Local failure (LF)

LF was defined as failure at area of original primary. There were 22 LF, and 61 patients died without observed local

failure. Median local FFS (LFFS) was 44 months. Three- and five-year LFFS were 54% (95% CI: 46.4–62.4) and 42% (95% CI: 34.0–51.7).

Median LFFS for the low SGR group was 56 months and the five-year LFFS was 44% (95% CI: 33.5–58.9). For the high SGR group, the median LFFS was 28 months and the five-year LFFS was 41% (95% CI: 30.5–53.8) ( $P = 0.03$ ).

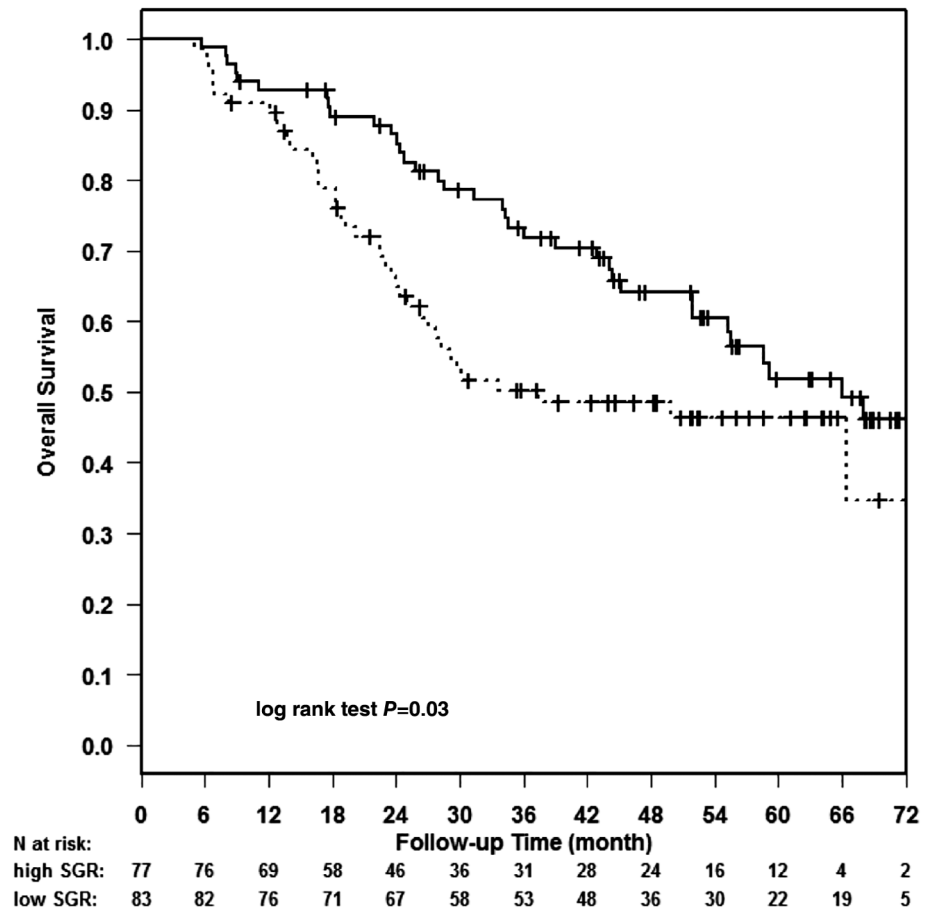
Using death as a competing risk, there was no statistically significant difference in cumulative incidence rate of LF between both high (15.4%) and low SGR cohorts (13.9%) (Gary's test  $P$ -value = 0.81).

### Regional failure (RF)

RF was defined as failure in nodal region in proximity to primary tumor. There were 12 RF, and 66 patients died without observed RF. The median regional FFS (RFFS) was 56 months. Three and five-year RFFS were 60% (95% CI: 53.0–68.8) and 47% (95% CI: 38.8–56.6).

The median RFFS for the low SGR cohort was 66 months and for the high SGR cohort was 30 months ( $P = 0.007$ ).

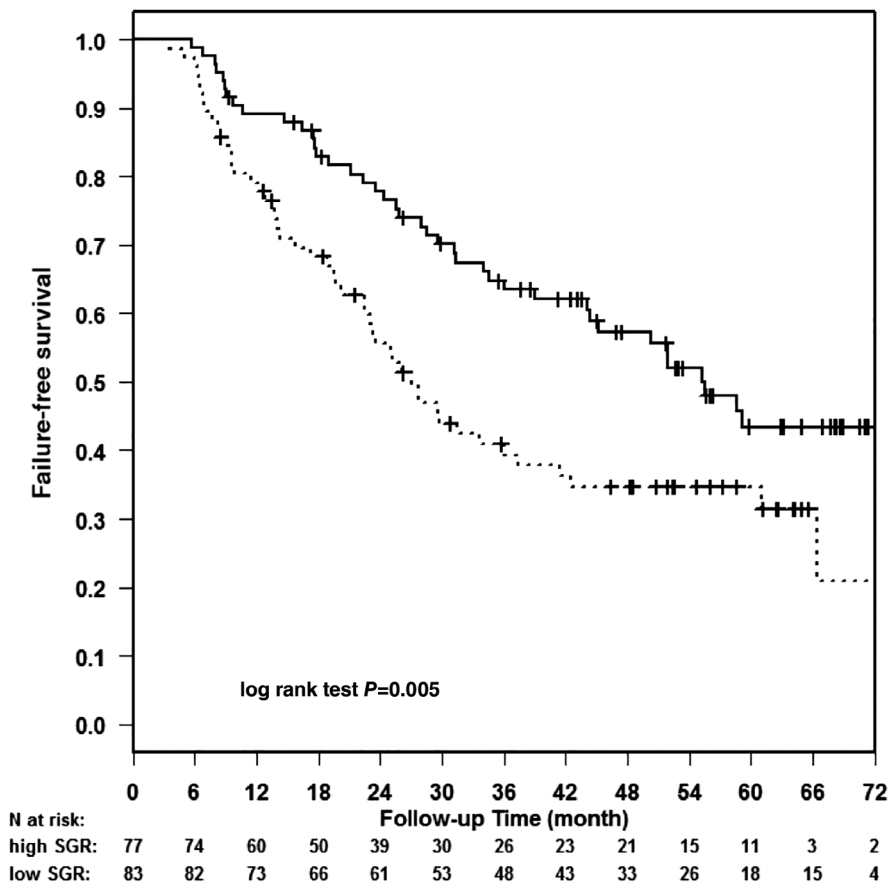
**Figure 2** Kaplan Meier curve for high and low specific growth rate (SGR) - overall survival (OS) (high SGR is  $\geq 0.43 \times 10^{-2}$ ). (.....) high SGR (—) low SGR.



**Table 2** Univariable and multivariable analysis for overall and failure-free survival (FFS)

	Overall survival (OS)				Failure-free survival (FFS)			
	Univariable		Multivariable		Univariable		Multivariable	
	<i>P</i>	CI	<i>P</i>	CI	<i>P</i>	CI	<i>P</i>	CI
Age	1.02 (0.99–1.05)	0.31			0.31			
Gender (male vs. female)	2.33 (1.47–3.70)	<0.001	2.13 (1.33–3.39)	0.002	2.39 (1.57–3.63)	<0.001	2.21 (1.45–3.38)	<0.001
T stage, T2 vs. T1	2.41 (1.47–3.97)	<0.001			2.24 (1.41–3.57)	<0.001		
Current smoking	1.30 (0.82–2.06)	0.26			1.21 (0.79–1.83)	0.38		
Histology		0.25				0.56		
Others vs. Adenocarcinoma	1.30 (0.72–2.35)	0.38			1.27 (0.75–2.14)	0.38		
SCC vs. Adenocarcinoma	1.70 (0.96–3.01)	0.07			1.34 (0.79–2.28)	0.28		
SGR, high vs. low	1.64 (1.04–2.61)	0.03	1.50 (0.94–2.38)	0.09	1.81 (1.19–2.75)	0.006	1.66 (1.08–2.53)	0.02
PS (ECOG)	1.02 (0.77–1.35)	0.89			0.951 (0.737–1.227)	0.70		
GTV2, log scale	1.57 (1.24–1.99)	<0.001	1.45 (1.14–1.85)	0.002	1.432 (1.152–1.781)	0.001	1.31 (1.05–1.63)	0.02

GTV2, gross tumor volume on planning CT; PS (ECOG), Eastern Cooperative Oncology Group Performance Status; SGR, specific growth rate; SCC, squamous cell carcinoma.



**Figure 3** Kaplan Meier curve for high and low specific growth rate (SGR) – Failure-free survival (FFS) (high SGR is  $\geq 0.43 \times 10^{-2}$ ). (.....) high SGR (—) low SGR.

Using competing risk analysis, there was a statistically significant difference in three-year cumulative incidence rate of RF between high SGR (10.8%) and low SGR (3.7%) (Gray’s test  $P$ -value = 0.04, Fig 4).

**Distant failure (DF)**

There were 21 distant failures, and 59 patients died without observed DF. The median distant FFS (DFF) was 52.7 months. Three and five-year DFFS were 61.0% and 44.3%, respectively. The median DFFS was 59.2 months and 33.6 months for low and high SGR, respectively ( $P$  = 0.01). The cumulative incidence of DF, using death as a competing risk, was 7.6% (95% CI: 1.7–13.5) for low SGR and 11.0% (95% CI: 3.7–18.2) for high SGR at three-years (Gary’s test  $P$ -value = 0.35).

**Discussion**

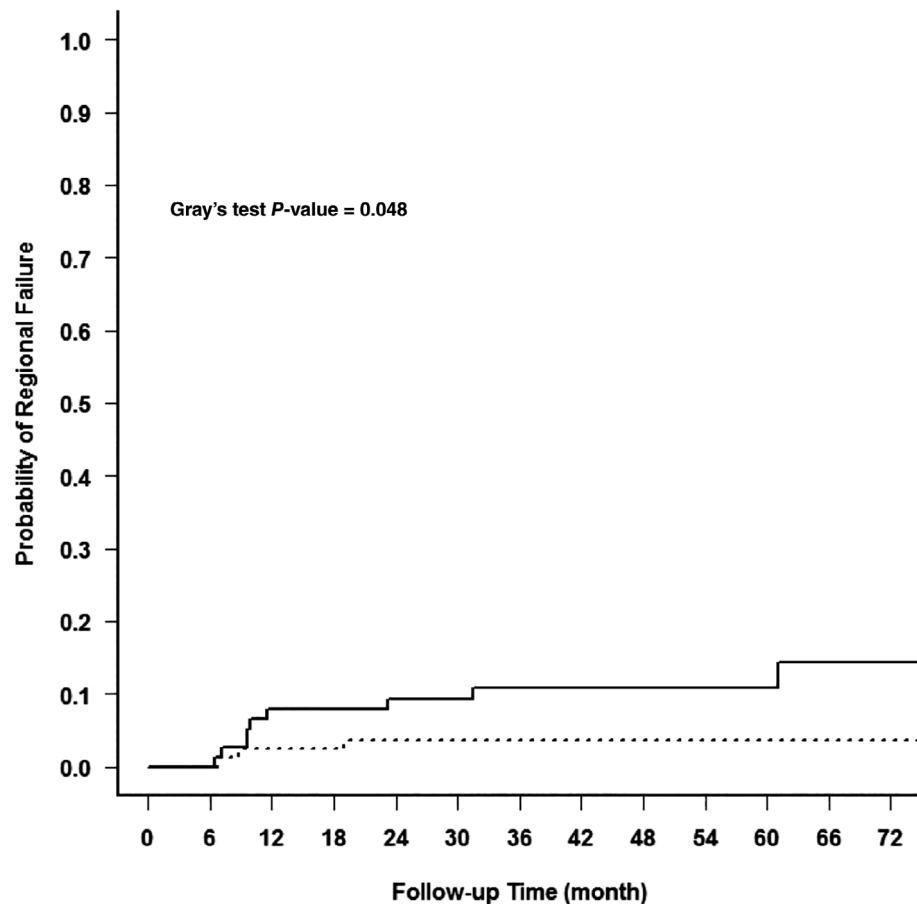
**Pretreatment growth rate**

In this study, a predefined SGR cutoff segregated SBRT patients from a different institution into high and low risk groups with significant differences in multiple cancer

outcomes. In our previous report, SGR was correlated with both median survival and FFS in patients with stage I NSCLC treated with SBRT.<sup>13</sup> SGR was used to quantify for pretreatment tumor growth rate and its median ( $0.43 \times 10^{-2}$ ) was used as a cutoff to group patients into high and low SGR cohorts. Patients with high SGR tumors had lower OS and FFS in addition to higher cumulative incidence of RF. To our knowledge, this was the first report using SGR as a metric for tumor growth rate as well as the first one to assess its impact on clinical outcome. In the current study, similar results were reproduced using the initially reported median value in an independent dataset from a different large tertiary cancer-care institution. High SGR consistently remained associated with significant worse FFS and poorer median survival in addition to higher incidence for RF. The median SGR was almost identical to the previously reported median ( $0.42 \times 10^{-2}$  compared with the previous dataset median of  $0.43 \times 10^{-2}$ ).

Furthermore, tumor volume at the time of treatment planning (GTV2) remained an independent prognostic factor together with the male gender for both OS and FFS. The median GTV2 was higher than that of the GTV1 in both current and previous datasets. GTV2 was 6 cc for

**Figure 4** SGR and the probability of regional failure (high SGR is  $\geq 0.43 \times 10^{-2}$ ). (—) high SGR (.....) low SGR.



both datasets and GTV1 was 3.9 cc for the current dataset and 3.4 cc for the previous dataset.

### Volumetric measurement

In our study, SGR was calculated using tumor volume. Volumetric measurement is believed to be a more accurate than bidimensional measurement. In this study, GTV volume on the planning dataset (average images) was used as GTV2. We acknowledge that volume in average image might be slightly larger or smaller than a diagnostic breath-hold CT. In practice, tumors might be spherical, ellipsoid, or of irregular shape and measuring the whole volume by contouring each slice of the CT might be more reflective of the actual tumor measurement rather than uni/bidimensional measurement. In a study by Mozley *et al.* volumetric measurements for advanced NSCLC were more reproducible with a significantly higher sensitivity in detecting partial response and progressive disease compared with maximum tumor diameter.<sup>16</sup> A comparison of volumetric, unidimensional and bidimensional measurements of 67 CT scans of lung cancer patients has been

reported. A total of 10 radiologists obtained the measurements and repeated them after at least five months. The analysis proved that volumetric measurement has minimal variability compared with the other two measurements.<sup>17</sup> Furthermore, in the current dataset (as in our previous analysis), we noted the presence of very low or even negative SGR values ( $n = 21$ ). This could be explained by intraobserver contouring variation, clearance of the inflammatory response component, or rare occasions of spontaneous regression.

### Prognostic factors and predictive models for stage I NSCLC treated with SBRT

Several prognostic factors for early stage NSCLC treated with SBRT have been identified.<sup>5</sup> Loganadane and colleagues<sup>18</sup> reviewed the potential predictive factors for local recurrence of early stage NSCLC treated with SBRT. Slower tumor growth rate, smaller GTV, lower pretreatment SUVmax  $\leq 3$ , and shorter waiting time ( $\leq 4$  weeks) between diagnostic and planning CT were associated with both better local control and OS. Poor ECOG performance status

and high SUVmax predicted a higher distant failure rate. Matsu and his colleagues,<sup>8</sup> identified tumor size as a significant prognostic factor for OS, local and distant failure. Recently, two nomograms were introduced to predict for the outcome of early stage NSCLC treated with SBRT. The VU group developed a RPA and a nomogram to predict for OS of early stage NSCLC treated with SBRT using 703 patients. Using Cox regression analysis, two distinct risk classes were found based on tumor diameter, age, WHO performance status (PS), and Charlson comorbidity index (CCI). Using multivariate analysis, a nomogram was constructed for five-year OS. Both the RPA and the nomogram were externally validated in surgical and SBRT independent datasets. The RPA had a moderate discrimination in the SBRT dataset but was limited in the surgical dataset. The nomogram was validated well both internally and externally in both the surgical and the SBRT datasets. The Amsterdam prognostic model consisting of both RPA and a nomogram is a valuable tool for identifying high-risk patients for poor OS; however, it does not predict for locoregional recurrence.<sup>9</sup> A Chinese group created a nomogram to predict for disease progression using a smaller sample size of 182 patients with stage I NSCLC treated with SBRT. Independent prognostic factors for both OS and locoregional control in training group were used to design a nomogram which was subsequently validated in the validation group. Only tumor size was correlated with two-year OS. Both SUVmax and tumor size was significantly related to two-year locoregional control and two-year progression-free survival.<sup>10</sup> Adding to the efforts to identify patients with poor outcome, Klement and colleagues reviewed 904 patients with early lung cancer to identify patients at high risk of early death from any reason other than lung cancer within less than six months after radiation. The probability of early death was modeled by multivariate logistic regression analysis. Age, gender, ECOG PS, CCI, FEV1, and operability were considered for model building. On multivariable analysis, poor ECOG PS was the strongest predictor for early death followed by high CCI and nonoperability of lung cancer patients.<sup>19</sup> However, the previous publications did not address tumor biological behavior as a risk factor for early death, nor used tumor growth rate parameter in conjunction with other clinical variables for nomogram design.

Tumor growth rate is a reflection of the biology of the cancer and host response and can be calculated using available scans at diagnosis and planning. SGR could be used in conjunction with other well-known predictive factors to formulate a practical predictive model to estimate individual patient recurrence risk after SBRT.

This study validates a predefined SGR threshold in patients treated with SBRT, but it is important to highlight differences in the study population from the previous

work. In both the development and validation studies most of the patients were female, had T1 disease, adenocarcinoma histopathology, and good performance status (ECOG-0). All validation study patients had pathologically confirmed diagnosis, whereas in the development study, 18% did not, despite having suspicion of malignancy due to progression on serial CTs and FDG-PET uptake. Interestingly, the median SGR value was almost identical in both study cohorts as were the median GTVs (6 cc) and the GTV2/GTV1 ratio (1.5X). Both studies identified SGR as an independent prognostic factor for FFS. SGR was independently associated with OS in the development study only, probably due to sample size. However, there was a consistent significant difference in the median survival for high and low SGR groups in both the development and validation studies.

We acknowledge the limitations of our study including its retrospective nature, the limited number of patients, and relatively short follow-up. The difference in slice thickness between diagnostic and planning CT scan might influence the volumetric measurement. Several reports showed significant difference in image noise and quantitative image features with various slice thickness. Alshipli and Kabir scanned a Catphan 600 phantom using different slice thickness at 0.6, 1, 2, 3, 4, 5, and 6 mm and reported less noise with increase of slice thickness. There was significant difference between slice thickness from 0.6 to 3 mm but not for 3 to 6 mm.<sup>20</sup> Petrou and colleagues compared a reconstructed image dataset using three slice thickness/reconstruction interval: 1.25 mm/0.625 mm, 2.5 mm/2 mm, and 5 mm/2.5 mm. The study reported significant volume variability with change in slice thickness for smaller nodules (3–10 mm).<sup>21</sup> In our current study, the maximum tumor diameter ranged from 7–60 mm with a median of 21 mm.

Future work will attempt to incorporate SGR into a predictive model for personalized treatment or even making the no treatment decision such as for low SGR tumors with a central location where treatment harm might outweigh the benefit. SGR may also be useful in guiding systemic treatment decisions (eg, immunotherapy). Calculating SGR might not be practical for busy oncology clinics, so additional efforts will be needed to automate calculation of SGR from diagnostic imaging and treatment planning data.

In conclusion, this analysis of an independent dataset confirmed the utility of pretreatment SGR median value identified in our previous study. High SGR was associated with poorer outcome in patients with early-stage NSCLC treated with SBRT. SGR can be used in conjunction with other well-known predictive factors to formulate a practical predictive model to identify subgroups of the patient at higher risk of recurrence after SBRT.



## Disclosure

The authors declare that there are no conflicts of interest

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