CURRENT ONCOLOGY
A Canadian Cancer Research Journal

ORIGINAL ARTICLE

Metabolic tumour volume is prognostic in patients with non-small-cell lung cancer treated with stereotactic ablative radiotherapy

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ABSTRACT

Introduction Stereotactic ablative radiotherapy (SABR) is a relatively new technique for the curative-intent treatment of patients with inoperable early-stage non-small-cell lung cancer (NSCLC). Previous studies have demonstrated a prognostic value for positron emission tomography–computed tomography (PET/CT) parameters, including maximal standardized uptake value (SUV_{max}), metabolic tumour volume (MTV), and total lesion glycolysis (TLG) in lung cancer patients. We aimed to determine which PET/CT parameter is most prognostic of local control (LC) and overall survival (OS) in patients treated with SABR for NSCLC.

Methods We conducted a retrospective review of patients treated with SABR for stage I inoperable NSCLC at BC Cancer between 2009 and 2013. The Akaike information criterion was used to compare the prognostic value of the various PET/CT parameters.

Results The study included 134 patients with a median age of 76 years. Median tumour diameter was 2.2 cm, gross tumour volume was 8.1 mL, SUV_{max} was 7.9, MTV was 2.4 mL, and TLG was 10.9 SUV·mL. The 2-year LC was 92%, and OS was 66%. On univariate and multivariate analysis, imaging variables including tumour size, gross tumour volume, SUV_{max}, MTV, and TLG were all associated with worse LC. Tumour size was not associated with significantly worse OS, but other imaging variables were. The PET/CT parameter most prognostic of LC was MTV. Compared with SUV_{max}, TLG and MTV were more prognostic of OS.

Conclusions In patients with early-stage NSCLC treated with SABR, MTV appears to be prognostic of LC and OS.

Key Words Metabolic tumour volume, positron-emission tomography–computed tomography, PET/CT, non-small-cell lung cancer, NSCLC, stereotactic ablative radiotherapy, SABR, prognosis

Curr Oncol. 2019 Feb;26(1):e57-e63 www.current-oncology.com

INTRODUCTION

Lung cancer is the most common cause of cancer-related death worldwide[1]. Surgical resection is the current standard of care for patients with early-stage node-negative non-small-cell lung cancer (NSCLC)[2], but stereotactic ablative radiotherapy (SABR), also called stereotactic body radiotherapy, has become the standard treatment for patients with early NSCLC who are unwilling or unable to undergo a curative resection[3].

For this group of patients with early-stage disease, who often have substantial comorbidities, relatively few clinical prognostic factors have been described. Performance status and TNM staging are used to predict outcome[4,5], but in themselves, are not adequate to identify patients most at risk for relapse or death after treatment. Nor are they able to differentiate patients within the same TNM stage.

With the integration of ^{18}F–fluorodeoxyglucose (FDG) positron-emission tomography (PET) into the staging of patients with NSCLC, interest in the prognostic value of

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PET has been increasing. The underlying assumption is that tumours that are more FDG-avid (and therefore more metabolically active) will exhibit more aggressive behavior. Previous studies have focused mainly on the maximal standardized uptake value (SUV_{max}), with most (but not all) studies showing that a greater SUV_{max} is associated with worse outcomes[6,7].

The SUV_{max} has not, however, been integrated into staging systems or standard treatment selection. The SUV_{max} represents the single most metabolically active voxel within the tumour, but it might not be representative of overall tumour behaviour. Volumetric measurements of metabolic tumour burden have more recently emerged as potential prognostic factors to identify patients with more metabolically active (and potentially more aggressive) tumours, which might benefit from alterations in therapy. Volumetric measures can include metabolic tumour volume (MTV), which is defined as the volume of tissue demonstrating increased FDG uptake on PET imaging, or total lesion glycolysis (TLG), which is the product of MTV and mean SUV[8]. A prior meta-analysis showed MTV and TLG to be prognostic of poor outcome in patients with all stages of NSCLC, treated with any modality[9].

It remains unclear whether the prognostic utility of MTV or TLG applies to patients with early-stage disease treated using SABR with curative intent[10]. Retrospective studies in this population have generally included small numbers of patients. Furthermore, the significance of some findings has been hampered by the use of multiple comparisons, which can increase the risk of a false-positive result.

The purpose of the present study was to assess the prognostic utility of the SUV_{max}, MTV, and TLG in patients treated with SABR, by retrospectively evaluating local control (LC) and overall survival (OS) in a population-based cohort treated with SABR for stage I inoperable NSCLC.

METHODS

Patients

The medical records of patients treated with SABR for stage I inoperable NSCLC at BC Cancer between May 2009 and December 2013 were retrospectively reviewed. We identified 183 tumours treated in 162 patients.

Inclusion criteria for treatment with SABR were disease staged T1/2aN0M0; a single lesion (or 1 or more lesions if they were thought to be synchronous primary lung tumours); medically inoperable disease or refusal of surgery; complete staging, including CT chest and upper abdomen, pulmonary function tests, and combined PET/CT imaging. Pathologic lymph node staging was required if nodal status was inconclusive based on the PET/CT results. Histologic confirmation of malignancy was preferred, but not required if the patient refused biopsy or was ineligible for biopsy because of medical comorbidities. In such cases, documented growth on CT and malignant FDG avidity were required.

Within the study period, 28 treated patients were excluded from analysis (Figure 1).

PET Imaging Protocol

All PET studies were performed at BC Cancer using one of two PET/CT machines (Discovery 690 or 600: GE Healthcare, Chicago, IL, U.S.A.) according to the standard provincial protocol. After a 6-hour fast, and ensuring that blood glucose was less than 11.1 mmol/L, patients were injected with a weight-based dose of FDG (370 MBq for a 70 kg patient). After a tracer uptake time of approximately 60 minutes, supine patients underwent non-contrast PET/CT imaging from base of brain to mid-thigh, with arms above head.

The tumour SUV_{max} (based on a 3-dimensional region of interest) and maximum tumour dimension were obtained from chart review, as reported by 1 of 4 experienced nuclear medicine physicians using dedicated workstations. Tumours were contoured in the MIMvista software system (version 5.1.2: MIMvista, Cleveland, OH, U.S.A.), and the PETedge tool (a previously validated gradient-based segmentation method)[11] was used to determine MTV and TLG. Measurements of MTV and TLG were made 3 times for each patient, with the median value used in the analyses.

SABR Procedure

The treating radiation oncologist contoured the gross tumour volume (GTV) on free-breathing CT images. An internal GTV was then generated by contouring a GTV on 4-dimensional maximal intensity projection planning images. Additional phases of the 4-dimensional planning images were used to verify the delineation of the internal GTV. A 5 mm planning target volume margin was then generated from the internal GTV. Peripheral lesions were treated with a dose of 48 Gy in 4 fractions[12]. Central lesions less than 2 cm from the proximal bronchial tree were often treated with an alternative fractionation scheme (Table I).

Patient Follow-Up

Patients were generally followed with CT chest imaging at 3, 6, 12, 18, and 24 months, and then yearly, although the follow-up schedule varied slightly between treating physicians. Follow-up or repeat imaging occurred sooner in patients who exhibited symptoms concerning for disease progression.

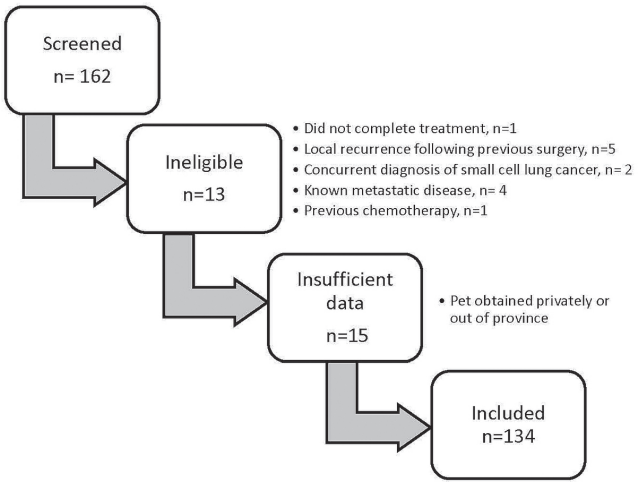

FIGURE 1 Patients screened for, and excluded from, the study.

Statistical Analysis

In patients with multiple tumours treated simultaneously, the most FDG-avid tumour was included. In patients with multiple tumours treated sequentially, the tumour treated first was included. Survival was calculated from the first day of radiation treatment. According to institutional practice and published guidelines[13], "local recurrence" was defined as growth more than 2 cm from the pretreatment CT image, increasing size and density, increasing size on serial CT images, growth outside the high-dose volume, or increased uptake on PET images. Local recurrence was assessed by the reporting radiologist and reviewed by a second radiologist and 2 radiation oncologists. Calculation of OS began with radiotherapy start and ended at the date of death from any cause. Living patients were censored at the date of last follow-up.

All data were analyzed using the SPSS (version 14.0: SPSS, Chicago, IL, U.S.A.) and R software applications (The R Foundation, Vienna, Austria). Institutional research ethics board approval was obtained for the study.

Univariate Analyses

Kaplan–Meier survival curves were used to estimate the LC and OS. Univariate analyses used Cox regression for continuous variables and the log-rank statistic from the Kaplan–Meier curve for categorical variables. To examine the significance of tumour histology (adenocarcinoma, squamous cell carcinoma, non-small-cell carcinoma not otherwise specified, or other), missing pathology data were randomly completed using a multinomial distribution of the non-missing pathology values. Those data were generated 1000 times, and a Kaplan–Meier analysis was run on each iteration.

Multivariate Analyses

Based on the univariate results, and using a larger p value cut-off of 0.3, variables were added into multivariate analyses. Using backward stepwise regression, final models were created.

Because the inclusion into a multivariate analysis of 2 or more variables that are highly correlated can increase standard errors and fail to determine the specific effect of each variable, a correlation matrix was calculated for the variables of interest in the present study. Highly correlated variables were not included in the same multivariate analysis. A separate multivariate analysis was conducted for each correlated variable (similar to the methods used by Satoh *et al.*[14]).

Comparisons

Models were compared using the Akaike information criterion (AIC) from each model, with a difference greater than 2.0 considered to be evidence for the superiority of one model over another[15,16]. All patients had complete information for all covariates used, allowing for the AIC to be used in comparing the multivariable models.

Exploratory Analysis

Using the median MTV, patients were dichotomized into low and high MTV subgroups, for whom Kaplan–Meier curves were generated. The log-rank test was used to compare LC and OS for those groups.

TABLE I Patient and tumour characteristics

Characteristic		Value
Patient		
Age at first treatment (years)		
Median		76
Range		43–94
Sex (%)		
Women		54
Men		46
Smoking status (%)		
Current		28
Former		64
Never		7
Score on the CCI[a]		
Median		2
Range		0–8
ECOG PS		
Median		1
Range		0–3
Tumour histology (%)		
Adenocarcinoma		37
Squamous cell carcinoma		19
NSCLC NOS		18
Other		4
No pathology diagnosis		22
Radiotherapy (%)		
48 Gy/4 fr.	(BED 106)	86
60 Gy/8 fr.	(BED 105)	4
50 Gy/10 fr.	(BED 75)	3
50 Gy/5 fr.	(BED 100)	1
52 Gy/4 fr.	(BED 120)	1
55 Gy/5 fr.	(BED 116)	1
55 Gy/10 fr.	(BED 85)	1
59 Gy/8 fr.	(BED 103)	1
60 Gy/10 fr.	(BED 96)	1
Tumour		
Diameter (cm)		
Median		2.2
Range		0.9–5.0
Gross volume (mL)		
Median		8.1
Range		1.0–48.2
SUV_{max}		
Median		7.9
Range		1.1–23.4
Metabolic volume (mL)		
Median		2.4
Range		0.1–33.4
Total lesion glycolysis		
Median		10.9
Range		0.1–364.2

[a] Not age-adjusted.

CCI = Charlson comorbidity index; ECOG PS = Eastern Cooperative Oncology Group performance status; NSCLC NOS = non-small-cell lung cancer not otherwise specified; fr. = fractions; BED = biologically effective dose.

RESULTS

The study included 134 patients (median age: 76 years; range: 43–94 years) with 154 lesions. Tumour histology was available for 78% of the patients. Treatment for 86% of the patients used 48 Gy in 4 fractions; the remaining 14% were treated with alternative fractionation schemes (Table I), 60 Gy in 8 fractions being the most common alternative. The biologically effective dose was 100 Gy or more in 95% of the patients. Median tumour diameter was 2.2 cm, GTV was 8.1 mL, SUV_{max} was 7.9, MTV was 2.4 mL, and TLG was 10.9 SUV•mL. Table I shows patient, treatment, and tumour characteristics.

Outcomes

At the time of censoring, 14 patients (10%) had experienced local recurrence, and 50 (37%), regional or distant recurrence; 91 patients (68%) had died. Median follow-up from the date of first treatment was 34 months (range: 0–95 months) and median survival was 33 months [95% confidence interval (CI): 24 months to 42 months] in the patients overall. The 2-year LC was 92%, and the OS was 66%.

Univariate Analyses

Table II summarizes the results of the univariate analyses. Patients with larger tumour diameter, larger GTV, higher SUV_{max}, higher MTV, higher TLG, and male sex experienced worse LC ($p < 0.05$). No relationship of histologic type with LC was evident. Patients with an Eastern Cooperative Oncology Group performance status of 2 or greater, a larger GTV, a higher MTV, or a higher TLG, and those treated with a biologically effective dose less than 100 Gy experienced worse OS ($p < 0.05$).

Multivariate Analyses

The SUV_{max}, MTV, TLG, and GTV were highly correlated and therefore assessed in separate multivariate models. Table III summarizes the results of the multivariate analyses. All imaging variables, including tumour size, GTV, SUV_{max}, MTV, and TLG were associated with worse LC ($p < 0.05$). Tumour size was not associated with significantly worse OS, but other imaging variables were.

Subset analyses excluding patients who lacked a pathology diagnosis, or those treated with a biologically effective dose less than 100 Gy, did not significantly alter the results of the multivariate analyses.

Comparison

For LC, the AIC of the model containing MTV was more than 2 points lower than the AIC of the models containing other imaging variables (Table IV), demonstrating the superiority of MTV as a prognostic marker. For OS, the AIC was lowest for the GTV, suggesting that it is the most important prognostic imaging feature. Among the PET/CT parameters, TLG and MTV were both superior to SUV_{max} (difference of >2 points in AIC).

Patients with Low and High MTV

When patients were dichotomized into low-MTV and high-MTV subgroups (MTV ≤ the median 2.4 and MTV >2.4 respectively), those in the high-MTV group experienced worse outcomes. At 2 years, LC was 100% in the low-MTV group (95% CI: not calculable) and 82.7% in the high-MTV group [95% CI: 72.4% to 93.0%; $p < 0.001$; Figure 2(A)]. Median OS was 48.3 months in the low-MTV group (95% CI: 42.0 months to 54.6 months) and 26.9 months in the high-MTV group [95% CI: 22.6 months to 31.1 months; $p = 0.01$; Figure 2(B)].

TABLE II Univariate analysis for local control and overall survival[a]

Variable	Local control			Overall survival		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Age (years)	1.03	0.96 to 1.10	0.39	1.00	0.97 to 1.02	0.75
Tumour size (cm)	2.53	1.58 to 4.03	<0.01	1.21	0.94 to 1.55	0.14
Gross tumour volume (mL)	1.12	1.07 to 1.17	<0.01	1.03	1.01 to 1.05	<0.01
Maximal standardized uptake volume	1.12	1.04 to 1.22	<0.01	1.04	1.00 to 1.09	0.06
Metabolic tumour volume (mL)	1.13	1.07 to 1.18	<0.01	1.04	1.01 to 1.07	0.01
Total lesion glycolysis	1.01	1.01 to 1.01	<0.01	1.01	1.00 to 1.01	<0.01

Variable	Comparator	Chi-square	*p* Value	Chi-square	*p* Value
Sex	Women vs. men	7.70	0.01	3.25	0.07
ECOG PS	≥2vs. <2	0.00	0.99	4.21	0.04
Score on the CCI	≥3 vs. <3	2.26	0.32	2.31	0.32
Smoking status	Ever vs. never	1.22	0.74	4.09	0.39
Pathology Dx	Presence vs. absence	2.90	0.09	2.40	0.12
Primary tumour	≥1 vs. 1	2.69	0.10	0.18	0.67
BED	≥100 Gy vs. <100 Gy	0.99	0.32	6.81	0.01

[a] Upper-panel variables were analyzed as continuous variables. Score on the CCI was stratified into low (0–2), and high (≥3) comorbidity categories. Smoking status was stratified as current and former, or never.

HR = hazard ratio; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; CCI = Charlson comorbidity index; Dx = diagnosis; BED = biologically effective dose.

TABLE III Multivariate analysis for local control and overall survival[a]

Variable	Local control			Overall survival		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Tumour size (per cm)	2.46	1.55 to 3.91	<0.001	1.17	0.93 to 1.47	0.187
Gross tumour volume (per mL)	1.11	1.06 to 1.16	<0.001	1.03	1.01 to 1.05	0.004
SUV_{max} (per unit SUV)	1.14	1.04 to 1.24	0.006	1.04	1.00 to 1.08	0.060
Metabolic tumour volume (per mL)	1.15	1.09 to 1.21	<0.001	1.04	1.01 to 1.07	0.009
Total lesion glycolysis (per unit SUV)	1.01	1.01 to 1.02	<0.001	1.01	1.00 to 1.01	0.003

[a] Only variables of interest are shown. All variables are analyzed as continuous variables. Each parameter was determined in a separate multivariate analysis. Covariates for local control included sex. Covariates for overall survival included Eastern Cooperative Oncology Group performance status, score on the Charlson comorbidity index, smoking status, age, and sex.

HR = hazard ratio; CI = confidence interval; SUV_{max} = maximal standardized uptake volume.

TABLE IV Akaike information criterion for local control and overall survival models[a]

Variable	Local control	Overall survival
Tumour size (per cm)	112.7	762.1
Gross tumour volume (per mL)	105.6	755.5
SUV_{max} (per unit SUV)	118.1	761.0
Metabolic tumour volume (per mL)	102.4	758.3
Total lesion glycolysis (per unit SUV)	107.3	756.9

[a] Covariates for local control included sex and age. Covariates for overall survival included Eastern Cooperative Oncology Group performance status, score on the Charlson comorbidity index, smoking status, age, and sex.

SUV_{max} = maximal standardized uptake volume.

For each tumour, MTV was measured 3 times. We found that more than half the measurements had a maximum discrepancy within 6% of the median, with the greatest discrepancy seen in small tumours with low MTV.

DISCUSSION

In this retrospective chart review, we found that a volumetric assessment of metabolic tumour burden—the MTV—was the PET variable most prognostic of LC and OS after SABR. Compared with SUV_{max}, the TLG and MTV were both more prognostic of OS, but the prognostic difference between TLG and MTV was not strong.

Our results agree with results from similar retrospective reviews in this patient population. Satoh *et al.*[14] reviewed 88 patients and found MTV and TLG to be prognostic of disease-free survival. Abelson *et al.*[17] retrospectively reviewed 53 patients and found MTV to be prognostic of OS at high-threshold MTV cutoffs (the volume of metabolically active tumour being defined as the volume having SUVs above 4, 7, and 10). Takahashi *et al.*[8] found MTV to be the imaging parameter most prognostic of OS (using a threshold SUV of 2) and TLG to be the parameter most prognostic of LC. The MTV has also been shown to be prognostic in patients with early-stage NSCLC treated surgically[18], in all stages of NSCLC treated definitively[9], and in other tumour sites, including esophageal cancer[19], cervical cancer[20], and head-and-neck cancer[21].

The SUV_{max} was prognostic in a systematic review and meta-analysis[6,7]. Whether its significance is retained when controlling for MTV or TLG is controversial[9]. In our study, SUV_{max} was not an independent prognostic factor, a finding that accords with results in a variety of tumour sites (including stage III NSCLC) in which MTV or TLG were also measured[22,23].

The strengths of our study include its relatively large sample size and access to a province-wide cohort of patients with early-stage NSCLC and good follow-up who had been treated with a uniform SABR protocol and who were staged using standardized imaging protocols with uniform acquisition and reconstruction parameters on one of a pair of single-vendor PET/CT machines.

Our study was retrospective in nature, and slight variances in the follow-up schedules could have limited early detection of local recurrence in patients receiving less-frequent CT imaging for surveillance. Furthermore, our methods would not always have identified cases in which distant progression preceded local recurrence (although the clinical relevance of that factor might be negligible).

Interpretation of our results is limited by difficulty in comparing our PET results with those in other studies. Measurements of SUV_{max} can vary from institution to institution based on accepted blood glucose level, fasting time, uptake time, and methods of attenuation correction and reconstruction[24]. Delineation of MTV is also variable clinically and in research. Investigators have used SUV threshold or gradient methods with little agreement about the best technique or the optimal threshold. In patients with advanced NSCLC, the metabolic activity volumes greater than 35% SUV_{max}[25], greater than 50% SUV_{max}[26,27], and greater than 70% SUV_{max}[28] have been shown to represent areas at greatest risk of local recurrence. Clinical trials in advanced lung cancer are examining the feasibility and effect of delivering a higher dose of radiotherapy to areas of FDG-avid disease exceeding 50% SUV_{max} on PET imaging[29,30]. To limit multiple comparisons and because the optimal threshold in patients with earlier (stage I) disease is not known, we used a gradient method for MTV delineation. In one study of patients with stage I adenocarcinoma of the lung, a gradient methods of MTV delineation was shown to have the highest accuracy in high-uptake large solid nodules, but a threshold method was best for low-uptake small nonsolid nodules[31]. In patients with head-and-neck

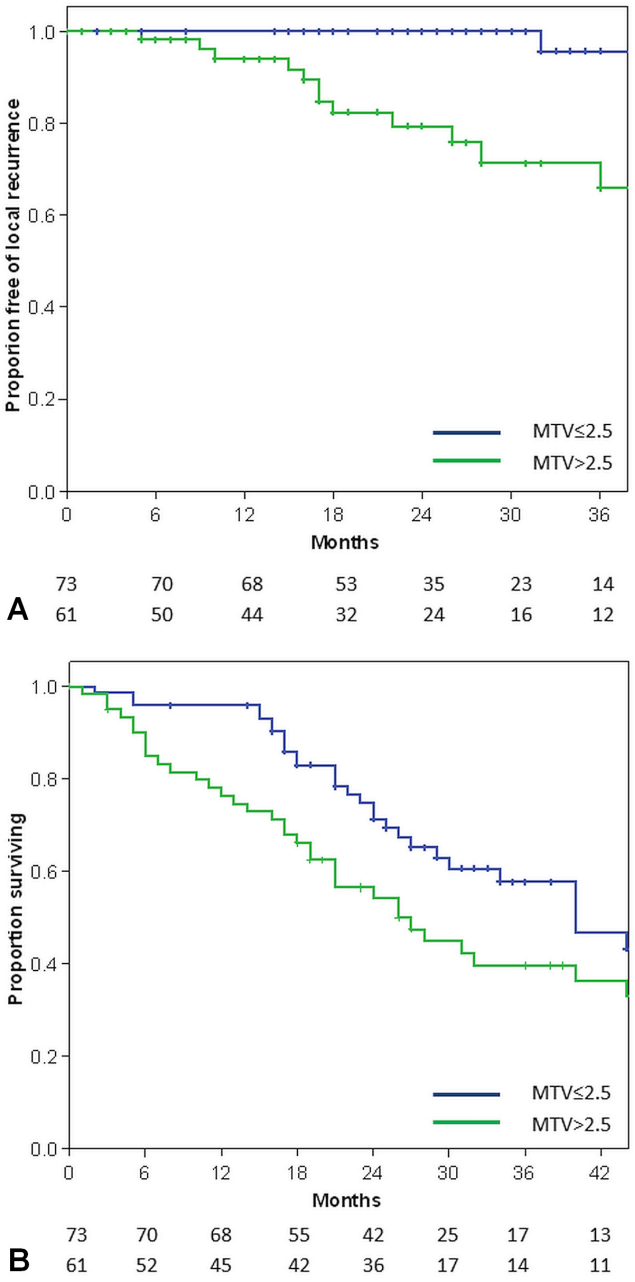

FIGURE 2 (A) Local control by patient metabolic tumour volume (MTV). (B) Overall survival by patient MTV. The MTV is dichotomized into the median value (2.4) or lower, and greater than the median value. Hash marks indicate censored patients. The numbers at risk for each time point are shown below each graph.

tumours, use of threshold or gradient methods to delineate MTV did not significantly influence the prognostic value of that variable[32]. Future research could confirm whether one method is superior in patients with early-stage NSCLC treated with SABR and could determine whether the greater than 50% SUV_{max} threshold used in advanced lung cancer also applies to the latter population.

We found that LC and OS at 12 months were relatively similar, despite the presumption that OS benefits are derived at least in part by improved LC. That observation might be attributable in part to temporal delay in identifying local recurrences after SABR. Serial CT imaging is often required to define a local failure[13], thereby delaying the time to diagnosis of local failure. Alternatively, the OS difference for patients with low compared with high MTV might be unrelated to LC. Tumours with a high MTV might perhaps be biologically more aggressive, with a higher likelihood of undetectable metastatic disease at the time of local therapy.

CONCLUSIONS

Based on our results, and those published by our colleagues, there appears to be a possible role within TNM staging for MTV to differentiate the biologic behavior of tumours, which could provide a means of further individualizing treatment. For example, an escalated radiation dose might be warranted for patients with metabolically aggressive lesions, a strategy that has shown some promise in the treatment of patients with stage III lung cancer[33]. Alternatively, patients with tumours having a high MTV might benefit from systemic therapy, if tolerable. Inclusion of PET parameters could have an important role in future patient care, but before widespread adoption, further research is needed, including retrospective reviews of large patient cohorts, prospective evaluation, and meta-analysis[34].

ACKNOWLEDGMENTS

We thank Lisa Tam and Tina M. Alden for assistance with data collection.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: DS receives speaker fees from Varian outside of the submitted work. The remaining authors have no conflicts of interest to disclose.

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