Advances in Radiation Oncology (2024) **9**, 101313

advances in radiation oncology

www.advancesradonc.org

Scientific Article

Pretreatment and Posttreatment Tumor Metabolic Activity Assessed by FDG-PET/CT as Predictors of Tumor Recurrence and Survival Outcomes in Early-Stage Non-Small Cell Lung Cancer Treated With Stereotactic Body Radiation Therapy

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Received 13 January 2023; accepted 9 June 2023

Purpose: Stereotactic body radiation therapy (SBRT) is considered the standard of care for medically inoperable early-stage non-small cell lung cancer. There is mixed evidence on the prognostic significance of tumor metabolic activity assessed by positron emission tomography combined with computed tomography (PET/CT) using F-18 fluorodeoxyglucose (FDG). The objectives of this study were to evaluate the maximum standardized uptake value (SUV_{max}) pretreatment and at 3 and 6 months after SBRT for prediction of tumor control and survival outcomes.

Methods and Materials: Consecutive patients from a single institution with T12N0M0 non-small cell lung cancer receiving primary treatment with SBRT with pretreatment FDG-PET/CT (n = 163) and follow-up FDG-PET/CT at 3 or 6 months (n = 71) were included. Receiver operator characteristic analysis was performed to dichotomize variables for Kaplan-Meier survival analysis. Multivariate analysis was performed with Cox proportional hazards regression.

Results: Median follow-up was 19 months. For the whole cohort, 1-year and 2-year local control, progression-free survival (PFS), and overall survival (OS) were 95.0% and 80.3%, 87.1% and 75.4%, and 67.0% and 49.6% respectively. The following pre-SBRT SUV_{max} cutoffs were significant: SUV > 4.0 for distant failure-free survival (adjusted hazard ratio [aHR], 3.33, $P = .006$), >12.3 for PFS (aHR, 2.80, $P = .011$), and >12.6 for OS (aHR, 3.00, $P = .003$). SUV_{max} decreases of at least 45% at 3 months (aHR, 0.15, $P = .018$), and 53% at 6 months (aHR, 0.12, $P = .046$) were associated with improved local failure-free survival.

Sources of support: This work had no specific funding.

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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https://doi.org/10.1016/j.adro.2023.101313

Conclusions: Pre-SBRT SUV_{max} cutoffs can predict distant failure, PFS, and OS. At both 3 and 6 months after SBRT, cutoffs for percentage change in SUV_{max} can potentially stratify risk of local recurrence.

Introduction

Lung cancer is a leading cause of cancer-related death, and non-small cell lung cancer (NSCLC) accounts for a majority of cases.[1,2] Stereotactic body radiation therapy (SBRT) has emerged as the standard of care for medically inoperable early-stage NSCLC (ES-NSCLC). Compared with conventional radiation therapy techniques, SBRT has demonstrated improved local control (LC) and overall survival (OS).[3-5]

Adjuvant chemotherapy for NSCLC has demonstrated improved OS and reduced distant relapse rates in patients treated with surgery; however, patients undergoing SBRT may not always have pathologic data to inform decision-making about risk stratification and adjuvant therapy.[6] A recent NCDB (National Cancer Database) analysis found that adjuvant chemotherapy after SBRT was more likely to be offered to younger patients, patients with tumor size >4 cm, patients with fewer comorbidities, and patients treated at community cancer programs.[7] Given the limited evidence on determining which patients are candidates for further therapy, the identification of prognostic data that stratifies risk of tumor failure and survival, both during pretreatment planning and in serial follow-up imaging, has significant clinical importance.

Positron emission tomography combined with computed tomography (PET/CT) using F-18 fluorodeoxyglucose (FDG) is a standard pretreatment imaging modality for NSCLC staging. However, evidence for the ability of FDG-PET/CT data to predict outcomes in ES-NSCLC are not well established. Multiple studies have noted that a higher pre-SBRT maximum standardized uptake value (SUV_{max}) is associated with poorer LC,[8-12] although many negative results have also been reported.[13-16] Evidence for the association between pre-SBRT SUV_{max} and OS is similarly equivocal. Higher pre-SBRT SUV_{max} has predicted worse OS in meta-analysis,[17] but multiple studies with large cohorts published since then have shown negative results.[18,19] As well, there is a paucity of available evidence for the predictive value of change in SUV_{max} between pre-SBRT imaging to post-SBRT FDG-PET/CT. The literature has often used arbitrary cutoff values for pretreatment SUV_{max}, and institutional protocols have differed in their time intervals for follow-up PET scans when investigating change in SUV_{max}.

Therefore, the primary objectives of the present study were to assess the tumor failure patterns and survival outcomes of early-stage NSCLC based on pretreatment SUV_{max} and percent change in SUV_{max} at the specific time intervals of 3 and 6 months after SBRT. To our knowledge, this study is the first to assess change in SUV_{max} at multiple time points after SBRT to predict clinical outcomes.

Methods and Materials

Cohort

We queried an institutional review board approved institutional database for patients receiving primary treatment for AJCC (American Joint Committee on Cancer) seventh edition T12N0M0 NSCLC with SBRT between 2012 and 2018 (study #20200251). Diagnosis was based on biopsy for a majority of patients; however, diagnosis by serial CT growth of FDG-PET/CT was permitted for patients unable or declining to undergo biopsy. Absence of regional or distant metastases was determined by initial FDG-PET/CT at diagnosis. Patients were either deemed medically inoperable by cardiothoracic surgery or pulmonology or had declined surgery. Patients were excluded if they had a history of prior primary lung cancer, other concurrent or active malignancy, or prior thoracic radiation therapy.

The technique used for SBRT has been previously described.[20,21] In this study, 50 to 60 Gy was delivered in 3 to 5 fractions per institutional protocol. Dose-fractionation schedules are displayed in Table 1. After SBRT, patients were scheduled for repeat FDG-PET/CT imaging in 3 or 6 months based on provider preference. Time to failure was determined from the date of the last SBRT fraction. Change in SUV_{max} was included if the follow-up FDG-PET/CT scan was performed within 14 days of date corresponding to 3 or 6 months after the date of the last fraction of SBRT. In general, patients were followed 1 month after completion of SBRT, then in 2- to 4-month intervals for the next 2 years, and then semiannually for 5 years. Response was assessed according to RECIST (Response Evaluation Criteria in Solid Tumors) criteria. PET-CT or biopsy were required to determine disease progression.

FDG-PET/CT imaging

Each patient underwent FDG-PET/CT for staging before SBRT after a standard clinical procedure. Patients were asked to fast for 4 to 6 hours before imaging. The

Table 1 Baseline cohort characteristics

Characteristic	Type	n	%
Pre-SBRT FDG-PET/CT, no.		163	
Pre- and post-SBRT FDG-PET/CT, no.		71	43.6%
Median age (range), y		75 (52-91)	
Female		78	48.9%
Histology	Squamous cell carcinoma	57	35.0%
	Adenocarcinoma	76	46.6%
	NOS	30	18.4%
Stage	T1a	72	44.2%
	T1b	58	35.6%
	T2a	29	17.8%
	T2b	4	2.5%
Dose-fractionation schedule	50 Gy/4 fx	56	34.4%
	50 Gy/5 fx	77	47.2%
	54 Gy/3 fx	27	16.6%
	55 Gy/5 fx	1	0.6%
	57.5 Gy/5 fx	1	0.6%
	60 Gy/5 fx	1	0.6%

Abbreviations: FDG-PET/CT = 18F-fluoro-deoxyglucose positron emission tomography computed tomography; fx = fractions; NOS = not otherwise specified; SBRT = stereotactic body radiation therapy.

blood glucose was obtained before FDG injection to ensure appropriate fasting. The activity for F-18 FDG ranged between 10.0 and 15.0 mCi on a weight-based protocol. According to the clinical imaging protocol, patients underwent PET imaging approximately 60 minutes after the FDG injection. PET/CT imaging was performed on a state-of the art scanner from Philips (Philips Healthcare, Cleveland, OH) and Siemens Biograph20 mCT PET/CT (Siemens Healthcare, Chicago, IL). Scanners were checked to performance at regularly indicated intervals. The acquisition time ranged between 2 and 3 minutes per bed position based on patient body weight. PET imaging included the torso with the arms up and a dedicated imaging of the head and neck with the arms down. A low-dose CT was used for attenuation correction. The PET images were iteratively reconstructed based on the ordered subset expectation maximization method. Image analysis was performed on a MIM workstation (MIM software, Beachwood, OH). Standardized uptake values based on the highest voxel activity (SUV_{max}) were obtained by placing a region of interest on target tumor lesions.

Statistical analysis

Patient information, imaging results, and tumor characteristics were obtained by retrospective chart review. Clinical endpoints included local (LFFS), regional, and distant failure-free survival (DFFS), progression-free survival (PFS), and OS.

Receiver operator characteristic (ROC) analysis was used to determine optimal thresholds to dichotomize variables for survival analysis similar to prior studies in this field.[22,23] Balanced error rates were calculated to determine optimal thresholds. The Kaplan-Meier method with log-rank testing was used to conduct survival analyses. Multivariate analysis with a Cox proportional hazards model including age, sex, T stage, histology, performance status, and SUV_{max} or change in SUV_{max} estimated hazard ratios (HRs) with a 95% CI. *P* values were 2-sided and considered statistically significant if less than .05. A Bonferroni correction for multiple comparisons was completed. All statistical analyses were conducted using R version 3.6.1 software.

Results

In the study, 227 cases of T1-2N0M0 NSCLC were identified, of which 171 underwent pretreatment FDG-PET/CT. Pretreatment FDG-PET/CT occurred a median of 36.5 days before the first fraction of SBRT (range, 1-250 days). In addition, 163 of these patients had a reported SUV_{max}, and 71 (43.6%) had both a pretreatment scan and a posttreatment FDG-PET/CT at 3 (n = 32) or 6 (n = 39) months. Baseline patient, tumor,

Table 2 Multivariate analysis of pretreatment SUV_{max} and change in SUV_{max} on tumor control and survival outcomes

Outcome	LFFS		RFFS		DFFS		PFS		OS	
	cut-off	aHR (CI)	cut-off	aHR (CI)	cut-off	aHR (CI)	cut-off	aHR (CI)	cut-off	aHR (CI)
Pre-SBRT SUV_{max}	>8.2	2.26 (0.87-5.87)	>4.7	1.06 (0.41-2.67)	>4	3.33* (1.42-7.84)	>12.3	2.80† (1.26-6.19)	>12.6	3.00* (1.56-5.76)
3-mo SUV_{max} percentage change	<−45.0%	0.15† (0.02-0.91)	<−44.6%	0.34 (0.02-6.71)	<−65.3%	1.07 (0.18-6.47)	<−50.0%	0.96 (0.33-2.75)	<−45.0%	0.63 (0.28-1.39)
6-mo SUV_{max} percentage change	<−53.0%	0.24† (0.06-0.94)	<−10.8%	0.12† (0.02-0.96)	<−3.7%	0.29 (0.03-2.65)	<−77.8%	0.50 (0.13-1.95)	<−39.8%	0.32 (0.08-1.28)

Abbreviations: aHR = adjusted hazard ratio; LFFS/RFFS/DFFS = local/regional/distant failure-free survival; OS = overall survival; PFS = progression-free survival; SBRT = stereotactic body radiation therapy; SUV_{max} = maximum standardized uptake value.

*$P < .01$.

†$P < .05$.

and treatment characteristics are shown in Table 1. Median follow-up was 18.9 months (range, 0.2-78.3). For the whole cohort, 1-year and 2-year LFFS, PFS, and OS were 95.0% and 80.3%, 87.1% and 75.4%, and 67.0% and 49.6%, respectively.

Table 2 displays results of the multivariate analysis for SUV_{max}-related variables. Pretreatment SUV_{max} cut-off points were significantly associated with DFFS (SUV_{max} >4.0; adjusted hazard ratio [aHR], 3.33; 95% CI, 1.42-7.84; $P = .006$), PFS (SUV_{max} >12.3; aHR, 2.8; 95% CI, 1.3-6.2; $P = .011$), and OS (SUV_{max} >12.6; aHR, 3.00; 95% CI, 1.6-5.8; $P = .003$). Patients with a SUV_{max} <12.3 had a median PFS of 16.9 months compared with 13.0 months for a SUV_{max} over 12.3. A SUV_{max} over 12.6 yielded a 3.5-month shorter median OS. Pre-SBRT SUV_{max} did not significantly predict local or regional tumor control (Fig. 1).

At 3 months after SBRT, a 45% decrease in SUV_{max} was associated with a longer LFFS (aHR, 0.15; 95% CI, 0.02-0.91; $P = .018$). A 6-month decrease in SUV_{max} >53% was also associated with improved LFFS (aHR, 0.24; 95% CI, 0.06-0.94; $P = .038$), and a decrease >11% demonstrated improved regional failure-free survival (aHR, 0.12; 95% CI, 0.02-0.96; $P = .046$). Figure 2 presents the LFFS between groups at 3 and 6 months.

Among other factors included in the multivariate analysis, performance status was significantly associated with PFS (aHR, 1.32; 95% CI, 1.04-1.67; $P = .022$) and OS (aHR, 1.47; 95% CI, 1.11-1.95; $P = .007$), and T stage was significantly associated with PFS (aHR, 4.34; 95% CI, 1.20-15.64; $P = .025$), but not with OS (aHR, 2.79; 95% CI, 0.40-19.55; $P = .30$).

Discussion

In the present study, we assessed SUV_{max} as a predictor of tumor control and survival outcomes. Our principal findings were (1) pre-SBRT SUV_{max} cutoff points can significantly predict DFFS, PFS, and OS, and (2) cutoff points in percentage change in SUV_{max} at both 3 and 6 months can predict for LC but are not associated with PFS or OS. Our study offers one of the larger cohorts among studies on a similar subject. Our study is also the first, to our knowledge, to report change in SUV_{max} at multiple time points after SBRT.

There have been several prior studies on the use of FDG-PET/CT in patients with NSCLC. Multiple meta-analyses and systematic reviews have noted that a high pretreatment SUV_{max} was a poor prognostic factor in cohorts of stage I to IV NSCLC, surgically resected stage I NSCLC, and NSCLC receiving any type of radiotherapy.[24-26]

SUV_{max} as prognostic data, especially during serial follow-up imaging, may be used for determination of adjuvant therapy in future studies which is not standard of

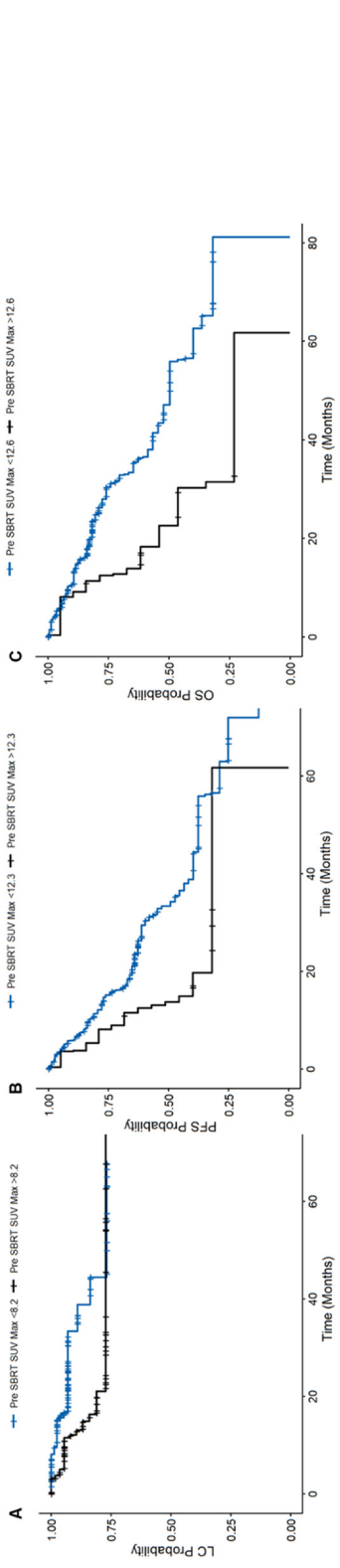

Figure 1 (A) Pre-SBRT SUV_{max} cutoffs for local control, (B) progression-free survival, (C) and overall survival. *Abbreviations*: LC = local control; OS = overall survival; PFS = progression free survival; SBRT = stereotactic body radiation therapy; SUV_{max} = maximum standardized uptake value.

care at present. Although the 3- and 6-month follow-up scans may be too late for the clinical determination of adjuvant therapy need, treatment intensification, or an increased frequency of serial imaging could still be considered, and randomized series may be warranted to study this. Tumor size has been shown to be a predictor of adjuvant chemotherapy in NSCLC after surgical resection, but our study showed that SUV_{max} was a stronger predictor of OS than T stage.[7] There are many potential mechanisms by which a higher SUV_{max} may lead to a poorer prognosis. Hypoxic conditions increase expression of hypoxia inducible factor 1α (HIF-1α), resulting in increased cell membrane glucose transporters that can increase FDG uptake.[27] Furthermore, hypoxia may decrease tumor radiosensitivity and response to other antitumor therapies, and multiple trials are ongoing to target intermediates in the hypoxia pathway in NSCLC.[28] A meta-analysis has demonstrated that HIF-1α expression of tumor tissues was negatively associated with OS.[29]

Cellular proliferation may also serve as a link between SUV_{max} and prognosis. FDG uptake is positively correlated with Ki-67, a DNA-binding protein expressed during cell proliferation.[30] A high Ki-67 proliferation index is associated with worse survival.[31] Although poor differentiation status was not studied here, it may have been partially accounted for given that squamous cell carcinomas tend to have a higher SUV_{max} than adenocarcinomas and histology was included in the multivariate analysis.[30]

SUV_{max} on staging FDG-PET/CT has previously demonstrated predictive ability in patients with NSCLC receiving primary treatment with SBRT; however, there are relevant methodological limitations to the available evidence. For example, one study demonstrated that a 3-month post-SBRT SUV_{max} reduction of <2.55 was associated with increased risk of distant failure, but the 3-month time point included post-SBRT PET scans done from 2.1 to 4 months (65-123 days) after SBRT.[8] It is unclear whether the earlier or later timing of the scan may have affected the results. Our study used stricter criteria for including scans at the 3- and 6-month post-SBRT time points. As well, the staging FDG-PET/CT may precede SBRT by a variable duration of time, raising the question of whether the SUV_{max} on the staging FDG-PET/CT represents the metabolic activity of the tumor at the time of SBRT. FDG uptake also varies with NSCLC histologic subtype, tumor differentiation, and tumor volume, which are not adjusted for in many analyses.[12,30]

Although a meta-analysis showed that there is a significant signal toward pre-SBRT SUV_{max} being a small negative predictor of OS (HR, 1.10; 95% CI, 1.01-1.15) and distant metastases (HR, 1.09; 95% CI, 1.03-1.16), the included studies demonstrated significant heterogeneity in both OS (I^2 = 70%, $P_{heterogeneity}$ = .003) and distant metastases (I^2 = 74%, $P_{heterogeneity}$ = .020), suggesting that publication bias against negative results, limited follow-up time, and unadjusted analyses may have played a role in

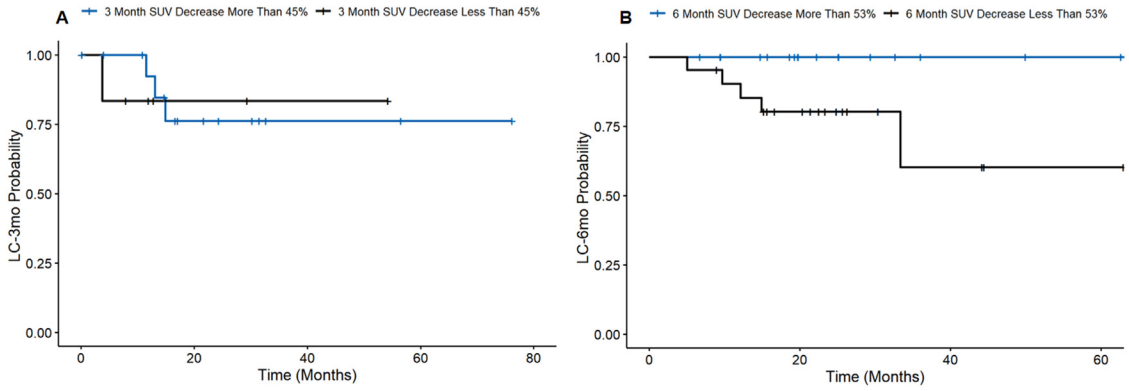

Figure 2 Cutoffs for percent change in SUV_{max} at (A) 3 months and (B) 6 months on local control. *Abbreviations*: LC = local control; SUV_{max} = maximum standardized uptake value.

their conclusions.[17] Studies have often dichotomized results into "high SUV" and "low SUV" groups, as was done in the present study, but the studies in the meta-analysis had SUV_{max} cut-offs ranging from 2.47 to 8, which affects the ability to group them into high and low SUV_{max} groups.[17]

The main limitation of our study was the small number of total events due to our stricter criteria for 3- and 6-month post-SBRT PET scans. This may have affected our estimation of differences in regional (3 events in 3-month group, 6 in 6-month group) and distant (5 events in 3-month group, 5 in 6-month group) failure. There may also be selection bias because all patients were recommended to receive PET scans. Those who completed serial imaging may have slower-progressing tumors or better health care access. Of note, the post-SBRT time intervals of 3 and 6 months for follow-up imaging were selected based on institutional protocol. Additional research may seek to determine the posttreatment time point at which change in SUV_{max} is most strongly associated with outcomes of interest in place of serial PET-CT scans. It may also be difficult to compare SUV_{max} across institutions as scan protocol and reconstruction methods are not standardized. As this study was retrospective in nature, our results should be considered hypothesis-generating and require further study. The present study attempted to account for some of these potential limitations by using a standardized FDG-PET/CT protocol, using only images obtained at our institution, and including results obtained by the same group of nuclear medicine physicians. Other measures of tumor metabolic activity such as peak standardized uptake value and metabolic tumor volume were unable to be included in this study as they were not frequently reported on radiology reports.

A previous pilot trial on serial FDG-PET/CT scans did not support their routine use over serial CT imaging after SBRT. This trial had a small population (n = 14) without any local recurrences, but it did note that a substantial proportion had a persistently elevated SUV_{max} at 12 months without evidence of local failure.[32] Other studies have shown FDG-PET/CT to be specific but insensitive for determination of recurrence and suggested that it was better reserved for evaluation of new CT findings.[22,33] Based on this study and the Clarke et al[8] report, there appears to be a potential prognostic utility of follow-up FDG-PET/CT data that may have gone unmeasured in the prior literature. The ideal role for serial FDG-PET/CT deserves additional study.

Finally, there are several ongoing clinical trials adding immunotherapy to SBRT, such as KEYNOTE-867 (NCT03924869) and PACIFIC-4 (NCT03833154) for which the present study has relevance. In particular, SWOG/NRG S1914 (NCT03775265) is a randomized phase 3 clinical trial assessing the addition of atezolizumab to SBRT in the neoadjuvant, concurrent, and adjuvant setting for high-risk, ES- NSCLC.[34,35] Notably, this trial uses an SUV_{max} greater than or equal to 6.2 as one of the risk factors that meets inclusion criteria. In our study, we found that an SUV_{max} >12.6 was a significant cutoff value for OS and would consider post hoc analysis of the patients over this cutoff to be prudent to see whether they derive more benefit. The S1914 differs from ours in that it includes T1-3 NSCLC while our study only included T1-2.[34,35]

Conclusion

Our study revealed that the cutoff values using ROCa-analysis that demonstrated that pre-SBRT SUV_{max} can predict PFS and OS. Additionally, the percent change in SUV_{max} on both 3- and 6-month follow-up FDG-PET/CT after SBRT can predict risk of local failure. A future study is required to investigate value of posttreatment PET at fixed time point in conjunction with serial CT scan to establish its role in SBRT treatment and evaluation.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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