North Clin Istanb 2019;6(2):129–133
doi: 10.14744/nci.2019.02212

Original Article RADIATION ONCOLOGY

Pretreatment SUV_{max} value to predict outcome in patients with stage III NSCLC receiving concurrent chemoradiotherapy

Gokhan Yaprak,[1] Melike Ozcelik,[2] Cengiz Gemici,[1] Ozgur Seseogullari[3]

[1]Department of Radiation Oncology, University of Health Sciences, Kartal Dr. Lutfi Kirdar Training and Research Hospital, Istanbul, Turkey,
[2]Department of Medical Oncology, Adiyaman University, Training and Research Hospital, Adiyaman, Turkey
[3]Department of Radiation Oncology, Biruni University, Medicana International Hospital, Istanbul, Turkey

ABSTRACT

OBJECTIVE: Stage III disease accounts for approximately one-fourth of all non-metastatic non-small cell lung cancer (NSCLC). The patients who are not candidates for curative resection are offered concomitant chemoradiotherapy. In this subgroup, which is difficult to manage, studies that address the role of PET-CT to predict outcome measures specifically for stage III NSCLC receiving concurrent chemoradiotherapy may help better risk stratification. This study aimed to assess whether baseline PET maximum standardized uptake value (SUV_{max}) value in stage III NSCLC treated with concurrent chemoradiotherapy would independently identify patients with high risk of progression and death.

METHODS: The study population consisted of patients aged 18 years or more with unresectable stage III histologically or cytologically proven NSCLC who received concurrent chemoradiotherapy. From 2007 to 2014, medical records of patients admitted to our institution were retrospectively analyzed. Pretreatment PET-CT SUV_{max} values were recorded for each patient. These values were categorized as low or high according to the median SUV_{max} measure of the study population.

RESULTS: A total of 175 patients were analyzed. The median follow-up time was 23 months (range 6–109). The PET-CT SUV_{max} values ranged from 3.5 to 46 with a median value of 14. The median overall survival was 25 months in SUV_{max} <14 and 18 months in SUV_{max} ≥14 group (p=0.023). The median progression-free survival was 16 months in SUV_{max} <14 and 11 months in SUV_{max} ≥14 group (p=0.033). Multivariate analysis revealed that both PET-CT SUV_{max} value (p<0.001) and age (p=0.016) were independent significant predictors for overall survival (OS).

CONCLUSION: The results of this study involving patients with stage III NSCLC receiving concurrent chemoradiotherapy provide evidence that suggests that high values of pretreatment SUV_{max}, an indicator of metabolic tumor burden, predicted a higher risk of disease progression and death.

Keywords: Chemoradiotherapy; PET scan; stage III NSCLC; SUV_{max}.

Cite this article as: *Yaprak G, Ozcelik M, Gemici C, Seseogullari O. Pretreatment SUV_{max} value to predict outcome in patients with stage III NSCLC receiving concurrent chemoradiotherapy. North Clin Istanb 2019;6(2):129–133.*

In patients with initial non-metastatic non-small cell lung cancer (NSCLC), PET scanning identifies those with subclinical metastatic disease who otherwise would have underwent unnecessary surgery or definitive chemoradiotherapy. As PET-CT positively affects the therapeutic decision and has significantly higher accuracy in staging than contrast-enhanced CT alone, it is the preferred imaging tool for the work-up of patients with NSCLC [1–4].

Received: September 07, 2018 *Accepted:* December 18, 2018 *Online:* June 12, 2019

Correspondence: Dr. Melike OZCELIK. Saglik Bilimleri Universitesi, Umraniye Egitim ve Arastirma Hastanesi, Tibbi Onkoloji Klinigi, Istanbul, Turkey.
Tel: +90 506 297 97 94 e-mail: drmelike.ozcelik@gmail.com

In addition to its value on clinical staging, at least some data suggest that it has role in predicting outcome [5, 6]. Tumor maximum standardized uptake value (SUV_{max}), a measure of cellular metabolic activity of the tumor, defined by PET-CT was reported to be an independent predictor of survival and relapse in early-stage NSCLC. Most of the existing studies included surgically resected patients with NSCLC, excluding the majority of the stage III disease, and suggested that patients with tumors who exhibit intense FDG uptake may be considered at a high risk of treatment failure and may benefit from more aggressive adjunctive treatment [7–10].

Stage III disease accounts for approximately one-fourth of all NSCLC. It is the most frequently relapsed group. Although it represents a heterogeneous entity, many patients are not candidates for curative resection, and they are offered concomitant chemotherapy and radiotherapy (RT). Concomitant chemoradiotherapy achieves both local control of disease and improves survival, but many patients still suffer recurrence after definitive therapy, demonstrating the lethality of the disease [11–14].

Studies addressing the role of PET-CT to predict outcome measures specifically for stage III NSCLC receiving concurrent chemoradiotherapy may help better risk stratification in this difficult-to-manage subgroup. We aimed to assess whether baseline PET SUV_{max} value in stage III NSCLC treated with concurrent chemoradiotherapy would independently identify patients with a high risk of progression and death.

MATERIALS AND METHODS

Study Design

The study population consisted of patients aged 18 years or more with unresectable stage III, histologically or cytologically proven NSCLC who received concurrent chemoradiotherapy. From 2007 to 2014, medical records of patients admitted to our institution were retrospectively analyzed. Staging was defined according to the TNM seventh edition. Unresectability was determined after discussion among radiologist, chest surgeons, and medical and radiation oncologists. Pretreatment PET-CT SUV_{max} values were recorded for each patient, and these values were categorized as low or high according to the median SUV_{max} measure of the study population.

Clinicopathological characteristics including gender, age, weight loss, performance status, stage, histological subtype, and utilized chemotherapy regimen were also collected. During concurrent chemoradiotherapy phase, any of the chemotherapy regimens recommended with high-quality evidence (category 1/grade 1A) were accepted. However, the utilization of induction and/or consolidation chemotherapy was not allowed to provide a more homogeneous study sample. The local institutional review board approved the study.

Statistical Analysis

Descriptive analysis was used to evaluate the characteristics of patients. Overall survival (OS) was defined as the time from the beginning of concurrent chemoradiotherapy to death from any cause or to last follow-up evaluation. Progression-free survival (PFS) was defined as the time between the beginning of concurrent chemoradiotherapy and the date of disease progression or death, whichever comes first. The Kaplan–Meier method and log-rank test was used to estimate and compare OS and PFS. Multivariate analysis was performed by means of cox proportional hazards model. All statistical analyses were carried out using SPSS 17.0 version (IBM Corp., Armonk, NY, USA). P value below 0.05 was accepted as statistically significant.

RESULTS

A total of 175 patients were analyzed. There were 22 females and 153 males. At the time of diagnosis, 87 patients were stage IIIA and 88 patients were stage IIIB. The predominant histological subtype was squamous cell carcinoma. Chemotherapy regimen administered concurrently with RT was carboplatin + paclitaxel in 69 patients (39.4%), cisplatin + docetaxel in 67 patients (38.2%), and cisplatin + etoposide in 39 patients (22.2%). Baseline characteristics of the patients in relation to SUV_{max} values are shown in Table 1. The median follow-up time was 23 months (6–109). The PET-CT SUV_{max} values ranged from 3.5 to 46 with a median value of 14. The median OS was 25 months in SUV_{max} <14 and 18 months in SUV_{max} ≥14 group (p=0.023). Accordingly, three-year and five-year survival rates were 36.8% and 24% versus 28.4% and 13.2% in SUV_{max} <14 and SUV_{max} ≥14 group, respectively. OS in relation to SUV_{max} values is detailed in Figure 1.

The median PFS was 16 months in SUV_{max} <14 and 11 months in SUV_{max} ≥14 group (p=0.033). Three-year and five-year survival rates were 20.7% and 15.8%

TABLE 1. Baseline characteristics of patients in relation to SUV_{max} values

	SUV_{max} >14 group		SUV_{max} <14 group		p
	n	%	n	%	
Age	61 (38–76)		62 (44–82)		0.71
Gender					
Female	7	8	15	17	0.07
Male	81	92	72	83	
Histological variant					0.003
Adenocarcinoma	16	18	35	22	
Squamous cell	56	64	45	46	
NOS	16	18	7	32	
Substage					0.18
IIIA	39	44	48	55	
IIIB	49	56	39	45	
ECOG PS					0.43
0	46	52	38	44	
1	33	38	41	47	
2	9	10	8	9	
RT dose (median)	60 Gy		60 Gy		
Concomitant CT					0.87
Carboplatin+paclitaxel	36	41	33	38	
Cisplatin+docetaxel	32	36	35	40	
Cisplatin+etoposide	20	23	19	22	

ECOG PS: Eastern Cooperative Oncology Group, performance status; CT: Chemotherapy.

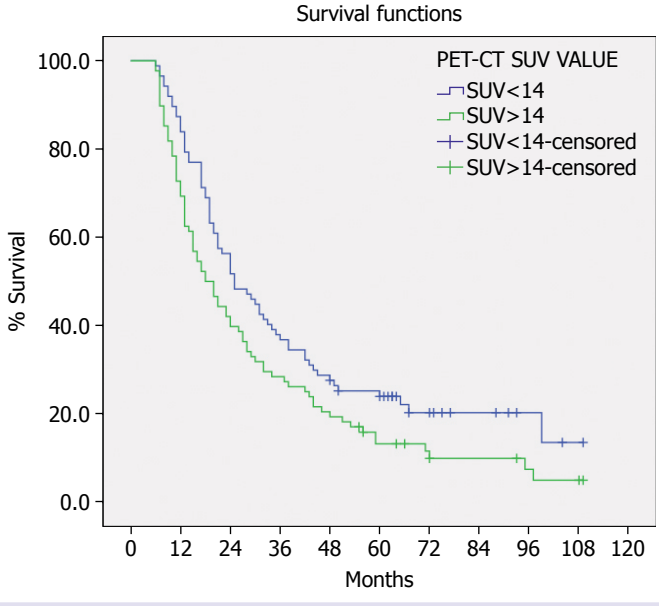

FIGURE 1. Overall survival rate of patients in relation to SUV_{max} values.

versus 15.9% and 9% in SUV_{max} <14 and SUV_{max} ≥14 group, respectively. The PFS according to SUV_{max} levels is shown in Figure 2.

In univariate analysis, age (p=0.028) was the only statistically significant prognostic parameter for OS. Gender (p=0.67), substages IIIA or IIIB (p=0.10), histological variant (p=0.83), concurrent chemotherapy regimen (p=0.08), and performance status (p=0.66) were not found to be related with OS. Multivariate analysis revealed that both PET-CT SUV_{max} (HR: 1.04, 95% CI: 1.02–1.06; p<0.001) and age (HR: 1.02, 95% CI: 1.00–1.04; p=0.016) were independent significant predictors for OS.

DISCUSSION

Patients with primary tumors characterized by high pretreatment uptake of 18F-FDG on PET have been shown to have poor survival outcome. Carcinomas of lung, head and neck, nasopharynx, pancreas, esophagus, and cervix are the most studied examples. In this study, we explored

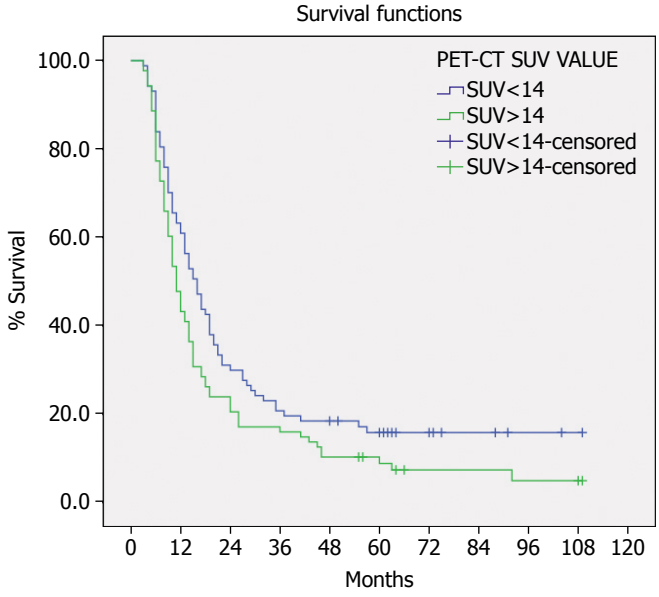

FIGURE 2. Progression-free survival time of patients according to SUV_{max} values.

the specific subgroup of NSCLC, stage III disease, where the combination of RT and chemotherapy seemed more effective than either treatment alone but nevertheless inadequate for cure in the majority.

Patients with stage III NSCLC treated with combined chemoradiotherapy are at varying risks of developing either resistant or recurrent disease. Some clinical features are useful to stratify patients into groups that are more or less likely to relapse. Individuals who had an ECOG PS of 2–4 at diagnosis, were old, and male in gender were more likely to have a poor prognosis [15]. Tumor burden is also independently associated with worse outcome. In addition to anatomically defined tumor burden, metabolic tumor burden, measured as SUV_{max}, metabolic tumor volume (MTV), and total lesion glycolysis (TLG) acquired from PET scan, may have a role of predicting survival outcomes for patients with stage III NSCLC. However, most of the regarding reports to date included few patients with stage III disease [7–10, 16]. A recent meta-analysis of 36 studies comprising of 5807 patients concluded that high values of SUV_{max} predicted a higher risk of recurrence or death in patients with surgical NSCLC [7]. The study allowed for the inclusion of only <5% stage IIIB and IV tumors. Another meta-analysis by Na et al. [17] evaluated the relation of pre- and post-RT primary tumor SUV_{max} with the outcome of patients with NSCLC treated with RT. Patients with high levels of both pre- and post-RT SUV_{max} seemed to have poorer outcome in terms of OS and local control. Although the meta-analysis comprised of studies including patients with stage III NSCLC, the authors reported as a potential weakness that most of the data were derived from patients with stage I NSCLC. Additionally, as the relevant patients with stage III NSCLC were treated with only RT, most of them might have had more limited disease or comorbidity precluding the chemotherapy utilization. However, our study involves patients all of whom were treated with combination of chemotherapy and RT, and to our knowledge is the first one providing more in-depth research exclusively into this disease subset receiving concurrent chemoradiotherapy.

Several methods across the studies identify the cut-point for primary tumor SUV_{max}, some of which are finding the median SUV_{max} of the study sample, using receiver-operating characteristic curve analysis, referring to the validation results from another article, and estimating by log-rank test [17]. We used the median SUV_{max} of the study sample and chose SUV_{max} ≥14 as defining patients with poor prognosis. Similarly, in their retrospective analysis, Nair et al. [18] reported that SUV_{max} of 7, the median value, was the cut-off for identifying high-risk disease. Tumors with SUV_{max} >7 were associated with worse regional recurrence-free and distant metastasis-free survival. However, they collected T1-T2/N0 tumors that were treated with conventional or stereotactic curative RT; this might be the possible explanation of the lower median SUV_{max} compared to our study. Similarly, Vansteenkiste et al, [19] concluded that cut-off SUV of 7 had the best discriminative value and greater than 7 was correlated with poor survival. But again, they analyzed the follow-up of patients with stage I–IIIB NSCLC, about two-thirds of whom underwent complete resection, demonstrating a more favorable population than those in our study.

Our study has some limitations. First is the possible selection bias due to the retrospective design. The second is that other potential prognostic measures derived from PET scan like MTV and TLG were not collected in this population. The last is the relatively small sample size.

In conclusion, the results of our retrospective study involving patients with stage III NSCLC receiving concurrent chemoradiotherapy suggest that high values of pretreatment SUV_{max}, an indicator of metabolic tumor burden, predicted a higher risk of death. Shorter PFS was also seen in patients who had high baseline SUV_{max} levels. The patients with stage III NSCLC should be

stratified based on this feature to identify subsets that might benefit from different treatment approaches.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Authorship Contributions: Concept – GY, CG; Design – GY, CG; Supervision – MO, OS; Materials – GY, CG, MO; Data collection and/or processing – GY, CG, MO, OS.; Analysis and/or interpretation – GY, MO; Writing – MO, GY; Critical review – GY.

REFERENCES

1. Silvestri GA, Gonzalez AV, Jantz MA, Margolis ML, Gould MK, Tanoue LT, et al. Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e211S–50S.
2. Pieterman RM, van Putten JW, Meuzelaar JJ, Mooyaart EL, Vaalburg W, Koëter GH, et al. Preoperative staging of non-small-cell lung cancer with positron-emission tomography. N Engl J Med 2000;343:254–61.
3. Fischer B, Lassen U, Mortensen J, Larsen S, Loft A, Bertelsen A, et al. Preoperative staging of lung cancer with combined PET-CT. N Engl J Med 2009;361:32–9. [CrossRef]
4. De Wever W, Stroobants S, Coolen J, Verschakelen JA. Integrated PET/CT in the staging of nonsmall cell lung cancer: technical aspects and clinical integration. Eur Respir J 2009;33:201–12. [CrossRef]
5. Dong M, Liu J, Sun X, Xing L. Prognositc significance of SUV_{max} on pretreatment 18 F-FDG PET/CT in early-stage non-small cell lung cancer treated with stereotactic body radiotherapy: A meta-analysis. J Med Imaging Radiat Oncol 2017;61:652–9. [CrossRef]
6. Kocher MR, Sharma A, Garrett-Mayer E, Ravenel JG. Pretreatment 18F-Fluorodeoxyglucose Positron Emission Tomography Standardized Uptake Values and Tumor Size in Medically Inoperable Nonsmall Cell Lung Cancer Is Prognostic of Overall 2-Year Survival After Stereotactic Body Radiation Therapy. J Comput Assist Tomogr 2018;42:146–50.
7. Liu J, Dong M, Sun X, Li W, Xing L, Yu J. Prognostic Value of 18F-FDG PET/CT in Surgical Non-Small Cell Lung Cancer: A Meta-Analysis. PLoS One 2016;11:e0146195. [CrossRef]
8. Konings R, van Gool MH, Bard MP, Zwijnenburg A, Titulaer BM, Aukema TS, et al. Prognostic value of pre-operative glucose-corrected maximum standardized uptake value in patients with non-small cell lung cancer after complete surgical resection and 5-year follow-up. Ann Nucl Med 2016;30:362–8. [CrossRef]
9. Billè A, Okiror L, Skanjeti A, Errico L, Arena V, Penna D, et al. The prognostic significance of maximum standardized uptake value of primary tumor in surgically treated non-small-cell lung cancer patients: analysis of 413 cases. Clin Lung Cancer 2013;14:149–56. [CrossRef]
10. Downey RJ, Akhurst T, Gonen M, Vincent A, Bains MS, Larson S, et al. Preoperative F-18 fluorodeoxyglucose-positron emission tomography maximal standardized uptake value predicts survival after lung cancer resection. J Clin Oncol 2004;22:3255–60. [CrossRef]
11. Aupérin A, Le Péchoux C, Rolland E, Curran WJ, Furuse K, Fournel P, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol 2010;28:2181–90. [CrossRef]
12. Le Chevalier T, Arriagada R, Quoix E, Ruffie P, Martin M, Tarayre M, et al. Radiotherapy alone versus combined chemotherapy and radiotherapy in nonresectable non-small-cell lung cancer: first analysis of a randomized trial in 353 patients. J Natl Cancer Inst 1991;83:417–23.
13. Dillman RO, Herndon J, Seagren SL, Eaton WL Jr, Green MR. Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. J Natl Cancer Inst 1996;88:1210–5. [CrossRef]
14. Curran WJ Jr, Paulus R, Langer CJ, Komaki R, Lee JS, Hauser S, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. J Natl Cancer Inst 2011;103:1452–60. [CrossRef]
15. Finkelstein DM, Ettinger DS, Ruckdeschel JC. Long-term survivors in metastatic non-small-cell lung cancer: an Eastern Cooperative Oncology Group Study. J Clin Oncol 1986;4:702–9. [CrossRef]
16. Wang XY, Zhao YF, Liu Y, Yang YK, Wu N. Prognostic value of metabolic variables of [18F]FDG PET/CT in surgically resected stage I lung adenocarcinoma. Medicine (Baltimore) 2017;96:e7941. [CrossRef]
17. Na F, Wang J, Li C, Deng L, Xue J, Lu Y. Primary tumor standardized uptake value measured on F18-Fluorodeoxyglucose positron emission tomography is of prediction value for survival and local control in non-small-cell lung cancer receiving radiotherapy: meta-analysis. J Thorac Oncol 2014;9:834–42. [CrossRef]
18. Nair VJ, MacRae R, Sirisegaram A, Pantarotto JR. Pretreatment [18F]-fluoro-2-deoxy-glucose positron emission tomography maximum standardized uptake value as predictor of distant metastasis in early-stage non-small cell lung cancer treated with definitive radiation therapy: rethinking the role of positron emission tomography in personalizing treatment based on risk status. Int J Radiat Oncol Biol Phys 2014;88:312–8. [CrossRef]
19. Vansteenkiste JF, Stroobants SG, Dupont PJ, De Leyn PR, Verbeken EK, Deneffe GJ, et al. Prognostic importance of the standardized uptake value on (18)F-fluoro-2-deoxy-glucose-positron emission tomography scan in non-small-cell lung cancer: An analysis of 125 cases. Leuven Lung Cancer Group. J Clin Oncol 1999;17:3201–6. [CrossRef]