Is There Any Prognostic Significance of the Level of Change in SUVmax after SBRT in Patients with Early Stage NSCLC?

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ABSTRACT

We aimed to evaluate the prognostic significance of the level of change in SUVmax (ΔSUVmax) on pre and post-treatment PET/CT in early stage non-small cell lung cancer (esNSCLC) patients treated with stereotactic body radiotherapy (SBRT). Between November 2009-February 2018, pathologically proven esNSCLC patients (T1-2N0M0) treated with CyberKnife as primary treatment alone and who had pre and post-treatment PET/CT were retrospectively identified. The ΔSUVmax was calculated using formula ΔSUVmax= (PreSBRT SUVmax- PostSBRT SUVmax) / (PreSBRT SUVmax). A total of 48 patients were identified. All patients had biopsy-confirmed NSCLC. Median dose was 45 Gy / 3 fr (range: 45-60 Gy / 3-5 fr). According to EORTC metabolic response criteria at 12-16 weeks after SBRT, 8 (16.7%) patients achieved complete response, 35 (72.9%) patients achieved partial response. AUC was calculated as 0.62 for cutoff ΔSUVmax. Median PFS was 15 (range: 6-54) vs 59 (range: 10-92) months (p= 0.012) and median OS was 36 (range: 10-75) vs 70 (range: 23-92) months (p= 0.045) in patients with ΔSUVmax < 0.62 and ≥ 0.62, respectively. In both univariate and multivariate analysis, the lower ΔSUVmax (as both dichotomous and continuous variable) was determined as a negative prognostic factor on PFS and it has been showed that the lower ΔSUVmax (only as a dichotomous variable) is a negative prognostic factor on OS in multivariate analysis. In conclusion, in esNSCLC patients who were treated with SBRT, a ΔSUVmax higher than 0.62 demonstrates better PFS and OS.

Keywords: Stereotactic body radiotherapy (SBRT), Early stage non-small cell lung cancer, SUVmax, Positron Emission Tomography/Computed Tomography (PET/CT)

ÖZET

Erken Evre Akciğer Kanserli Hastalarda SBRT Sonrası SUVmax Değişiminin Prognostik Önemi Varmı?

Stereotaktik vücut radyoterapisi (SBRT) ile tedavi edilen erken evre küçük hücre dışı akciğer kanseri (esNSCLC) hastalarında tedavi öncesi ve sonrası PET / BT'deki SUVmax'taki değişim seviyesinin prognostik önemini değerlendirmeyi amaçladık. Kasım 2009-Şubat 2018 arasında patolojik olarak ispatlanmış esNSCLC (T1-2N0M0) nedeniyle CyberKnife ile tedavi edilen, tedavi öncesi ve sonrasında PET / CT'si olan hastalar geriye dönük olarak değerlendirildi. ΔSUVmax, ΔSUVmax= (PreSBRT SUVmax - PostSBRT SUVmax) / (PreSBRT SUVmax) formülü kullanılarak hesaplandı. Toplam 48 hasta dahil edildi.Tüm hastalarda biyopsi ile onaylanmış KHDAK tanısı mevcuttu. Ortanca doz 45 Gy / 3 fr (range: 45-60 Gy / 3-5 fr) idi. SBRT'den 12-16 hafta sonra EORTC metabolik cevap kriterlerine göre, 8 (%16.7) hastada tam yanıt, 35 (% 72.9) hastada kısmi yanıt elde edildi. AUC ile ΔSUVmax cutoff değeri 0.62 olarak hesaplandı.

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ΔSUVmax < 0.62 ve ΔSUVmax ≥ 0.62 olan hastalarda sırasıyla ortanca PFS 15 ay'a (range: 6-54), 59 ay (range: 10-92) (p= 0.012) iken,ortanca OS 36 ay'a (range: 10-75),70 ay (range: 23-92) (p= 0.045) idi. Hem tek değişkenli hem de çok değişkenli analizlerde, düşük ΔSUVmax (hem ikatagorik hem de sürekli değişken olarak) değeri, PFS üzerinde negatif bir prognostik faktör olarak belirlenmişken, çok değişkenli analizde düşük ΔSUVmax (sadece katagorik değişken olarak) değerinin OS üzerinde negatif prognostik faktör olduğu gösterilmiştir.Sonuç olarak, SBRT ile tedavi edilen esNSCLC hastalarda, 0.62'den yüksek bir ΔSUVmax daha iyi PFS ve OS gösterir.
Anahtar Kelimeler: Stereotaktik beden radyoterapisi, Erken evre küçük hücre dışı akciğer kanseri, Suvmax, Pozitron emisyon tomografisi/Bilgisayarlı Tomografi (PET/BT)

INTRODUCTION

Stereotactic body radiotherapy (SBRT) is a rising innovation that is profoundly effective and precise radiation beams are utilized to convey high dosages in one to five fractions to tumor targets.[1] Over the past years, SBRT has been utilized progressively in early-stage non-small cell lung carcinoma (esNSCLC) patients. SBRT is a powerful and alternative treatment to surgery for patients with esNSCLC and is accepted as a standard treatment for esNSCLC patients who are not qualified for surgery.[2,3] 3-year survival and local control rate has been reported as 55.8% and 90.6% as a result of prospective RTOG 0236 study.[3] Additionally, it has been shown that the 5-year in overall survival (OS) for SBRT (42%) was significantly better as than that for 3D conformal radiotherapy (CRT) (20%) in patients with medically inoperable stage I esNSCLC.[4] In view of the result of a retrospective and two randomized studies, it has been suggested that SBRT could be a suitable alternative for patients with operable esNSCLC.[5,6]

It is recognized that positron-emission tomography / computed tomography (PET/CT), which is a metabolic imaging procedure, demonstrates treatment response at an earlier time than conventional anatomic imaging strategies.[7] Morphological imaging strategies have limitations such as about separation between residual tumor and necrotic or fibrotic scar tissue.[8] Eschmann et al. has reported the sensitivity, specificity and accuracy of PET/CT in identifying residual tumor as 95%, 80% and 91%, respectively. In addition, a longer survival has been reported in patients with metabolic complete response or reduction over 80% in SUVmax compared with those who showed partial metabolic response.[9]

^{18}F-Fludeoxyglucose (FDG) uptake in PET/CT can give extra information about tumor's biological characteristics and it might be a useful biomarker to identifying high risk esNSCLC patients for disease progression.[10] The predictive impact of PET/CT for assessment of response after SBRT in patients with NSCLC has been investigated in trials and it has been observed that metabolic changes in tumor occurring at 12 weeks after SBRT are extremely significant.[11] Also, PET/CT in various timings after SBRT has been studied and in these trials the correlation between tumor response / prognosis and various parameters which are acquired from pre and post-treatment PET/CT in esNSCLC patients who were treated with SBRT has been investigated.[12-17] In our study, we aimed to assess the prognostic significance of the level of change in maximum standard uptake value (ΔSUVmax) between pre and post SBRT in esNSCLC patients. For this aim, here, we tried to identify a ΔSUVmax cutoff value to predict more aggressive disease in patients with esNSCLC which is a potentially curable disease with SBRT.

PATIENTS AND METHODS

Patients

After excluding patients who do not have PET/CT at 3rd month after SBRT, we retrospectively identified 48 of 66 patients with pathologically proven esNSCLC (T1-2N0M0) who were treated with SBRT using CyberKnife as primary treatment alone between November 2009 and February 2018. Patients who did not fulfill have one of these the following criteria were excluded from this study; (1) histologically confirmed NSCLC; (2) T1 or T2/N0 lung cancer on pretreatment staging; (3) SBRT treatment as curative intent; (4) pretreatment PET/CT scan; (5) posttreatment PET/CT scan. This

study was started after the approval was obtained of the ethics committee of the authors' institution.

Radiotherapy Technique and Specifications

All patients in the study were treated with the CyberKnife Robotic Radiosurgery System (Accuray, Inc, Sunnyvale, CA). Immobilization was achieved with vacuum couch in supine position. Simulation CT (GE Healthcare, Waukesha, WI, USA) was performed using 1.25-mm thick slices by administering intravenous contrast material. All lesions were treated with median 45 Gy / 3 fr (range: 45-60 Gy / 3-5 fr) every other day. To select the optimal treatment plan, dose-volume histograms were calculated for the target and critical structures. Median reference isodose of the prescription dose to the PTV was 87% (range: 70%-92%). Lower PTV coverage with most appropriate plan was accepted if surrounding organs-at-risk were deemed to be at excess risk for toxicity. We calculated the Biologically Equivalent Dose (BED) for tumor in all patients according to the linear-quadratic formulation (tumor α/β= 10). Three image guidance systems (the XSight Spine Tracking System, the Synchrony Respiratory Motion Tracking System, and the Fiducial Tracking System) onboard the CyberKnife platform was used. The motion correlation between the external infrared emitters and internal fiducial markers updated periodically during treatment.

Table 1. Clinicopathological characteristics

	Level of Change in SUVmax		p
	< 0.62 n (%)	≥ 0.62 n (%)	
Gender			
Female	2 (6.5)	2 (11.8)	NSD
Male	29 (93.5)	15 (88.2)	
Age at diagnosis (years)			
Median	67	67	NSD
Range	54-84	56-82	
KPS			
Median	90	80	
Range	60-100	60-90	NSD
< 80	4 (12.9)	6 (35.3)	
≥ 80	27 (87.1)	11 (64.7)	
Tumor Size (mm)			
Median	27	20	NSD
Range	15-43	11-45	
T stage			
T1	21 (67.7)	13 (76.5)	NSD
T2	10 (32.3)	4 (23.5)	
NSCLC histology			
Squamous	13 (41.9)	9 (52.9)	NSD
Adenocarcinoma	8 (25.8)	5 (29.4)	
Other/unidentified	10 (32.3)	3 (17.6)	

KPS= Karnofsky Performance Score, NSCLC= Non-small cell lung cancer, NSD= No Significant Difference

Analysis of 18F-Fluorodeoxyglucose PET

All patients had pretreatment PET/CT in 3 weeks before SBRT and post treatment PET/CT at 12-16 weeks after SBRT. The level of change in SUVmax (ΔSUVmax) was also calculated from pre and post treatment PET/CT by using formula ΔSUVmax= (PostSBRT SUVmax- PreSBRT SUVmax) / (PreSBRT SUVmax). ΔSUVmax= (PreSBRT SUVmax-PostSBRT SUVmax) / (PreSBRT SUVmax)

Statistical Analysis

Continuous variables were analyzed with Kruskal-Wallis tests or Mann Whitney-U tests. Categorical variables were analyzed with Pearson chi-square or Fisher exact tests. We used a receiver operating characteristic (ROC) curves to determine an appropriate cut-off value for the ΔSUVmax to predict OS and PFS, which was above and below cut-off value. Patients were divided into two groups according with this result. Kaplan Meier method was applied to estimate the survival data and it was compared by use of the Mantel-Cox log-rank test. It has been determined by Cox proportional hazards regression whether ΔSUVmax, age, KPS, gender, T stage, PTV volume, tumor histology, BED10 influenced outcomes. Progression free survival (PFS) was defined as the time from biopsy to any of first event such as local, regional and/or distant relapse or death from any cause. The overall survival (OS) was defined as the time from dates of diagnosis biopsy until death from any cause. SPSS

Table 2. Treatment characteristics

	Level of Change in SUVmax		p
	<0.62 n (%)	≥0.62 n (%)	
PTV volume (cc)			
Median	41.86	36.01	NSD
Range	11.95-85.14	14.59-91.35	
Reference Isodose line			
Median	87	86	NSD
Range	70-92	70-91	
SBRT dose (Gy) / fr			
Median	45 / 3	45 / 3	
Range	45 - 60 / 3 - 5	45-60 / 3-5	NSD
BED10 (Gy)			
Median	112.5	112.5	NSD
Range	100 - 180	100-151	
Tumor-tracking system			
X-Sight Lung	25 (80.6)	14 (82.4)	NSD
X-Sight Spine	3 (9.7)	1 (5.9)	
Gold Fiducial	3 (9.7)	2 (11.8)	

PTV = Planning Target Volume, SBRT = Stereotactic body radiotherapy, BED = Biologically equivalent dose, NSD = No Significant Difference

Table 3. Patients' progress

	Level of Change in SUVmax		p
	<0.62 n (%)	≥0.62 n (%)	
Local Failure			
Yes	12 (38.7)	4 (23.5)	0.04
No	19 (61.3)	13 (76.5)	
Regional Failure			
Yes	9 (29.0)	2 (11.8)	0.02
No	22 (71.0)	15 (88.2)	
Distant Failure			
Yes	14 (45.2)	2 (11.8)	0.02
No	17 (54.9)	15 (88.2)	
Last Situation			
Alive	16 (51.6)	13 (76.5)	0.04
Exitus	15 (48.4)	4 (23.5)	

software (version 21.0; SPSS Inc., Armonk, NY, USA) was used to perform all statistical analyses. p values < 0.05 were considered statistically significant.

RESULTS

Patient characteristics

Analysisized of all patients in the present study and their clinicopathological and treatment characteristics are presented in Table 1 and 2. A total of 48 patients with median age of 67 (range: 54-84) years old were identified between November 2009 and February 2018. All patients had biopsy-confirmed NSCLC, with 22 (45.8%) having squamous cell carcinoma and 13 (27.1%) having adenocarcinoma. The median tumor size was 26 mm (range: 11-45). According to the AJCC 7th edition, tumor T-stage distribution was as follows; T1: 34 (70.8%), T2: 14 (29.2%).

Metabolic Response

The median pretreatment SUVmax was 11.37 (range: 3.30-26.00). All patients had at least one PET/CT scan in follow-up. At the first PET-CT scan after SBRT according to EORTC criteria for metabolic response, 8 (16.7%) patients achieved complete responses, 35 (72.9%) patients achieved partial response, 3 (6.3%) patients had stable disease, and 2 (4.2%) patients had progressive disease. The median posttreatment SUVmax was 4.30 (range: 1.0-14.30).

Findings on the ΔSUVmax Values Between Pre-post SBRT PET/CT Scans

As a result of ROC curve analysis, cutoff ΔSUVmax was calculated 0.62 with maximum sensitivity and specificity (sensitivity 79%, specificity 45%). Median ΔSUVmax was 0.56 maximum ΔSUVmax was 0.94 in favor of regression, and maximum ΔSUVmax was 0.34 in favor of progression. Metabolic complete or partial response assessed by the EORTC criteria was 90% at 12-16, weeks. In 7 of 8 patients with complete response after SBRT ΔSUVmax was > 0.62 and in 2 patients with progression ΔSUVmax was ≤ 0.62.

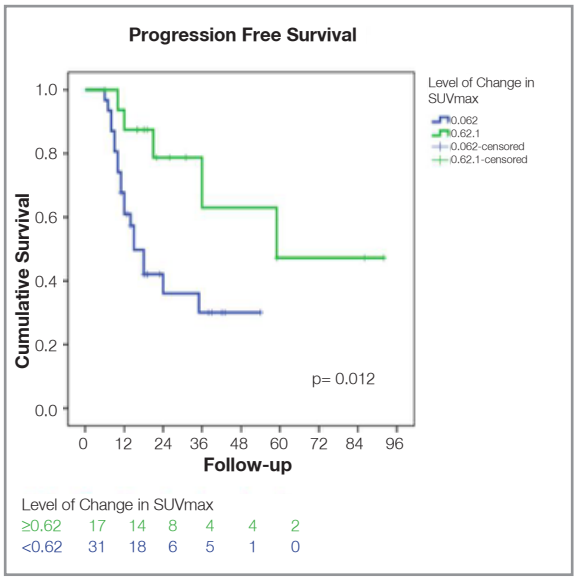

Figure 1. Progression free survival stratified by ΔSUVmax below and above 0.62

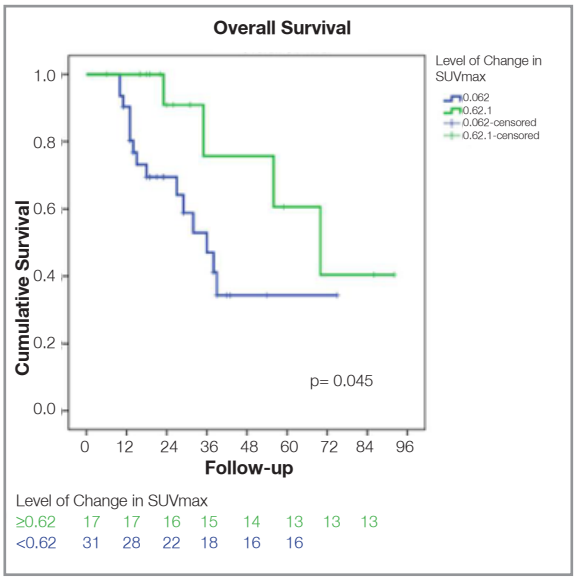

Figure 2. Overall survival stratified by ΔSUVmax below and above 0.62

Clinical Outcomes

Median follow-up was 23 (range: 6-92) months and in this period local, regional and distant relapse were developed after SBRT in 16 (33.3%), 11 (22.9%), and 16 (33.3%) patients, respectively. Twenty nine (60.4%) patients were alive at the time of analysis (Table 3).

In patients with ΔSUVmax < 0.62, median PFS was 15 (range: 6-54) months and 1-, 3- year PFS rates were 61%, 30%, respectively. In patients with ΔSUVmax ≥ 0.62, median PFS was 59 (range: 10-92) months and 1-, 3- year PFS rates were 87%, 63%, respectively (p= 0.012) (Figure 1). In patients with ΔSUVmax < 0.62, median OS was 36 (range: 10-75) months and OS rates for 1, 3 and 5 year were 90.3%, 47% and 34%, respectively. In patients with ΔSUVmax ≥ 0.62, median OS was 70 (range: 23-92) months and OS rates for 1, 3 and 5 year were 90.9%, 75% and 60%, respectively (p= 0.045) (Figure 2). In univariate analysis, sex, age, KPS, tumor histology, T stage, PTV volume, and BED10 was not significantly associated with and both PFS, and OS. In both univariate and multivariate analysis, the lower ΔSUVmax level (as both dichotomous and continuous variable) was determined as a negative prognostic factor on PFS. In

Table 4. Univariate and multivariate Cox proportional hazards regression analysis

	Univariate Cox proportional hazards regression analysis			
	ΔSUVmax (<0.62 vs ≥0.62)		**ΔSUVmax (Continuous)**	
	HR (95% CI)	**p**	**HR (95% CI)**	**p**
Progression free survival	3.6 (1.22-10.6)	0.02	6.89 (1,95-24.31)	**0.003**
Overall survival	3.1 (0.98-9.83)	0.55	3.04 (0.74-13.13)	0.14
	Multivariate Cox proportional hazards regression analysis			
Progression free survival	4.06 (1.35-12.23)	0.013	6.86 (1,96-23.87)	**0.003**
Overall survival	3.1 (0.98-9.82)	0.05	2.26 (0.49-10.45)	0.3

addition to this, in multivariate analysis it has been showed that the lower ΔSUVmax level (only as a dichotomous variable) is a negative prognostic factor on OS (Table 4).

DISCUSSION

Inflammatory reactions after radiotherapy may cause false positive assessments in PET/CT images in the first 6-12 weeks and for this reason it is recommended to perform the PET/CT at the earliest 2-3 months after radiotherapy. The value of PET/CT for predicting treatment outcomes and prognosis in esNSCLC patients treated with SBRT has been investigated in several studies. In these studies SUVmax is the most frequently tested vigorous and reproducible parameter. However SUV is adjusted according to body weight and it is not independent of body mass and size. As body mass index and body weight increase, the level of SUV in the blood and normal tissues also increases. So, ideal body weight, lean body mass or body surface area values are used instead of body mass in SUV calculation.[18] Because of SUVmax only gives information for a point of voxel (volumetric pixel) within the tumor and does not fully reflect tumor size and heterogeneity, some of studies showed pretreatment SUVmax to be a prognostic factor, while some did not do so.[10,19-21] It has been reported that SUVmax was a predictor for survival and intensive treatment regimens may improve outcomes in patients with high SUVmax.[10] Nair et al., and others reported conflicting results regarding the idea that various cut off levels of SUVmax on PET/CT were associated with poor results in patients with esNSCLC managed with radiation alone.[19,22-24] For this reason, it has been followed by studies involving volume based parameters (VBP) such as metabolic tumor volume (MTV) and total glycolysis (TLG).[25] Contradictory results on this subject have been reported in a few studies. For example, Vu et al. could not show any correlation between SUVmax, but Satoh et al. showed that SUVmax, MTV and TLG were significantly associated with DFS.[26,27] Although there are some advantages of VBP in measuring the metabolic response, there is still controversy about the most appropriate method to measure MTV and TLG.[28] In addition, it was reported that treatment response and PFS, OS could be evaluated by TLG as early earliest at as the 2nd week after the beginning of treatment in patients with locally advanced NSCLC.[29,30]

In a meta-analysis of 9 studies involving 1166 patients with stage I NSCLC who were treated with curative surgery, the median overall survival in the high FDG uptake group was 70% (range: 17-87%) compared with 88% (range: 74-100%) in the low FDG uptake groups.[31] In another meta-analysis, it has been revealed that the SUVmax value of the primary tumor was positively correlated with the prognosis in heterogeneous NSCLC patient groups.[32] Dong et al., demonstrated correlations between pre-treatment SUVmax with the OS, local control and distant metastases. But this analysis identified significant heterogeneity in the methods of studies such as SBRT dose and fractionations, scanner of PET, cut-off level for SUV value and softwware.[33] Changes in FDG uptake during and after SBRT has been observed by Wiegman et al. and they reported that PET/CT during SBRT could not predict the outcomes of treatment.[34] Henderson et al. also did not support using of routine PET/CT imaging for follow-up after SBRT in patients with stage I NSCLC.[15] However, post-treatment tumor FDG uptake has been demonstrated as an important prognostic factor in locally advanced NSCLC patients treated with concurrent chemoradiotherapy in a large prospective trial.[35] A significant correlation between post-SBRT tumor SUVmax and distant failure in patients with medically inoperable esNSCLC has been showed in only one study in the literature. In this study, it has been reported that 2 and higher value of post-SBRT SUVmax and lower than 2.55 reduction SUVmax after SBRT is associated with a higher risk of distant failure.[36] At the same time, Bollineni et al. reported that FDG uptake on PET/CT at 12 weeks after SBRT could predict local control for stage I NSCLC.[17]

Due to the inadequacy of SUVmax use alone and the difficulties in measuring and evaluating the volumetric parameters, in present study, we investigated the prognostic significance of ΔSUVmax which is an easily calculated and evaluated parameter. As a result of our analysis we can suggest that the PFS and OS are better in esNSCLC patients with ΔSUVmax higher than 0.62 after SBRT. In the literature, there are various studies involving

NSCLC patients at with in different stages. As mentioned above, Clarke et al., showed that reduction of < 2.55 in SUVmax after SBRT is associated with a higher risk of distant failure. However, this negative effect has not been reflected in survival.[36] Pöttgen et al., in their study involving 50 patients with locally advanced NSCLC, assessed treatment response as regularly by PET/CT in patients treated with 3 cycles of induction chemotherapy followed by chemoradiotherapy. After the treatment response evaluation, 37 patients were accepted as resectable and the surgery was performed, it was reported that 45-62% declines in SUVmax on PET/CT after completion of treatment correlated with histopathologic response.[37] Cerfolio et al. in their study involving 56 patients showed that 80% or more reduction and complete response in SUVmax after neoadjuvant chemotherapy is associated with complete response independently of cell type.[38] Similarly, Vansteenkiste et al. showed that 50% reduction in SUVmax after induction chemotherapy was associated with better survival in studies involving patients with locally advanced NSCLC.[39]

CONCLUSION

Although, there are some limitations of this study including short follow-up time, small sample size and retrospective design, we demonstrated that ΔSUVmax is a prognostic factor in esNSCLC patients who were treated with SBRT and patients with ΔSUVmax higher than 0.62 have better PFS and OS.

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