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Original Article

Semi-quantitative investigation of primary tumor and bone metastasis in lung cancer patients using the PET-CT approach

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Abstract: Background: Although advanced diagnostic and therapeutic development are achieved, lung cancer is the most leading cause of death. The stage of tumor is still the most important factor in determining the prognosis of cancer. Purpose: The overarching goal of this study is to understand the relationship between the maximum standard uptake value (SUVmax) and bone metastasis using the PET-CT approach in lung cancer prognosis and survival research. Materials and methods: The PET-CT analyses of previously diagnosed totally 86 lung cancer patients were retrospectively studied. Primer tumor standard uptake values for each patient were meticulously calculated and correlated with bone metastasis. Results: The demographics of the 86 patients is as follows; 79 man, 7 women with an age average of 59.44 ± 5.99, youngest being 46 and oldest 72. The number of small cell (SCC) and non-small cell lung cancer (NSCLC) patients were 10 (11.6%) and 76 (88.4%), respectively. Additionally, bone metastasis was detected in 35 (40.7%) patients. The patients were divided in 4 categories based on the observed primer tumor sizes of 0-3 cm (23.3%), 3-5 cm (27.9%), 5-7 cm (32.6%), and larger than 7 cm (16.3%). Patients with bone metastasis (35 in total) were divided in 2 categories based on the number of metastasis of being less than 3 (45.7%) and more than 3 (54.5%). We also used SUVmax values to clarify the study. 31.4% of the total patients had the SUVmax value lower than 10 and 68.6% of them had higher. 68.6% of the bone metastasis patients had SUV values lower than 8 and 31.4% of them had higher than 8. Conclusion: The present study suggests a 27.2% positive relationship in primary tumor SUVmax value and tumor size. Although the average bone metastasis SUV with primary tumor SUV values higher than 10 is higher than the ones lower than 10, this difference did not generate a statistically significant data for cancer patients.

Keywords: Bone metastasis, fluoro-2-deoxy-D-glucose positron emission tomography, lung cancer, standard uptake value

Introduction

Lung cancer still remains the cause of the highest death rate despite the remarkable improvements in diagnosis. After diagnosis of the disease, the average 5 year survival rate is reported to be 5-10%. Since it is virtually impossible to detect cancerous activity at the early stages, the diagnosis is only viable in later stages. As one can expect a successful surgical effort requires early diagnosis [1-3].

An important portion (40%) of the diagnosed lung cancer patients develops distant organ metastasis in thorax, brain, adrenal glands, liver, bone, kidneys and abdominal lymph nodes [4, 5]. The late stage diagnosis is the biggest reason for high mortality rate of lung cancer [6].

The stage of the tumor is vital to determine the prognosis of the lung cancer patients. A differentiation system developed by the International Association of Lung Cancer is used to describe the stages of disease. Availability of a distant metastasis (M) around lymph nodes (N) of a primary tumor is used for differentiation [7]. Bronchoscopy, transbronchial needle aspiration, mediastinoscopy, thoracotomy, open lung

Table 1. General properties of patients

		N	%
Primary Tumor SUVmax	≤ 10	27	31.4
	> 10	59	68.6
Tumor Size (cm)	0-3 cm	20	23.3
	3-5 cm	24	27.9
	5-7 cm	28	32.6
	> 7 cm	14	16.3
Pathology	Small Cell	10	11.6
	Non-Small Cell	76	88.4
Bone metastasis	Positive	35	40.7
	Negative	51	59.3
The number of Bone metastasis (n = 35)	≤ 3	16	45.7
	> 3	19	54.3
Bone metastasis SUV (n = 35)	≤ 8	24	68.6
	> 8	11	31.4

cm: centimeter, SUV: Standard Uptake Value.

Table 2. The correlation between primary tumor size and primary tumor maximum uptake value

All Patients	Primary Tumor Maximum Standard Uptake Value/ Primary Tumor Size
R	0.272
p	0.011*

*p < 0.05, SUV: Standard Uptake Value. Pearson Correlation Analysis.

biopsy, sputum cytology, direct lung radiographs, computerized tomography (CT), positron emission tomography (PET) and magnetic resonance imaging (MRI) are the most common techniques to diagnose lung cancer.

Over the last two decades, PET technology has become an important tool for oncological imaging mostly because of its strength in differentiating biochemical and metabolic activity. PET/CT hybrid is an imaging technique developed by combining PET and CT instruments. CT provides information for anatomic details and PET monitors the glucose usage of pathological and normal tissues via previously injected radiopharmaceutical agent [8]. Above 500 radiopharmaceutical agents responsible for different functional pathways are identified for PET usage. Among them, Fluor (F)-18 tagged fluorodeoxyglucose (FDG) stands out mostly because of its easy synthesis and high clinical efficiency in tissue glucose usage. Recent improvements in PET/CT hybrid imaging technique made the metabolic and morphological evaluation possible in clinical applications. The advantages features of this characterization technique offer in-situ correlation of anatomic data, functional and metabolic activities.

Compared to conventional imaging approaches for cancer tissue development, positron emission tomography provides up to 30% changes in treatment planning [9-11]. In the terminology of PET/CT analysis, FDG retention time in lesion is called Standard Uptake Value (SUV). SUV is a semi-quantitative parameter in lesion characterization and prognosis evaluation.

Herein we report the relationship between primary tumor SUV and bone metastasis in lung cancer prognosis and survival determination using PET-CT hybrid characterization.

Materials and methods

Patient selection

Our patient selection criteria; Patients with bone metastasis, lymph nodes metastasis, distant organ metastasis, primer tumor (determined by PET-CT) or previously lung cancer diagnosed patients. Patients with blood sugar level higher than 160 mg/dl, lung cancer related surgery, and previously lung cancer diagnosed patients, and patients who exposed to chemotherapy and/or radiotherapy were excluded from the scope of this study.

Imaging

The PET-CT imaging experiments were performed using PET-CT equipment manufactured by G.E. Discovery STE. Each patient was fasting for 4 hours prior to imaging. 296-555 MBq (8-15 mCi) FDG was injected intravenously to the patients with glucose values lower than 160 mg/ml. Each patient was advised to stay idle for 45 to 60 minutes to accurately monitor the radiopharmaceutical agent bio-dispersion and ideal tumor retention. Subsequent to bladder drainage, each patient was positioned onto supine on a PET-CT monitoring bed. Three dimensional emission and transmission screening of vertex were completed through thigh using the integrated PET-CT camera. All the

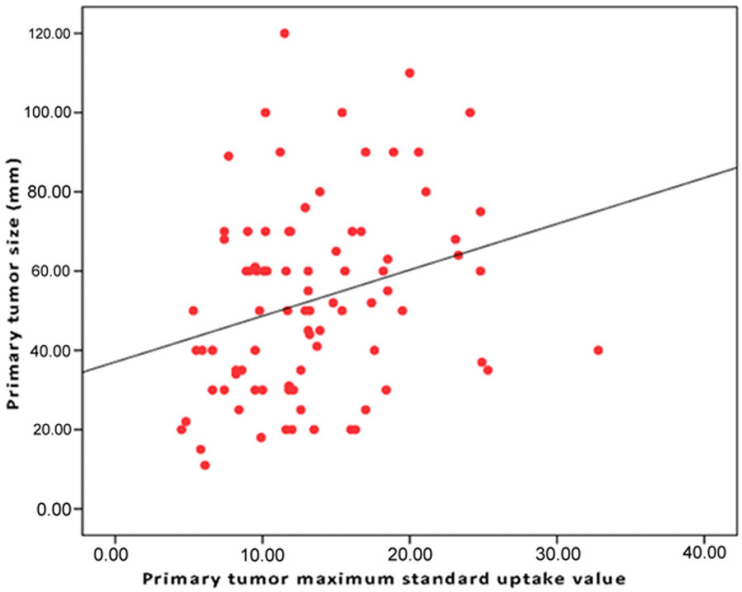

Figure 1. The relationship between the tumor size and primary tumor maximum standard uptake value.

Table 3. The evaluation of average bone standard uptake values based on primary tumor maximum standard uptake values

Patients with bone metastasis	Primary Tumor SUVmax		*p
	≤ 10	> 10	
	Average ± SD	Average ± SD	
The number of bone metastasis	4.30 ± 2.72	5.27 ± 5.23	0.543
The average bone metastasis SUV	6.45 ± 1.87	8.42 ± 4.05	0.060

*Student t test. *SUV: Standard Uptake Value.

imaging activity was completed in 30 minutes with average 7-8 bed positions. The scope of the monitored regions covered axial, coronal and sagittal plans and 0.6 cm thick sequential cross-section were prepared. The abnormal FDG deposits were evaluated with SUV calculation. Standard retention value was automatically calculated using the following equation: Standard retention value = tissue concentration in interested region (mCi/ml)/total injected dosage (mCi)/body weight (kg).

The standard uptake values were calculated using ROI imaging. Primer tumor size, primer tumor SUV and metastasis SUV were detected.

Image analysis

This study covers the following; 1- The correlation between the primer tumor length, the number of bone metastasis and average bone SUV. 2- The correlation between the primer tumor and the primer tumor SUV. 3- The SUV difference between the non-small cell and the small cell lung cancer patients. 4- The difference between average SUV (especially the ones with SUV values ≤ 10 or > 10) and the number of bone metastasis). 5- The correlation between the number of bone metastasis and primer tumor SUV. 6- The difference between the bone metastasis size (0-3 cm, 3-5 cm, 5-7 cm, > 7 cm) and the bone metastasis number. 7- The correlation between the average primer tumor SUV (especially the ones with SUV values ≤ 8 or > 8) and the number of bone metastasis. 8- The difference between the average primer tumor SUV (especially the ones with SUV values ≤ 3 or > 3) and the average bone metastasis SUV were studied.

Statistical analysis

The data was analyzed using the Number Cruncher Statistical System (NCSS) 2007 & PASS 2008 Statistical Software (Utah, USA). Quantitative average results ± standard deviation (SD) and categorical results were provided in numbers and the percentages. In addition to descriptive statistical methods (average, standard deviation), quantitative data comparison (One-Way ANOVA test) was used due to the suitability of normal distribution. Student-t test was used to compare the parameters in two groups. Pearson correlation analysis was used to investigate the relationship between parameters. All the significance tests were in both ways and $p < 0.05$ criteria was used for statistical significance.

Results

The demographics of the 86 patients is as follows; 79 man, 7 women with an age average of 59.44 ± 5.99, youngest being 46 and oldest 72. The number of small cell and non-small cell lung cancer patients were 10 (11.6%) and 76 (88.4%), respectively. Additionally, bone metastasis was detected in 35 (40.7%) patients. The patients were divided in 4 categories based on the observed primer tumor sizes of 0-3 cm

Table 4. The clinical characteristics of the patients

Patient No	Gender	Age	Primary Tumor SUVmax	Tumor Size (mm)	Bone metastasis account	Bone metastasis mean SUV max	Patient No	Gender	Age	Primary Tumor SUVmax	Tumor size (mm)	Bone metastasis account	Bone metastasis mean SUV max
1	E	63	12	20	1	8.6	44	E	59	8.6	35	0	(-)
2	E	66	10.2	100	15	8.1	45	E	56	5.8	15	0	(-)
3	E	64	18.2	60	1	4.8	46	E	52	13.1	45	0	(-)
4	E	63	10.3	60	8	5.9	47	E	54	17	25	0	(-)
5	K	72	9.8	50	7	7.3	48	E	56	11.8	31	0	(-)
6	E	70	6.6	30	6	6.5	49	E	61	7.7	89	0	(-)
7	E	70	13.5	20	2	4.1	50	E	55	10.1	60	0	(-)
8	E	64	16.1	70	1	10	51	E	58	13.9	80	0	(-)
9	E	64	4.8	22	6	7.5	52	K	59	20	110	0	(-)
10	E	63	24.9	37	2	5.5	53	E	58	23.3	64	0	(-)
11	E	66	7.4	68	4	6.9	54	E	59	12.9	50	0	(-)
12	E	63	25.3	35	4	16.1	55	E	56	10.1	60	0	(-)
13	K	53	10	30	6	7.1	56	K	58	16.7	70	0	(-)
14	E	61	19.5	50	10	10.5	57	E	57	5.5	40	0	(-)
15	E	57	16	20	10	13.5	58	E	52	15.6	60	0	(-)
16	E	53	9.9	18	2	5.8	59	E	53	18.4	30	0	(-)
17	E	53	13.7	41	21	6.8	60	E	60	24.1	100	0	(-)
18	E	54	12.6	35	4	11	61	E	50	13.2	50	0	(-)
19	E	54	12.1	30	2	6.1	62	E	46	20.6	90	0	(-)
20	E	56	13.1	60	1	18.6	63	E	50	16.3	20	0	(-)
21	E	58	15	65	3	7.1	64	K	63	14.8	52	0	(-)
22	E	59	18.9	90	9	12.1	65	E	63	13.9	45	0	(-)
23	E	59	15.4	100	5	5.4	66	E	62	15.4	50	0	(-)
24	E	61	7.4	70	9	5.4	67	K	71	23.1	68	0	(-)
25	E	58	24.8	60	1	3.1	68	E	63	5.9	40	0	(-)
26	E	59	10.2	70	5	6.2	69	E	65	17.4	52	0	(-)
27	E	57	8.2	34	1	3.5	70	E	70	5.3	50	0	(-)
28	E	58	9	70	1	6.8	71	E	62	6.1	11	0	(-)
29	E	51	11.6	60	1	11.5	72	K	67	4.5	20	0	(-)
30	E	51	11.8	30	8	4.8	73	E	62	12.9	76	0	(-)
31	E	51	7.4	30	1	4.1	74	E	63	18.5	55	0	(-)
32	E	48	11.9	70	2	5.5	75	E	68	18.5	63	0	(-)
33	E	48	6.6	40	4	7.1	76	E	66	24.8	75	0	(-)
34	E	49	9.5	61	7	11	77	E	69	9.5	30	0	(-)
35	E	51	9.6	60	2	4.9	78	E	62	9.5	40	0	(-)
36	E	59	13.1	55	0	(-)	79	E	67	21.1	80	0	(-)
37	E	56	11.7	50	0	(-)	80	E	67	17.6	40	0	(-)
38	E	58	8.9	60	0	(-)	81	E	64	17	90	0	(-)
39	E	58	8.2	35	0	(-)	82	E	63	32.8	40	0	(-)
40	E	60	11.8	70	0	(-)	83	E	68	11.2	90	0	(-)
41	E	58	13.2	44	0	(-)	84	E	63	11.6	20	0	(-)
42	E	55	8.4	25	0	(-)	85	E	66	11.5	120	0	(-)
43	E	54	12.6	25	0	(-)	86	E	64	9.1	60	0	(-)

(23.3%), 3-5 cm (27.9%), 5-7 cm (32.6%), and larger than 7 cm (16.3%). Patients with bone metastasis (35 in total) were divided in 2 categories based on the number of metastasis of being less than 3 (45.7%) and more than 3 (54.5%). We also used SUVmax values to clarify the study. 31.4% of the total patients had the SUVmax value lower than 10 and 68.6% of them had higher. 68.6% of the bone metastasis patients had SUV values lower than 8 and 31.4% of them had higher than 8 (**Table 1**).

Investigation of bone metastasis patients did not deliver a meaningful correlation in tumor size, bone metastasis SUV, primary tumor SUVmax. On the other hand, all the patients showed a statistically meaningful ($p < 0.05$) and positive (27.2%) relationship in primary

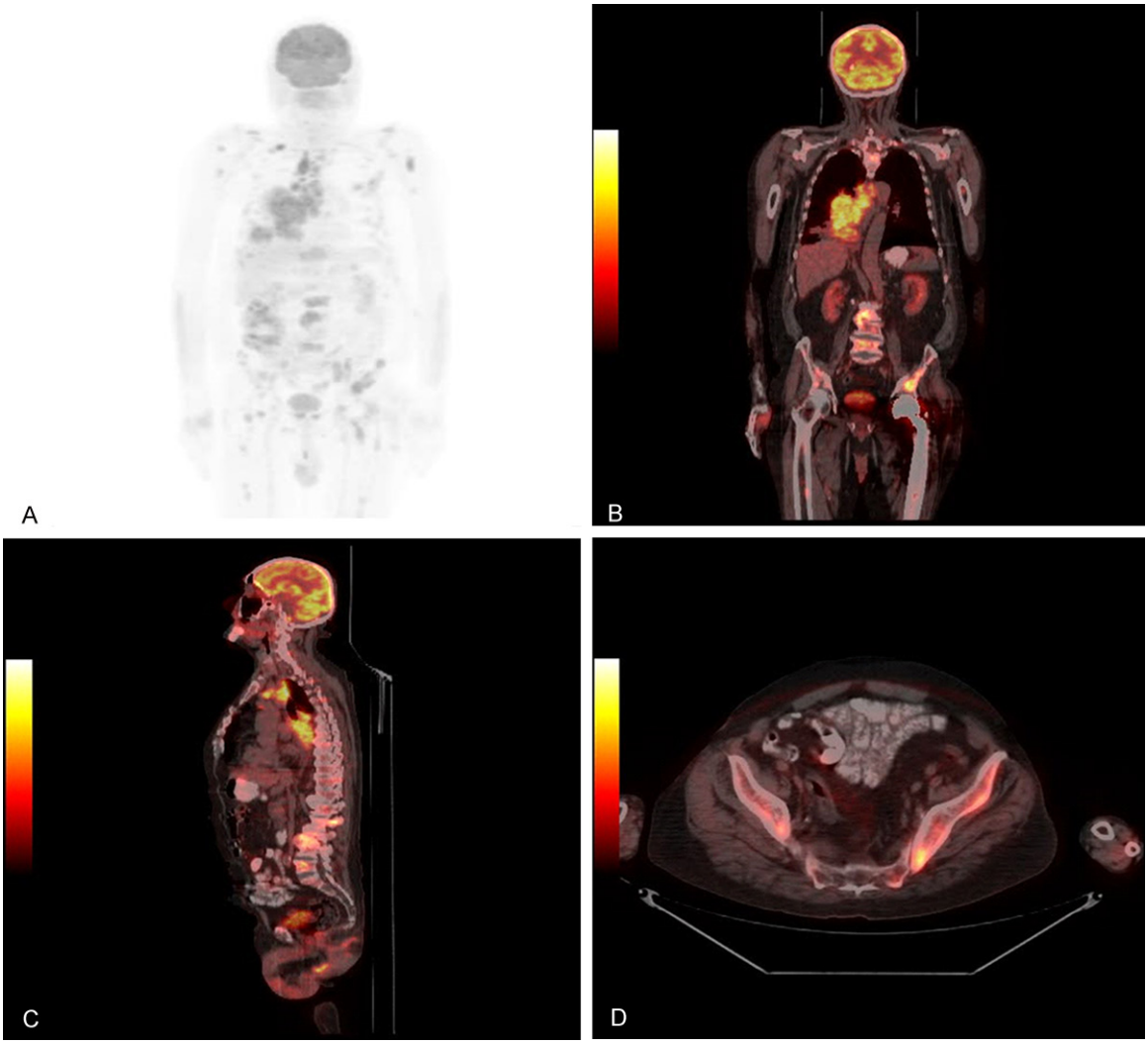

Figure 2. Multiple bone metastasis in a 66 year old male patient diagnosed with small cell lung cancer (patient number 2): A: Positron emission tomography image. B: Coronal PET-CT image. C: Sagittal PET-CT image. D: Axial PET-CT image.

tumor SUVmax and primary tumor size (**Table 2**, **Figure 1**).

Although the average bone metastasis SUV with primary tumor SUV values higher than 10 is higher than the ones lower than 10, this difference did not generate a statistically significant data ($p > 0.05$) (**Table 3**).

There is no statistically meaningful correlation between primary tumor size and primary tumor SUVmax values ($p > 0.05$) (**Table 4**; **Figures 2** and **3**).

Discussion

Distant organ metastasis was detected in 40% of the diagnosed lung cancer patients. Except thorax, the highest rate of the metastasis was observed in brain, adrenal glands, liver, bone, kidneys and abdominal lymph nodes [1, 2]. In our study, 40.7% of the patients developed bone metastasis.

The late stage diagnosis is the biggest reason for high mortality rate of lung cancer [3]. The stage of the tumor is vital to determine the prognosis of the lung cancer patients. TNM evolution was used to plan lung cancer treatment strategy, project prognosis and compare different studies. A differentiation system developed by the International Association for the Study of Lung Cancer (IASLC) is used to describe the stages of disease. The treatment type was selected based on the correct evolution [4].

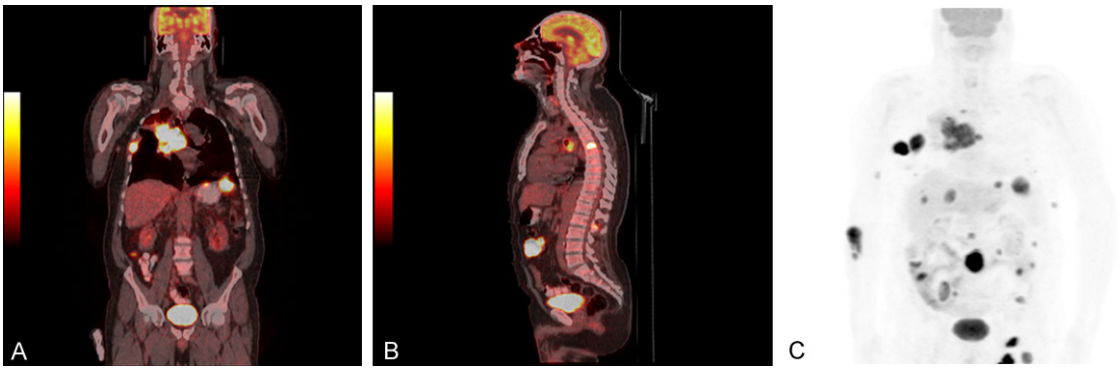

Figure 3. Multiple metastasis in a 61 year old non-small cell lung cancer diagnosed male patient (patient number 14): A: Coronal PET-CT image. B: Sagittal PET-CT image. C: PET image.

FDG/PET-CT approach is primarily used in malign-benign differentiation, staging, recurrence determination and treatment evaluation. The prominent risk factors in lung cancer include age, tobacco usage and prior lung cancer diagnosis [5-7]. Malignancy risk increases for patients older than 48 as reported by Lillington et al. [6]. We found that the average cancer patient age is 59.44 ± 5.99 (46-72). The literature reports the majority of cancer patients to be male (90%). Patient selection in our group also follows a similar trend as 91.9% of them were male (79 patients).

According to El-Torky et al. [8] reported the lung cancer sub-classes as follows; epidermoid carcinoma (32%), adenocarcinoma (31%), small cell lung cancer (21%), large cell carcinoma (15%). The 11.6% of the patients in our study has small cell lung cancer, on the other hand, 88.4% of the patients has non-small cell lung cancer.

Maximum standard uptake value is used as a parameter for semi-quantitative evaluation of PET-CT screening. Lesions with the SUV values lower than 2.5 are benign with 96% confidence. However, lesions with low metabolic activity and smaller size (10 mm) might be misleading in carcinoid tumor or bronchoalveolar carcinoid.

SUVmax values differentiate based on tumor histopathology. Although NSCLC's like squamous cell carcinoma and adenocarcinoma show high retention, tumors with slow growth rate having intense mucinous such as bronchoalveolar carcinoma and carcinoid tumor display low levels of retention [9]. Brown et al. compared histological data of adenocarcinoma, epidermoid carcinoma and large cell carcinoma patients (23 in total) using SUVmax values. The aforementioned study suggests a positive correlation in SUVmax value and tumor size growth. Unlike to the correlation between adenocarcinoma tumor size and SUV value, a meaningful correlation was not detected in epidermoid and large cell carcinoma [10]. Li et al. suggest a correction factor in SUV value due to partial volume effect for small size tumors [11].

Dhital et al. observed a very weak correlation between the squamosous cell carcinoma and the primer tumor SUVmax value [12]. However, any meaningful correlation was not accessible for the other tumor sub-groups in lung cancer histopathology. Similarly, we also note that small cell lung cancer patients (10 total) and non-small cell lung cancer patients (76 total) did not show a statistically meaningful primer tumor SUVmax value ($p > 0.05$).

One of the prognostic factors in lung cancer is the primer lesion SUVmax value. Increased SUV value translates in a higher degree of proliferation [12]. Literature also suggests an inverse relationship between SUV value and prognosis. Mortality risk in lung cancer patients with SUVmax value greater than 7 is 6.3 times higher than the patients with SUVmax value lower than 7 as reported by Jeong et al. [13]. Similarly, Vansteenkiste et al. reported higher 2-year life expectancy rate for the patients with SUV value lower than 7 [14].

Another study on 255 lung cancer patients by Peiou et al. reports an increase in mortality risk when the primary tumor SUV value is higher

than 10 and accompanied with bone hypermetabolism [15]. Our study also shows an increase in bone metastasis SUV values when primary tumor SUV value is higher than 10. However, this result was statistically not meaningful presumably due to the low number of patients.

The autopsy series in lung cancer patients suggests a 30% bone metastasis rate [16]. Bone metastasis can be considered as the first indication of lung cancer. The early diagnosis of bone metastasis is vital in the selection of right diagnosis approach, prediction of prognosis and life quality improvement. Marom et al. reports 24% of distant metastasis in PET scanning of 100 lung cancer patients with 19% of skeleton localization [17]. Ursavaş et al. describes bone metastasis in 33 patients of 106 NSCLC patients (31.1%). Our work reports 35 bone metastasis cases out of total 86 lung cancer patients (40.7%) [18]. Additionally, we evaluate the relationship between SUVmax value and bone metastasis. Statistically meaningful relationship was not accessible in our study ($p > 0.05$).

As the tumor size increases, SUV value also increases in lung cancer patients reported by Bellek et al. [19]. Li et al. retrospectively investigated 107 NSCLC stage I-IV patients and detected a positive correlation in tumor size and SUVmax value [11]. Peiou et al. [15] and Vesselle et. al. [20] also came up with a similar conclusion in 135 patients with NSCLC. This can be explained as follows: As tumor size increases, metabolically active tumorigenic cell block, FDG retention and SUV value increase. On the other hand, some research groups report contradictory studies on this topic [21]. Our study suggests a 27.2% positive relationship in primary tumor SUVmax value and tumor size ($p < 0.05$).

Patient's weight, blood glucose level, uptake period, partial volume effect, recovery coefficient and the property of the focused area are the important factors that affect SUV value. Furthermore, reactive hyperplasia indistinguishable to malignancy or granulomatous inflammation can cause benign nodal growth associated with glucose retention. Boellaard et al. argues that the SUV value can be affected from variety of different stimuli [21]. Blood sugar levels higher than 160 mg/dl, long duration periods between FDG injection and the PET scanning can cause statistically meaningless results. Additionally, lack of muscle relaxation, inflammation and patients stress level can also lead wrong assessments. In addition to low number of patients, we cannot retrospectively evaluate the maintenance of these standards.

Although the present study is statistically meaningless, we found the relationship between primary tumor value and bone metastasis to be valuable. Prospective, multi-centered studies with higher number of patients are required to identify the relationship between lung cancer primary tumor SUV value, prognosis of metastasis bone SUV value and FDG retention.

Disclosure of conflict of interest

None.

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