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Is positron emission tomography/computed tomography useful for interpreting the lung cancer subtype according to the localization

Pozitron emisyon tomografi/bilgisayarlı tomografi yerleşim yerine göre akciğer kanseri alt tipi değerlendirmesinde yararlı mıdır?

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ABSTRACT

Background: This study aims to investigate the relationship between histopathological subtypes, anatomical distribution, and maximum standardized uptake value of lung cancer in positron emission tomography/computed tomography.

Methods: A total of 281 lung cancer patients (258 males, 23 females; mean age 65.7±10.0 years, range 37 to 87 years) with invasive and/or noninvasive diagnostic findings were retrospectively evaluated between May 2011 and June 2014. Distributions of histopathological subtypes and the maximum standardized uptake values of lung cancer were evaluated according to the primary tumor localization.

Results: We detected that maximum standardized uptake values of squamous cell carcinoma were significantly higher compared to adenocarcinoma in tumors localized in right upper lobe, left upper lobe, left lower lobe, right main bronchus, and left main bronchus ($p<0.05$).

Conclusion: Although the definitive diagnosis of lung cancer is established by histopathological analysis, positron emission tomography/computed tomography evaluation may help to interpret various histopathological subtypes according to maximum standardized uptake values in some localizations. To our knowledge, this is the first study regarding the usefulness of positron emission tomography/computed tomography in interpreting lung cancer subtypes according to the localization. Further clinical studies are required to shed light on this issue.

Keywords: Cancer; lung; positron emission tomography.

ÖZ

Amaç: Bu çalışmada, pozitron emisyon tomografi/bilgisayarlı tomografide akciğer kanserinin histopatolojik alt tipleri, anatomik dağılımı ve maksimum standardize tutulum değeri arasındaki ilişki araştırıldı.

Çalışma planı: Mayıs 2011 - Haziran 2014 tarihleri arasında invaziv veya invaziv olmayan tanı bulguları olan 281 akciğer kanserli hasta (258 erkek, 23 kadın; ort. yaş 65.7±10.0 yıl, dağılım 37-87 yıl) retrospektif olarak değerlendirildi. Histopatolojik alt tiplerinin dağılımları ve akciğer kanseri maksimum standardize tutulum değerleri primer tümör yerleşim yerine göre değerlendirildi.

Bulgular: Skuamöz hücreli karsinomun sağ üst lob, sol üst lob, sol alt lob, sağ ana bronş ve sol ana bronş yerleşimlerindeki tümörlerde maksimum standardize tutulum değerlerinin adenokarsinomdan anlamlı şekilde daha yüksek olduğu tespit edildi ($p<0.05$).

Sonuç: Akciğer kanserinin kesin tanısı histopatolojik inceleme ile koyulsa da pozitron emisyon tomografi/bilgisayarlı tomografi değerlendirmesi bazı yerleşim yerlerinde maksimum standardize tutulum değerlerine göre bazı histopatolojik alt tiplerinin yorumlanmasında yardımcı olabilir. Bildiğimiz kadarıyla, yerleşim yerine göre akciğer kanseri alt tiplerinin yorumlanmasında pozitron emisyon tomografisi/bilgisayarlı tomografinin yararı hakkında yapılan ilk çalışma budur. Bu konuda ileri klinik çalışmaların yapılması gerekmektedir.

Anahtar sözcükler: Kanser; akciğer; pozitron emisyon tomografi.

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Lung cancer (LC) incidence has increased since the beginning of the 20th century and LC is the main cause of cancer mortality in both men and women.[1] Non small cell LC accounts for 85 to 90% of all LCs and includes three main types: squamous-cell carcinoma, adenocarcinoma, and large-cell carcinoma.[1] Squamous cell carcinomas are also predominantly associated with smoking history and tend to form larger tumors in the center of the lung.[1] On the contrary, adenocarcinomas usually occur at the lung periphery.[1] The small cell LC is the most aggressive lung tumor as a consequence of its high metastatic potential as compared to other forms of LC.[2] The overall five-year survival for LC remains comparatively around 10%.[3] Imaging techniques play an essential role in the diagnosis, staging, and follow-up of patients with LC.[4] Chest X-rays, computed tomography (CT), bronchoscopy, and transthoracic needle aspiration biopsy may also be considered for diagnosis of pulmonary lesions.[4]

Positron emission tomography (PET)/CT has become an important novelty in LC imaging. 2-18F-fluoro-2-deoxy-D-glucose (FDG)-PET alone is reputed to be an accurate noninvasive imaging test, with a meta-analysis reporting 96.8% sensitivity and 77.8% specificity for malignant nodules.[5,6] Based on the fact that malignant cells show higher rates of glycolysis than most surrounding normal structures.[7,8] Positron emission tomography/CT with the glucose analog FDG is based on the enhanced glucose metabolism of LC cells.[4] Positron emission tomography can detect functional abnormalities and may be useful for the detection of viable tumor cells, and PET/CT is more accurate than conventional imaging for the assessment of therapy response. So FDG distribution in the body by the PET camera allows differentiation between normal and malignant tissues.[4]

As a result, PET/CT is a diagnostic method which is used with increasing frequency in the evaluation and staging of lung lesions. Thus, in this study, we aimed to investigate the relationship between histopathological subtypes, anatomical distribution, and maximum standardized uptake value (SUV_{max}) of LC in PET/CT.

PATIENTS AND METHODS

A retrospective analysis was performed on the invasive (bronchoscopic and surgical) and/or noninvasive (PET/CT) diagnostic findings in a total of 281 LC patients (258 males, 23 females; mean age 65.7±10.0 years, range 37 to 87 years) between May 2011 and June 2014. The demographic features, primary tumor SUV_{max}, and tumor size of the histopathological subtypes were evaluated. All histopathological subtypes were diagnosed by bronchoscopic or surgical procedures and classified as small cell carcinoma, squamous cell carcinoma, adenocarcinoma or large cell carcinoma. The localization findings were also obtained with these invasive diagnostic procedures. In addition to the tumor localization and SUV_{max} values, were assessed by PET/CT in all patients. Localizations were divided as right upper lobe (RUL), right middle lobe, right lower lobe, left upper lobe (LUL), left lower lobe (LLL), right main bronchus (RMB), and left main bronchus (LMB). Histopathological subtype distributions and the SUV_{max} values of LC were evaluated according to the primary tumor localization.

Statistical analysis

The software package IBM SPSS for Windows version 21.0 (IBM Corporation, Armonk, N.Y., USA) was used for statistical analysis. Descriptive statistics included mean and standard deviation. Cross tables were reported as percent ratio. Variables with continuous data were statistically compared using the unpaired t test or the Mann-Whitney U test, depending on whether the data were normally distributed, as indicated by the shape of the distribution pattern in the Shapiro-Wilk test. Variables with categorical data were statistically compared using chi-square or Fisher's exact tests. Group comparisons were carried out using Bonferroni test. Two-sided *p* value above 0.05 was considered statistically significant.

RESULTS

There were 50 (17.8%) small cell (mean age 64±11 years), 139 (49.5%) squamous cell (mean age 67±90 years), 88 (31.3%) adenocarcinoma (mean age 65±10 years), and four (1.4%) large cell (mean age 58±80 years) LCs detected in this study. Of the patients, 17.4% with small cell, 47% with squamous cell, 26% with adenocarcinoma, and 1.4% with large cell were male. Of the patients, 17.8% with small cell carcinoma, 47.7% with squamous cell carcinoma, 26.7% with adenocarcinoma, and 1.4% with large cell carcinoma were smokers. Primary tumor SUV_{max} values were detected as 13.3±4.2 in patients with carcinoma, 18.1±7.3, 11.8±4.4, and 15.2±5.8 in small cell carcinoma, squamous cell carcinoma, adenocarcinoma and large cell carcinoma, respectively. Squamous cell tumors had higher SUV_{max} than those of other histopathological subtypes ($p<0.05$). Primary tumor sizes were 82.9±29.5, 74.7±31.1, 70.2±36.8, and 104.5±37.3 mm in small cell carcinoma, squamous cell carcinoma, adenocarcinoma, and large cell carcinoma,

Table 1. Demographic features, primary tumor maximum standardized uptake value and tumor size of histopathological subtypes

Histopathological subtypes	Age (years)	Gender (male)	Smoking	Primary tumor SUV_{max}	Tumor size (mm)
	Mean±SD	%	%	Mean±SD	Mean±SD
Small cell carcinoma (n=50)	64±11	17.4	17.8	13.3±4.2	82.9±29.5
Squamous cell carcinoma (n=139)	67±90	47.0	47.7	18.1±7.3	74.7±31.1
Adenocarcinoma (n=88)	65±10	26.0	26.7	11.8±4.4	70.2±36.8
Large cell carcinoma (n=4)	58±80	1.4	1.4	15.2±5.8	104.5±37.3
P	0.04	0.003	0.001	0.0001	0.048

Descriptive statistics (age, SUV_{max}, and tumor size) included mean and standard deviation; Cross tables (gender and smoking) were reported as percentage ratio. Variables with continuous data were statistically compared using the Mann-Whitney U test. Variables with categorical data were statistically compared using chi-square tests. Two-sided *p* value above 0.05 was considered statistically significant; SUV: Standard uptake value.

respectively. Demographic features, primary tumor SUV_{max}, and tumor sizes of histopathological subtypes are summarized in Table 1.

Distributions of histopathological subtypes according to the primary tumor localization are shown in Table 2. Squamous cell lung carcinoma was detected more in RUL (13.9%) and in LUL (10.7%) ($p<0.05$).

The SUV_{max} evaluation of LC according to the primary tumor localization is evaluated in Table 3. In terms of mean SUV_{max}, differences between squamous cell (17.2±6.6) and adenocarcinoma (12.2±4.5) were statistically significant in RUL (p=0.02); differences between squamous cell (18.0±7.2) and small cell (10.6±2.2) were statistically significant in LUL (p=0.016); differences between squamous cell (18.0±7.2) and adenocarcinoma (12.9±3.7) were statistically significant in LUL (p=0.007); differences between squamous cell (17.1±5.9) and adenocarcinoma (10.6±4.6) were statistically significant in LLL (p=0.024); differences between small cell (13.7±3.6) and squamous cell (21.8±8.1) were statistically significant in RMB (p=0.003); differences between squamous cell (21.8±8.1) and adenocarcinoma (7.8±1.5) were statistically significant in RMB (p=0.001); and differences between squamous cell (17.9±9.7) and adenocarcinoma (9.4±1.7) were statistically significant in LMB (p=0.033).

DISCUSSION

2-18F-fluoro-2-deoxy-D-glucose-PET imaging can provide several measurements of radioactivity uptake, such as the SUV.[9] Standardized uptake value is a semi-quantitative measure widely used in PET studies. Standardized uptake value reflects the quantity of radiotracer within a tissue, normalized with injected activity and patient weight. There are many factors affecting the SUV, such as a patient's body habit, body composition, blood glucose level, length of uptake period, partial volume effect, definition of region of interest, image reconstruction method, and resolution.[9,10]

Although PET/CT is an accurate and noninvasive method in the staging of LC, it may also have many pitfalls. As a general rule, uptake of SUV_{max} ≥2.5 was considered to indicate a malignant lesion and SUV_{max} <2.5 was considered to indicate a benign lesion.[11,12] A number of benign lesions that have increased glucose metabolism may collect FDG and can be inaccurate as malignant, such as infection, inflammation, and infarct.[11,13] Iatrogenic reasons of focal or diffuse FDG uptake include healing wounds,

Table 2. Distributions of histopathological subtypes according to primary tumor localization

Histopathological subtypes	Primary tumor localization (%)							*p*
	RUL	RML	RLL	LUL	LLL	RMB	LMB	
Small cell carcinoma (n=50)	2.5	1.8	1.8	2.1	1.4	5	3.2	0.004
Squamous cell carcinoma (n=139)	13.9	1.1	5.7	10.7	6	5.3	6.8	
Adenocarcinoma (n=88)	11.4	1.1	3.6	7.8	3.2	1.4	2.8	
Large cell carcinoma (n=4)	1.1	0	0.3	0	0	0	0	

Variables with categorical data were statistically compared using chi-square tests. Group comparisons were carried out using Bonferroni test. Two-sided *p* value above 0.05 was considered statistically significant. RUL: Right upper lobe; RML: Right middle lobe; RLL: Right lower lobe; LUL: Left upper lobe; LLL: Left lower lobe; RMB: Right main bronchus: LMB: Left main bronchus.

Table 3. Maximum standardized uptake value evaluation of lung cancer according to primary tumor localization

	Primary tumor localization							
	RUL	RML	RLL	LUL	LLL	RMB	LMB	*p*
Small cell carcinoma (n=50)	11.1±4.5	14.8±4.5	15.1±6.2	10.6±2.2	14.7±5.3	13.7±3.6	13.6±3.9	0.369
Squamous cell carcinoma (n=139)	17.2±6.6	18.1±6.7	18.0±7.1	18.0±7.2	17.1±5.9	21.8±8.1	17.9±9.7	0.579
Adenocarcinoma (n=88)	12.2±4.5	14.6±6.6	11.7±6.0	12.9±3.7	10.6±4.6	7.8±1.5	9.4±1.7	0.164
Large cell carcinoma (n=4)	17.5±4.3	–	8.2±1.0	–	–	–	–	0.201
P	0.001	0.691	0.1	0.001	0.028	0.001	0.032	

Variables with continuous data were statistically compared using the Mann-Whitney U test. Variables with categorical data were statistically compared using chi-square tests. Two-sided *p* value above 0.05 was considered statistically significant. Group comparisons were carried out using Bonferroni test. RUL: Right upper lobe; RML: Right middle lobe; RLL: Right lower lobe; LUL: Left upper lobe; LLL: Left lower lobe; RMB: Right main bronchus: LMB: Left main bronchus.

granulation tissue, chest tubes, percutaneous needle biopsy, and mediastinoscopy.[11,14]

Glucose transporter type 1 in the cell membrane is primarily responsible for increased glucose affinity in LC and there is a positive relationship between the intensity of FDG uptake, the proliferative activity of tumor, cell differentiation, and aggressiveness.[15] Increased glucose consumption and glycolytic activity have been reported in non-small cell LC.[16] Glucose metabolism and tumor proliferative activity alterations associated with non-small cell LC can be assessed *in vivo* by PET using FDG.[16,17]

Main histological categories of LC include non-small cell LC, small cell LC, and neuroendocrine tumor.[1] Squamous cell and large cell carcinomas are the most FDG accumulating types and particularly well-differentiated adenocarcinomas use less glucose, while carcinoid tumors exhibit low affinity for glucose and may lead to false negative results.[15]

2-18F-fluoro-2-deoxy-D-glucose-PET has been reported to be useful in characterizing solitary pulmonary nodules,[1] LC staging,[1] determining recurrence and restaging,[15] guiding therapy[1] monitoring treatment response,[1] radiation therapy planning,[15] and predicting outcome.[1]

2-18F-fluoro-2-deoxy-D-glucose-PET/CT is a new method for staging of LC, providing prognostic data on both initial and recurrent tumors.[18] Correct staging of patients with non small cell LC is crucial in identifying treatment strategy and estimation of the prognosis.[11] Tumor staging is the most important prognostic factor as well as the determining factor in deciding for the most proper treatment modality.[19]

Tumor node metastasis staging system is based on a combination of findings: the location and extent of the primary tumor (T), evaluation of intrapulmonary, hilar or mediastinal lymph node metastases (N), and evaluation of extrathoracic metastases (M).[11] Tumor staging identifies the location, size, and extension of the primary tumor and the evaluation of satellite nodules. Computed tomography is an important imaging modality for the evaluation of primary tumors thanks to its perfect anatomical resolution,[20] while whole-body PET is attractive in oncology since many tumors preferentially take up FDG. Functional and anatomical information are provided simultaneously with PET-CT.[21]

2-18F-fluoro-2-deoxy-D-glucose-PET gives more information about the metabolic changes of the neoplasm.[11] Because of the exact CT correlation with the extent of 18F-FDG uptake, the location of the primary tumor may be defined exactly.[11] On the other hand, PET is limited in identifying microscopic tumor, correctly assessing extension of tumor and biological low metabolism tumor, such as bronchoalveolar cell carcinoma and carcinoid tumors.[11,22]

In this study, we evaluated the relationship between anatomical distribution, histopathological subtypes, and SUV_{max} of LC. To our knowledge, no such comparison has been reported in the literature. In several studies investigating the relationship between histological subtypes of LC and their localization in the lungs, some cancers were shown to be more frequently localized in certain lobes.[23-25] It is known that squamous and small cell LCs are more often centrally located, while adenocarcinoma and large cell cancers are generally peripherally located. In addition, the upper lobe, particularly the right upper lobe, was reported more due to inhalation of cigarette smoke.[23,25]

According to Bülbül et al.[23] and Çelikoğlu et al.,[25] squamous cell cancer is more often located in the upper lobes, large cell cancer in the right upper lobe, and small cell LC in the right main bronchus and left upper lobe, while they did not demonstrate

any such finding for adenocarcinoma. According to the study of Bülbül et al.[23] and Özyurt et al.,[24] squamous cell cancers are more often located in the upper lobe of the right main bronchus and bronchus intermedius. Small cell cancer was more frequently observed in the left upper lobe bronchus, main bronchus, and bronchus intermedius. Bülbül et al.[23] have not detected any relationship between tumor cell types and localization.

In conclusion, although the definitive diagnosis of lung cancer is established by histopathological analysis, positron emission tomography/computed tomography evaluation may help to interpret various histopathological subtypes according to maximum standardized uptake values in some localizations. We have shown that maximum standardized uptake values of squamous cell carcinoma were significantly higher compared to adenocarcinoma in tumors localized in right upper lobe, left upper lobe, left lower lobe, right main bronchus, and left main bronchus. To our knowledge, this is the first study regarding the usefulness of positron emission tomography/computed tomography in interpreting lung cancer subtypes according to the localization. Still, further clinical studies are required to shed light on this issue.

Declaration of conflicting interests

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