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Research Article

Comparative Evaluation of Lymph Node SUV max Values and Density Measurements in the Differentiation of Patients with Lung CA and Covid-19 Pneumonia showing Mediastinal Lymph Node involvement

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Abstract

Objectives: The differentiation between infectious and tumoral lymph node (LN) causes diagnostic difficulties in lung cancer (CA) patients concurrent with Covid-19 pneumonia. In our study, we evaluated the contribution of CT density and PET/CT SUV max measurements to the diagnosis in the differentiation of mediastinal LNs.

Methods: In our retrospective study, 20 lung CA and 20 Covid-19 patients with mediastinal lymph node involvement with PET CT were included.

Results: The mean LN density value of the participants in the Covid-19 group was 51±1.45 Hounsfield units (HU), and the mean SUV max value was 4.43±0.47. Of the participants in the lung CA group, on the other hand, the mean density value was 38±8.08 HU, and the mean SUV max value was 8.97±3.07. The difference between the density and SUV max values showed a statistically significant difference.

Conclusion: We found that density and SUV max values can make a significant contribution to the differential diagnosis in the differentiation between mediastinal LNs of Covid-19 and lung cancer. Early characterization of lymph nodes in this patient group provides a high prognostic chance.

Keywords: Lymph node, density, SUV max

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In December 2019, a cluster of pneumonia caused by an unknown pathogen was first reported in Wuhan, a city in the central part of China, and the agent causing the pneumonia was identified as a new corona virus. This new virus, named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread all over the world and has turned into a public health emergency.[1] In the diagnosis of COVID-19, although reverse transcriptase polymerase chain reaction (rRT-PCR) test performed on samples taken from the respiratory tract is the gold standard method, imaging techniques such as chest computed tomography (CT) take important place in the diagnosis and treatment of the disease.[2] In the COVID-19 pandemic, oncology patients are more vulnerable than healthy individuals and are at serious risk. Patients with cancer are particularly susceptible to respiratory tract pathogens as they are in an immunosuppressive state due to the malignancy and antitumor treatment they receive. Oncology patients experience Covid-19 pneumonia

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more seriously, the disease progresses faster, the need for intensive care arises and life-threatening complications that may result in death may occur.[3] This situation causes an increase in the mortality rate in cancer patients suffering Covid -19 pneumonia compared to the general population.[4] For this reason, early diagnosis and treatment of Covid-19 are of greater importance in oncology patients. Early diagnosis of asymptomatic Covid-19 pneumonia in patients with primary oncology disease is not always easy, especially in patients with negative RT-PCR test. During the Covid-19 pandemic, patients has been diagnosed with incidental asymptomatic Covid-19 in 18F-fluorodeoxyglucose PET/computed tomography (18F-FDG PET/CT) examinations performed either for the provisional diagnosis of lung mass and mediastinal lymph node or for the evaluation of staging, response to treatment and recurrences of oncology patients.[5] In the patient group with concurrent Covid-19 pneumonia and malignant neoplasia in the lung, existing parenchymal lesions and mediastinal lymph nodes in the lung cause confusion in the clinician. In Covid-19 pneumonia concomitant with lung CA, lung findings and mediastinal lymph nodes cause diagnostic difficulties.

Mediastinal involvement in lung cancer is a very important prognostic factor for survival and proper staging of the mediastinum would accurately identifies patients who will benefit most from surgery and medical oncological treatment.[6] Again, mediastinal involvement belonged to Covid-19 pneumonia is of vital importance for oncology patients in the risk group. Differentiating the lymph nodes in which Covid -19 involvement is monitored from tumoral involvement in these patients will completely change the oncological treatment process of the disease. It will prevent false staging of the disease with false positive results CT findings of COVID-19 infection are usually bilateral, peripheral ground-glass opacities (GGO), subpleural, crazy paving appearance, air space consolidation, bronchovascular thickening in the lesion, traction bronchiectasis. In addition, lymphadenopathy (LAP), pleural effusion and diffuse small lung nodules, occur in a smaller number of cases.[7] Mediastinal lymph node involvement can be seen in most malignant oncological patients as well. Increased FDG uptake can be observed in mediastinal lymph nodes, especially in early stage Covid-19 pneumonia and oncological diseases.[8] For this reason, to be able to find the mean SUV max values and CT densities of the mediastinal lymph nodes belonged to Covid-19, we included the patient group in our study, who underwent PET/CT with the provisional diagnosis of malignancy and who were diagnosed with incidental Covid-19 disease on PET/CT and whose malignant processes were ruled out. We predict that the density values and SUV max values will be a guide in this differentiation. Thereby, we are of the opinion that by ensuring that patients quickly reach the correct diagnosis and receive the right treatment, their survival will increase

Methods

Necessary permissions were obtained from the Firat University Non-Interventional Research Ethics Committee (approval number: 2021/13-22) and the scientific research platform of the Ministry of Health of the Republic of Turkey. The study was conducted retrospectively at Elazig Medical Park Hospital in Turkey. The medical files of 675 patients who applied to our radiology clinic with a provisional diagnosis of malignant process between January 2021 and October 2021 were retrospectively scanned. Thorax CT and PET/CT examinations were reviewed retrospectively. Twenty Lung CA and 20 Covid-19 patients with mediastinal involvement that was suspected by radiological imaging methods and confirmed by histopathological and laboratory tests were included in the study. The patients with Covid-19 pneumonia included in the study were those who had been incidentally detected on PET/CT taken with a provisional diagnosis of mediastinal neoplasia and lung parenchymal malignant neoplasia. The diagnosis of Covid-19 pneumonia in these patients had been confirmed by clinical follow-up and RT-PCR examination. In these patients, ground-glass opacities in the lung parenchyma areas and FDG uptake in the mediastinal lymph nodes were observed in the PET/CT examination. Of the lung CA patients included in our study, 18F-FDG uptake was present in lung masses and mediastinal lymph nodes on PET/CT. These patients had undergone radical surgery and mediastinal lymph node dissection, and the diagnosis had been histologically confirmed.

The CT and FDG uptake findings suggestive of lung and mediastinal involvement of the SARS-CoV-2 and Lung CA patients were characterized in detail. In the both patient groups, the density values in the CT component of mediastinal lymph nodes with FDG uptake and SUV max values on PET/CT were measured and recorded. The results were analyzed, and the patients without FDG uptake in mediastinal lymph nodes during PET/CT examination were excluded from the study. Additionally, despite being suspected by radiological imaging, the Lung CA patients whose Covid-19 pneumonia was not confirmed with RT-PCR test and who had no histopathological diagnosis were excluded from the study.

Whether the variables were normally distributed was tested with the skewness and kurtosis coefficients, and normally

distributed variables were given as mean and standard deviation. The independent sample t-test was employed to analyze the differences between the two groups.

The statistical analysis of the data was performed using IBM SPSS Statistics 22.0 software. The significance level was taken as 0.05.

Results

A total of 40 patients, 20 with lung cancer and 20 with Covid-19 pneumonia, were included in our study. In the retrospective review, PET/CT examinations showed that all 20 patients with lung CA had FDG uptake in their mediastinal LNs. Likewise, all 20 patients with Covid-19 pneumonia had FDG uptake in their mediastinal LNs on PET/CT.

The mean CT density values in LNs with FDG uptake on PET were found to be 38±8.08 HU in the lung CA patients and 51±1.45 HU in the Covid-19 patients. It was found that the CT density values showing the FDG uptake was higher in Covid-19 than in lung CA (Fig. 1). The difference in the mean Hounsfield unit between these groups was statistically significant.

18F-FDG PET/CT uptake was present in mediastinal LNs of all lung CA and Covid-19 patients (Fig. 2). The SUV max values of the defined lymph nodes were measured.

In the patients included in the study, the mean SUV max values were 8.97±3.07 for the lung CA patients and 4.43±0.47 for the Covid-19 patients. The SUV max values of malignant LNs in the lung CA patients were found to be higher than those of benign LNs in the Covid-19 patients (Table 1).

There was a statistically significant difference in terms of LN density and SUV max values between Covid-19 and lung CA patients ($p<0.05$). The LN density values in the Covid-19 group was higher compared to in the lung CA group. The SUV max values of the LNs belonged to the Covid-19 LN group were lower than those of the LNs belonged to the lung CA LN group (Table 2).

The LNs characterized by increased density values and low SUV max values in Covid-19 were evaluated as benign LN due to infection. Lung CA LNs showed FDG uptake, and decreased density values and increased SUV max values of these lymph nodes were evaluated as LNs showing tumoral involvement. In our study, we showed that we can shed light on the radiological differentiation of infectious and tumoral LNs by the quantitative measurement of SUV max values and density values.

Discussion

During the Covid-19 pandemic, viral interstitial pneumonias suspected of COVID-19 infection containing GGOs and areas of consolidation were incidentally diagnosed in asymptomatic oncology patients on 18F-FDG PET/CT. In the literature, radiological examinations of these cases and radiological findings of Covid-19 disease on PET/CT have been defined. PET/CT examinations have been performed on patients with the provisional diagnosis of malignant neoplasia, and in some of them, neoplasia has been ruled out and Covid-19

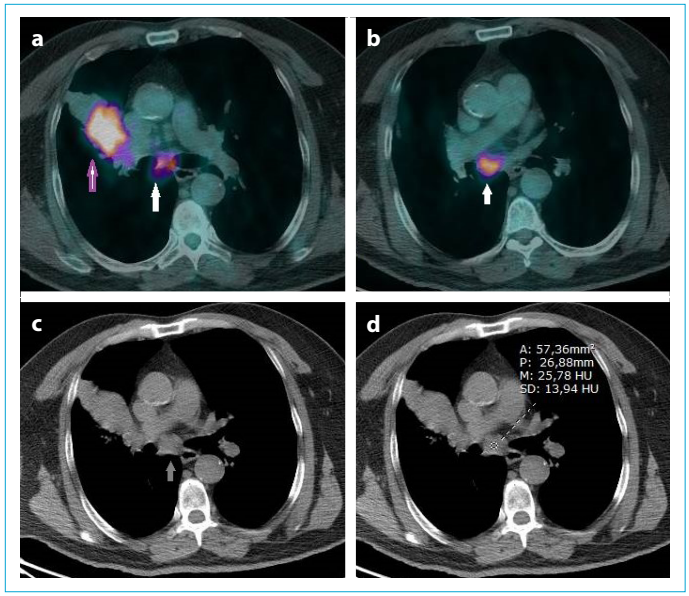

Figure 1. 72-year-old male patient with lung cancer in the right lung. **(a)** Right lung cancer (pink arrow) and subcarinal lymph node (white arrow) showed FDG uptake in axial sections on PET CT. **(b)** Axial image showed a lymph node in the subcarinal regio with hypermetabolism, and lymph node metastasis was highly suspected. **(c)** The transaxial non contrast CT images showed this lymph node(gray arrow. **(d)** The transaxial non contrast CT images showed this lymph nod (white circle, Density value is 25,78 HU).This metastatic lymph node was confirmed by histopathology finally.

Table 1. Descriptive Statistics regarding Density and SUV Max Values of the Groups

	Group	n	Mean	Standard Deviation	Min.	Max.
Covid-19 (HU)	Density	20	51	1.45	48	53
	SUV Max	20	4.43	0.47	3.4	5.6
Lung CA (HU)	Density	20	38	8.08	24	52
	SUV Max	20	8.97	3.07	4.2	15

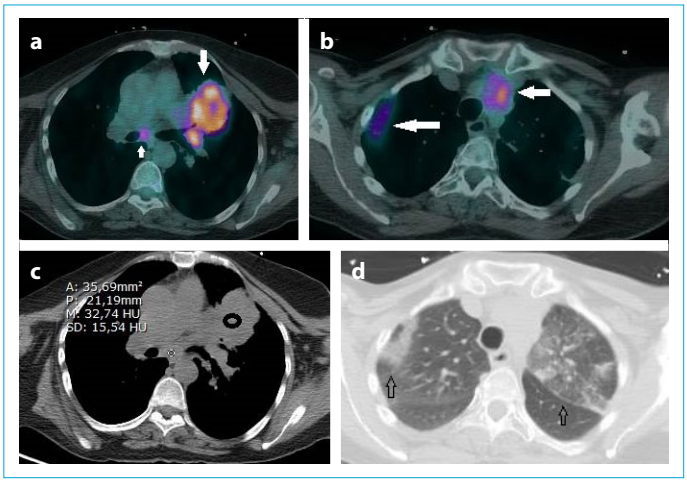

Figure 2. (a) 57-year-old female patient with simultaneous left lung cancer and Covid 19 pneumonia. Left lung cancer (long white arrow) and carinal lymph node (short white arrow) showed increased FDG uptake in axial sections on PET CT. **(b)** Axial image showed a paratracheal lymph node with hypermetabolism(short white arrow). PET CT for review Only showed [18F]FDG uptake at a well-defined ground glass density located peripheral unilaterally in the upper lobe of the right lung. (long white arrow) **(c)** The transaxial non contrast CT images showed this lung cancer(black circle) and lymph nod. In this image, decreased metastatic lymph node density was observed. (white circle, Density value is 32,74 For Review Only HU).This metastatic lymph node was confirmed by histopathology finally. **(d)** Toraks CT showed peripheral unilateral well-defined ground glass density in the upper lobe of the right lung(black arrows).

pneumonia have been diagnosed with PET/CT findings and the diagnosis has been confirmed by tests. Concurrent lung malignancy and Covid-19 pneumonia have been diagnosed in some patients.[5] In asymptomatic Covid-19 patients, FDG uptake has been detected in ground glass opacities in the lung parenchyma areas and mediastinal lymph nodes on PET/CT. Covid-19 pneumonia is also one of the factors that cause mediastinal lymphadenopathy. 18F-FDG uptake can be found in malignant diseases such as lung cancer and lymphoma.[9] Despite the fact that 18F-FDG PET/CT is commonly used in the staging of mediastinal lymph nodes in lung CA patients, the rate of false positives on lymph nodes is comparetively high, as granulomatous or other infections demonstrate hypermetabolism in the lymph nodes.[10] Therefore, all lymph nodes showing FDG uptake on PET/CT should not be considered as metastatic.[11] The differentiation between lung CA mediastinal metastasis and mediastinal involvement of COVID-19 infection is important for physicians, especially when it comes to patients undergoing 18F-FDG PET/CT, but its diagnosis is difficult. Although enlargement more than 1 cm in lymph nodes on CT is an important finding for involvement, the diagnosis needs to be confirmed with additional tests.

Even though the definitive diagnosis in mediastinal lymph nodes is lymph node sampling, directing patients to histopathological sampling with surgery at the first stage may cause delayed diagnosis and unnecessary surgery referral in Covid-19 patients. PET/CT and CT findings may contribute to the rapid implementation of diagnostic process steps and the prevention of unnecessary surgery. In order to prevent this, making correct diagnosis first with radiological imaging examinations in the diagnosis of patients and choosing the appropriate treatment can be a guide. For this purpose, we investigated the use of density and SUV max values in the radiological differentiation of Covid-19 and Lung CA mediastinal lymph nodes, which to our best knowledge is the first in the literature.

In the literature, there are studies in which mediastinal lymph node involvement have been detected incidentally on PET/CT in Covid-19 patients, especially in asymptomatic patients.[12] Tzu-Chuan Ho et al. observed in their study that the rate of thoracic lymph nodes showing 18F-FDG uptake was 40%. Again, in this study, they also showed the presence of thoracic LN involvement without pulmonary lesions, although rare, in asymptomatic Covid-19 patients.[9] In one other study, Xavier et al. stated that the rate of lymph node involvement in Covid-19 patients was 66%.[13] On the other hand, Francesco et al. reported a lymph node prevalence of 19%, and recommended that Covid-19 lymphadenopathy be defined as a "non-atypical" feature.[14] Lymphadenopathies seen in Covid-19 patients may also be a sign of a bacterial super-infection.[15] Recent studies have shown that the rate of lymph node involvement in Covid -19 patients increased and have pointed out that it may be a sign of severe infection. For this reason, determining

Table 2. The analysis of groups according to the density and SUV Max values

	Group	n	Mean	Standard Deviation	p
Density Values	Covid-19	20	51	1.45	<0.001
	Lung CA	20	38	8.08	
Suv Max Values	Covid-19	20	4.43	0.47	<0.001
	Lung CA	20	8.97	3.07	

P<0.05, Independent sample t-test.

the etiology of lymphadenopathies is of vital importance in Covid-19 patients and oncology patients. In this context, we identified the patients with lung CA and Covid-19 pneumonia who had mediastinal lymph involvement. Studies have shown that the lymph node involvement incidence rate of the disease also increases compared to at the beginning of the pandemic. If mediastinal involvement is due to Covid -19 disease, oncology patients in the risk group should be treated urgently. If mediastinal involvement is due to tumoral disease, the staging and treatment plan of oncology patients change. Whatever the cause, making rapid differential diagnosis for the both diseases increase the survival rate of the disease.

The standard density level of each organ or tissue is different. The density level of more solid organs will be higher. Although density values differs according to the tissues on CT, it has been observed that there is a difference in terms of tumor density values between benign and malignant lesions.[16] There are studies in the literature reporting that the histological grade of the tumor increases with an increase in the tumor density, and these tumors show a poor prognosis. If tumor grade can be predicted by tumor density on a CT scan, defining tumor density as a factor may also assist in staging and diagnosis of cancer. Using this principle, we detected the densities of mediastinal lymph nodes and the densities of tumoral lymph nodes, and found that the difference was significant.

Kim et al. reported that the mean Hounsfield units were 48±13 in malignant lymph nodes and 75±18 in benign lymph nodes on CT, among the nodal groups showing positive PET/CT involvement. They proved that the difference between malign and benign lymph node groups in terms of mean Hounsfield unit was statistically significant. They determined the optimal threshold value of the average Hounsfield units producing maximum sensitivity and specificity to be 71 HU for detecting individual lymph node metastases from the ROC analysis.[17] Jun Hua et al. found that metastatic mediastinal lymph node densities were lower than those of non-metastatic lymph nodes and the mean metastatic lymph node density was 38.0 HU.[10] In our study, we found that in the nodal groups showing positive PET/CT uptake on CT, the mean HU values were 38±8.08 HU in lung AC malignant lymph nodes and 51±1.45 HU in Covid-19 pneumonia lymph nodes. In the study by Budiawan et al., the mean HU values were 119.0±27.9 HU in metastatic LNs and 201.5±259.6 HU in benign LNs, which were significantly lower.[18] In accordance with the literature, we observed that tumoral mediastinal lymph node densities were lower compared to infectious lymph nodes densities.

In our study group, FDG uptake was present in mediastinal lymph nodes on PET/CT in the Covid-19 patients. Mediastinal lymph node FDG uptake may also occur due to various factors such as inflammatory and infectious processes apart from malignant causes. PET/CT is used to characterize infection and inflammation based on high glucose uptake of activated inflammatory cells besides malignant disease.[9, 19] Pulmonary infection or inflammation may cause localized 18F-FDG chest uptake that mimics pulmonary metastases and limit the specificity of whole-body scans conducted in patients with cancer.[20] In order to make this important differentiation, we utilized SUV max values to determine the lymph nodes belonged to Covid-19 pneumonia. Tzu-Chuan Ho et al. showed that 18F-FDG PET/CT uptake was present in multiple GGOs as well as in multiple mediastinal and hilar LNs. They also found that SUV max values in mediastinal lymph nodes were 5.8±2.93 (range 2.5 to 9.6).[9] We detected that the mean SUV max values of LNs showing positive PET/CT uptake was of 4.38±3.40 in the Covid-19 patients included in our study. These results were compatible with literature results reported previously. In patients with COVID-19 infection, increase in the size of lymph node lesions and signs of FDG uptake are associated with acute inflammatory conditions and infectious pulmonary changes, and are generally characterized by increased uptake of 18F-FDG.[5] In our study, we evaluated the SUV max values of Covid-19 lymph nodes as significant in favor of the infectious mediastinal lymph node.

The characterization of LNs in the diagnosis of lung cancer is very important to make a decision on the most appropriate treatment. The spread of cancer to LNs determines the stage, treatment decisions, and prognosis.[21]

18F-FDG PET/CT is widely used in the diagnosis and staging of lung CA and the evaluation of mediastinal lymph node involvement. Kubota et al. found that tumor cells, as well as their inflammatory components associated with the growth or necrosis of a tumor, showed FDG uptake. The insufficiency of existing blood flow during the growth of malignant lymph nodes causes oxygen and nutrient deficiency in the mass, creating a necrotic zone. Due to this necrosis, metastatic lymph nodes lead to decreased 18F-FDG uptake.[18] It was reported in a study conducted by Jun Hua et al. that the SUV max values of metastatic mediastinal lymph nodes were lower than those of non-metastatic lymph nodes in lung CA, and the SUV max value of metastatic mediastinal lymph nodes was 6.92.[10] Budiawan et al., on the other hand, reported that the SUV max values were 9.79±4.51 in metastatic lymph nodes and 4.96±2.08 in benign lymph nodes.[18] In our study, we determined the mean SUV max value of metastatic mediastinal lymph nodes to be 8.97±3.07. The SUV max values in metastatic lymph nodes have been stated to be significantly higher

than those in benign lymph nodes. In line with the literature, In our study, we also detected that the SUV max values of the metastatic lymph nodes of lung CA were higher than those of the lymph nodes of Covid-19.

Oncology patients can be diagnosed with asymptomatic Covid 19 by radiological examinations such as PET CT and CT performed during their routine controls. In patients incidentally detected by PET/CT, demonstrating with density and SUV max values that the mediastinal lymph nodes showing increased FDG uptake belong to primary malignancy or Covid-19 will improve diagnostic accuracy and patient prognosis. In this way, metabolic data such as PET/CT SUV max values and CT density values can be used as a guide in performing diagnostic procedures with an accurate analysis at the same time and can contribute to the rapid implementation of diagnostic and treatment steps.

Disclosures

Ethics Committee Approval: Necessary permissions were obtained from the Firat University Non-Interventional Research Ethics Committee (approval number: 2021/13-22) and the scientific research platform of the Ministry of Health of the Republic of Turkey.

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Conflict of Interest: None declared.

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