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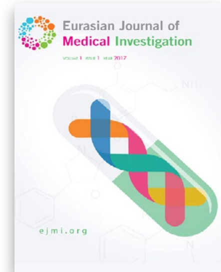

Research Article

Retrospective evaluation of Chest CTs and [^{18}F]-FDG PET/CTs in Oncological Patients with Unsuspected Asymptomatic Infection with COVID 19

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Abstract

Objectives: The aim of this study is to investigate the incidence of asymptomatic COVID 19 patients who underwent CT and PET/CT for oncological indications and to detect lung changes in CT and PET/CT in these patients.

Methods: Between March 2020 and September 2021, 3135 patients admitted to the nuclear medicine department were retrospectively analyzed. Our study involved the oncology patients with a history of contact, clinical and laboratory findings and possible COVID-19 disease, whose radiological findings at PET/CT and CT were compatible with viral pneumonia and confirmed by PCR testing.

Results: Lung imaging findings suspicious of SARS-Co V-2 infection were found in 78 of 3135 patients (2,48%) included. The most frequent finding was multiple ground glass opacities (GGOs). In our study, we found characteristic peripheral ground-glass opacities with high FDG activitiy with increased nodal FDG uptake in favor of reactive lymphadenitis in FDG-PET/CT.

Conclusion: Chest CT is used in the initial diagnosis and monitoring of COVID-19 progression as well as in the evaluation of complications. Although PET imaging is not typically considered among the primary research methods for the diagnosis of lower respiratory tract infections, it has made a significant contribution to the incidental diagnosis of especially asymptomatic COVID-19 oncological cases.

Keywords: COVID-19, Coronavirus, Chest CT, FDG PET/CT, Oncologic indications.

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Severe acute respiratory syndrome coronavirus 2 (SARS-Co V-2) causing the coronavirus disease (COVID-19) was first isolated in December 2019 in Wuhan, China. Severe acute respiratory syndrome Coronavirus (SARS-Co V-2) and the Middle East respiratory syndrome Coronavirus (MERS-Co V) have caused severe respiratory disease and death in humans.[1]

Many patients infected with COVID-19 present as asymptomatic or with nonspecific symptoms like fever, cough, dyspnea, fatigue, myalgia, headache, odynophagia, diarrhea, anosmia, dysgeusia. Clinical manifestations of COVID-19 have typically been associated with respiratory complaints, though gastrointestinal, neurologic, cardiac, and hematologic presentations have also been observed.[2]

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Cancer is a high-risk factor for viral infections, and patients with cancer usually demonstrate an indolent clinical course in response to several coronavirus infections such as Middle East respiratory syndrome coronavirus (MERS-Co V) and SARS-Co V-2.[3]

The most common test technique currently used for COVID-19 diagnosis is a real-time reverse transcription-polymerase chain reaction (RT-PCR). Chest radiological imaging such as computed tomography (CT) and X-ray have vital roles in early diagnosis and treatment of this disease.[4] In addition, Fluorine-18 fluorodeoxyglucose (18F-FDG) positron emission tomography-computed tomography (PET-CT) is an imaging technique that plays an important role in the evaluation, follow-up, and monitoring of treatment response in many oncological and inflammatory lung diseases. However, thanks to its noninvasive nature and its capability to provide physiological information, the main applications of this technique have significantly expanded. Although PET-CT modality is not routinely used in the management of COVID-19 patients, it can provide complementary information to other laboratory and radiological data in selected cases. Although most available data suggest that COVID-19 is mainly a localized respiratory disease, a distant organ involvement has been reported in some patients.[5]

Our aim in this study is to retrospectively examine the suspected COVID-19 imaging findings and incidence in CT and PET/CT performed in asymptomatic patients referred to our clinic with an oncological indication.

Methods

This study was approved by Elazıg Fırat University Non-Interventional Clinical Research Ethics Committee (approval number: 2020/17-16). The study was conducted retrospectively at Elazig Medical Park Hospital in Turkey. For the purpose of the study, we reviewed all [18 F]-FDG PET/CT and Chest CT scans performed from March 2020 to September 2021. The patients who were referred to the Nuclear Medicine department for PET/CT with oncological indications, and were asymptomatic for SARS-Co V-2 infection were included. According to current practice recommendations of Nuclear Medicine Department PET-CT is not performed in all patients with any clinical evidence of respiratory tract infection. In fact, the day prior the PET-CT examination, a nuclear medicine physician contacted the patients and screened respiratory symptoms, delaying the scan in case of the presence of these symptoms. The patients who were symptomatic and diagnosed with COVID-19 diagnosis were excluded from the study. A total of 3135 patients who met the criteria were included in the cohort. The PET-CT scans were retrospectively reviewed to identify those with CT findings suggestive of COVID-19 pneumonia. Previously described imaging findings such as ground-glass opacities with low [18 F]-FDG uptake were considered suspicious images for SARS CoV 2 infection. Also, the extent of radiotracer uptake in these lung lesions was investigated. The patients who were diagnosed with COVID-19 in the retrospective evaluation conducted at the outpatient clinic that referred the patient, and whose diagnosis was confirmed, and those whose diagnosis was confirmed by clinical and laboratory evaluations were included in the study. All other patients were excluded.

The CT examinations were performed with either a GE Optima 600 or GE Medical systems CT scanner. The patients were placed in a supine position, with the head advanced and breathing on hold for scanning. 18F-FDG PET/CT was acquired in fasting patients, who had previous low-carbohydrate, high-fat, high-protein meal, from the skull base to the tights approximately 1 h after [18 F]-FDG injection (activity range 200–300 MB q, according to weight) with a GE Biograph m CT-S (64) system. The images obtained were analyzed with the GE Syngo TrueD 3D VOI isocontour tool.

The scanning parameters were as follows: 120 kV; 100–250 mAs; collimation of 5 mm; pitch of 1–1.5; matrix, 512 × 512. No contrast was administered. All images were transmitted to the post-processing workstation to be reconstructed by high-resolution algorithms and conventional algorithms.

Statistical Analysis

The data were analyzed using the Statistical Package for the Social Sciences software version 20.0 (IBM Corp., Armonk, NY, USA). The normal distribution of the data was assessed using histograms and the Shapiro-Wilk test. The descriptive data were given as mean, standard deviation, ranges or number (n) and percentage (%).

Results

Between March 2020 and September 2021, 3135 patients admitted to the nuclear medicine department were retrospectively analyzed. Seventy-eight patients meeting the inclusion and exclusion criteria were included in the study. Lung imaging findings suspicious of SARS-Co V-2 infection were found in 78 of 3135 patients (2.48%) included.

Our study involved the oncology patients with a history of contact, clinical and laboratory findings and possible COVID-19 disease, whose radiological findings at PET/CT and

CT were compatible with viral pneumonia and confirmed by PCR testing. These criteria were met in all 78 patients in the study.

The study population consisted of 27 women and 51 men with the mean age of 62.29±11.17 (22–89) years. Primary tumor locations and oncological treatments are detailed in Table 1. Lung, breast and lymphoma were the most frequent indications for 18F-FDG PET/CT (48.7% of the patients). Among those included in the study, 32 patients had applied for the diagnosis and staging of malignancy. The other 46 (58.97%) patients were those who had received oncological treatment before PET/CT, and applied to our clinic for treatment response and recurrence evaluation.

None of the patients on screening day had symptoms suggestive of viral pneumonia, such as fever or cough. The lung findings were evaluated using the non-contrast Chest CT component (lung window) of the PET/CT procedure performed on the patients. In most of our patients, the lung CT findings, which are detected in the majority of confirmed cases and are characterized by bilateral, ground-glass infiltrates with well-defined borders, predominantly peripheral and localized in lower lobes, were observed (Fig. 1). Chest CT findings including ground-glass opacities, vascular enlargement, bilateral abnormalities, lower lobe involvement, and posterior predilection have been reported in 82 % of RT-PCR test–proven COVID-19 cases. Consolidation and other findings accompanying COVID-19 disease (linear opacity, septal thickening and/or reticulation, crazy-paving pattern, air bronchogram, pleural thickening, bronchiectasis, nodules, bronchial wall thickening) have been reported in 18% of possible COVID-19 patients.

In our study, we found characteristic peripheral ground-glass opacities with high FDG avidity with increased nodal FDG uptake in favor of reactive lymphadenitis in FDG-PET/CT. The [18 F]-FDG PET/CT findings, clinical data and epidemiological considerations strongly suggested a diagnosis of COVID-19. All 78 patients showed lung findings both in CT and [18 F]-FDG PET. The findings we obtained during the examination in all patients are presented in Table 2. The most frequent finding was multiple ground glass opacities (GGOs) that coincided with low [18 F]-FDG uptake (Figs. 2, 3). The mean maximum standardized value (SUV max) of the GGOs was 3.7±0.7 (range: 2.9-4.9).

In the study, we detected mediastinal lymph nodes that were evaluated as reactive in nine (11.5%) patients. The most frequent sites exhibiting an increased [18 F]-FDG uptake outside lung parenchyma were mediastinal and hilar nodes (SUV max 4.15±0.78, ranges: 2.6-5.4) with a size less

Table 1. Primary tumor location and oncological treatment status of the population included in the sample

Variables	Number n, (%)	Stating	Response to Treatment Suspected recurrence
Tumor location			
Lung ca	15 (19.2)	3	12
Breast ca	13 (16.7)	4	9
Lymphoma	10 (12.8)	4	6
Viral pneumonia	10 (12.8)	0	0
Colon ca	7 (9.0)	0	7
Gastric cancer	3 (3.8)	2	1
Pancreas ca	3 (3.8)	2	1
Nasopharyngeal carcinoma	3 (3.8)	0	3
Prostate ca	2 (2.6)	1	1
Multiple myeloma	2 (2.6)	2	0
Over ca	2 (2.6)	1	1
Larynx ca	1 (1.3)	0	1
Bladder cancer	1 (1.3)	0	1
Parotid ca	1 (1.3)	1	0
Renal cell ca	1 (1.3)	0	1
Squamous cell carcinoma	1 (1.3)	0	1
Ureter ca	1 (1.3)	1	0
Soft tissue sarcoma	1 (1.3)	1	0
Kaposi's sarcoma	1 (1.3)	0	1
Toplam	**78**	**22**	**46**

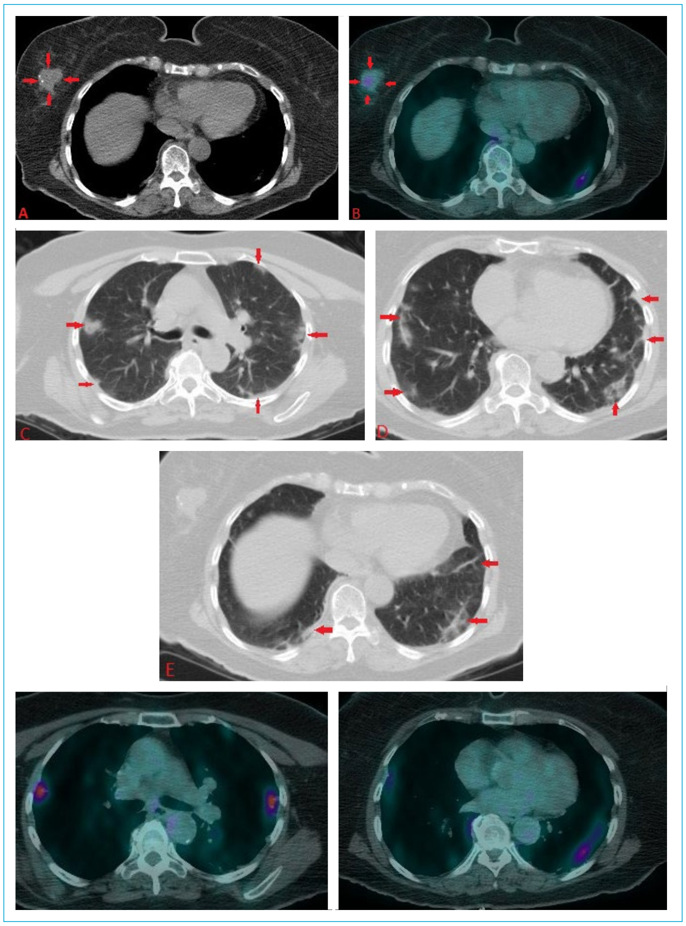

Figure 1. A 66 -year-old female with breast cancer. **(a)** Axial non-contrast chest CT and **(b)** PET CT show a mass in right breast (arrows). **(c-e)** CT shows bilateral , ground-glass infiltrates with well-defined borders, predominantly peripheral and localized in lower lobe (arrows). **(f,g)** PET CT shows increased [^{18}F]FDG uptake (SUV max 3.9).

Table 2. Characteristics of the image alterations found in the examinations

Distribution	
Periferal	69
Periferal and Central	9
Finding type	
Ground-glass opacities (GGOs)	64
Consolidation	14
Number	
Multiple	66
Unique	12
Mediastinal LAP	9

than 1 cm in all cases (Fig 4). These findings were interpreted as reactive inflammation.

The average SUV values of 10 patients who presented to our clinic with a preliminary diagnosis of malignancy were consistent with viral pneumonia, with bilateral peripheral ground-glass opacities in chest CT images. Several patients in this group had mediastinal lymphadenopathy. After PET/CT, COVID-19 diagnosis was confirmed in these patients. COVID-19 was considered in 10 out of 3135 (0.32%) patients with CT and PET/CT findings, and malignant processes were excluded (Fig. 4).

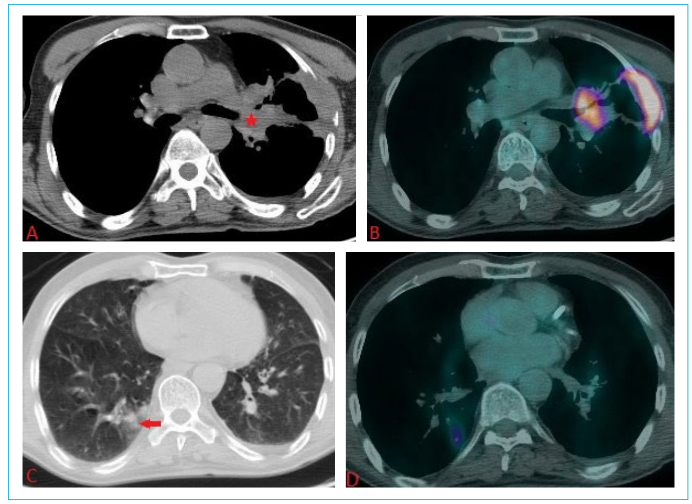

Figure 2. A 74-year-old male with lung cancer. **(a)** Axial non-contrast chest CT shows a mass in the left lung upper lob (star). **(b)** PET CT shows increased [^{18}F]FDG uptake in the mass. **(c)** CT shows unilateral, ground-glass infiltrates with well-defined borders, predominantly peripheral and localized in right lower lobe (arrow). **(d)** In this area, PET CT shows increased [^{18}F]FDG uptake (SUV max 4.9).

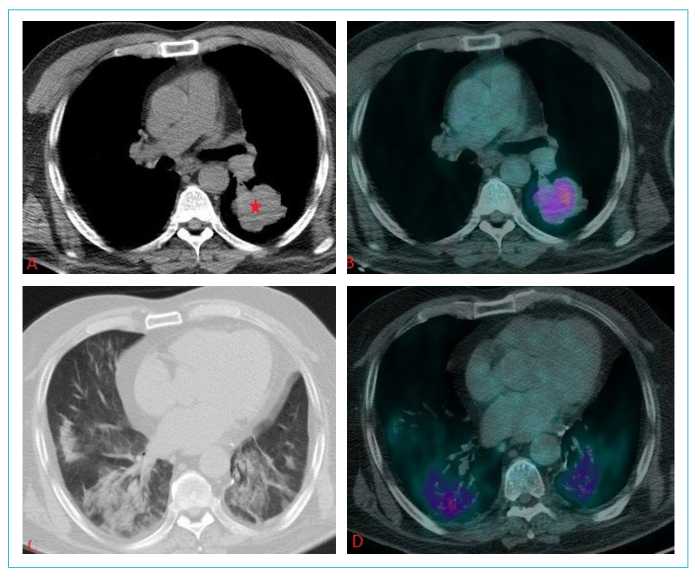

Figure 3. A 70-year-old male with lung cancer treated with surgery, chemotherapy and radiotherapy. PET CT was performed for the response of the disease to treatment and possible recurrence. **(a)** Non-contrast chest CT and **(b)** PET CT show a mass in the left lower lobe superior segment (star). **(c)** CT shows bilateral multifocal areas of patchy consolidation, predominantly peripheral and localized in lower lobes. **(d)** PET CT showed increased [^{18}F]FDG uptake (SUV max 3.5).

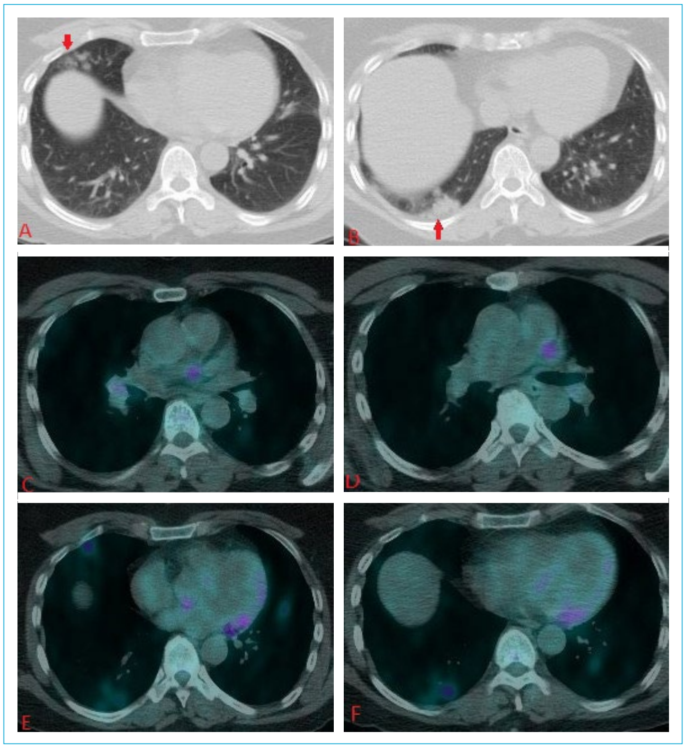

Figure 4. A 54-year-old patient who underwent PET CT with a preliminary diagnosis of mediastinal LAP and neoplasia, and viral pneumonia was considered on PET CT. CT shows bilateral, ground-glass infiltrates and focal consolidation predominantly peripheral and localized in the right medial lobes **(a)** and lower lob **(b)** (arrows). PET CT shows increased [^{18}F]FDG uptake in mediastinal nodes **(c)**, hilar nodes **(d)** and lung parancimal **(e,f)**.(SUV max 5.2)

Discussion

Limitations in the diagnosis of COVID-19, as the majority of patients infected with SARS-Co V-2 are asymptomatic or show scarce symptoms, were the reason for starting this retrospective study analyzing patients scanned with PET/CT. In the early days of the pandemic, it has been reported in various studies that the findings of COVID 19 CT scans were mistakenly evaluated as neoplasm in PET/CT. COVID 19 findings of some oncological patients who underwent PET/CT were missed.[6,7] Thus, the disease could not be diagnosed early in this risky group of patients and the disease exacerbated. At the same time, this group of patients created a public health risk.

Current studies have shown that lung imaging can manifest earlier than clinical symptoms. As detecting the disease quickly and accurately is of great significance, imaging plays a key role in preclinical screening. COVID-19 may be recognized early by detecting incidental findings in PET/CT, especially in asymptomatic cancer patients. Potential complications may be prevented by early diagnosis and anticancer therapy changes. Therefore, possible COVID-19 findings in PET/CT should be reported and the patient should be referred to a relevant clinician.

Only oncological patients undergoing PET/CT who had no clinical suspicion of SARS-Co V-2 infection before the procedure and had no fever or symptoms were included in the study. There are studies on PET/CT findings in COVID-19 patients, mostly symptomatic COVID-19 patients.[6]

In the literature, the articles by Albano et al., Polverani et al. and Cabrera Villegas A, et al. have been published on this subject.[6-8] We aimed to determine the incidence of COVID 19 disease in asymptomatic oncological patients. Compared to other studies in the literature, we retrospectively reviewed a larger patient group over a longer period of time. To the best of our knowledge, our study, which we completed with 3.135 patients, is the one including the highest number of patients in the literature. And we identified more patients (78) than any other studies in the literature in asymptomatic oncological patients who were considered probable COVID-19 by PET/CT and CT. Compared to the results reported by Albano et al. and Cabrera Villegas A et al. who studied on the largest patient group available in the literature, the incidence of incidental findings mentioned were slightly lower in our series that included a larger number of patients (>9%, >4.8%, respectively; versus 2.8% in our series).[6] The different detection rates may be explained by the large number of patients included and the exclusion of patients with non-oncological indications, as well as differences in incidence and prevalence among the populations. In addition, at the beginning of our study, the clinical and radiological findings of COVID-19 disease were better known than in the previous period. Most of the oncological COVID-19 patients had been identified by the relevant clinician before they were referred to the Nuclear Medicine Department. Our cohort involved a truly asymptomatic group of patients who were not felt to have COVID-19 by the referred clinician and by the persons themselves, and were not recognized in the evaluation prior to the examination. Therefore, it was more difficult to find a silent asymptomatic oncological patient group. In addition, since we conducted the study on a larger patient group, our accuracy rate could be considered to be higher.

Various chest CT findings such as ground glass opacities have been reported in the majority of COVID-19 cases confirmed by RT-PCR testing.[9] In our study, consistent with the literature, we found that the density of ground glass was the major finding in the oncology patients with COVID-19.

In addition, we found other clinical signs such as consolidation of pulmonary interstitial structures, septal thickening and/or reticulation, crazy laying pattern, air bronchogram, pleural thickening, reverse halo sign, bronchiectasis, nodules, bronchial wall thickening, pulmonary vascular enlargement, and reverse halo sign. The distribution of chest CT findings was typically bilateral, multifocal, diffuse and localized in the lower lobe, peripheral subpleural and posterior.[10] While not typical features of disease, pleural effusion, lymphadenopathy, tree-in-bud sign, central lesion distribution, pericardial effusion, and cavitating lung lesions have been reported in a minority of cases and may herald poorer clinical outcomes.[11] Other radiological findings were similar to the literature.

GGOs together with focal consolidation are thought to be indicators of organizing pneumonia, where lesion formation may be related to ongoing pulmonary edema and hyaline membrane formation. The presentation of COVID-19 pneumonia on imaging varies at different stages of the disease and usually corresponds to different stages of organizing pneumonia or diffuse alveolar damage.[12]

Knowledge of the natural temporal evolution of lung abnormalities in COVID-19 can assist radiologists in staging the disease and distinguishing them from potential complications when evaluating chest CT scans.

More recently, molecular imaging and nuclear medicine modalities such as single photon emission computed tomography and PET have been shown to provide high sensitivity in detecting pulmonary infection and inflammation.[13]

The ability of FDG-PET to identify infection and inflammation is essentially based on the same pathophysiological mechanism as malignancies, which involves a highly glycolytic activity and cellular metabolism occurred in the inflammatory response. Increased FDG uptake by inflammatory cells is mainly related to high levels of glucose transporters and hexokinase activity expressed by inflammatory cells.[14] Chefer et al. observed that the host response against MERS-Co V pneumonia increases monocytes in lymphoid tissue of an experimental model, causing an abnormal pulmonary FDG uptake. Although limited, these findings could explain the FDG uptake observed in the pulmonary interstitial tissue of our COVID-19 cases, even in the absence of clinical manifestations.[15]

Although 18F-FDG-PET/CT is not routinely applied in emergencies and specifically for the diagnosis of pneumonia types, its potential clinical value has already been demonstrated in pulmonary inflammatory/infectious conditions.[13] Correct and early differentiation of SARS-Co V-2 from other viral pneumonia, tumoral or post-therapeutic changes (e.g., radiation or cytostatic pneumonitis), or other inflammatory diseases carries a high prognostic and treatment relevance and could indicate a close follow-up in selected patients. In the literature, there are studies that have reported incidental detection of COVID-19 in PET/CT retrospectively. In these studies, increased nodal FDG uptake supporting reactive lymphadenitis and characteristic peripheral ground-glass opacities with high FDG avidity has been found.[16] Our most common finding was multiple GGOs, which coincided with low [18 F]-FDG uptake, similar to the literature. The mean SUV max of GGOs was 3.7±0.7 (range: 2.9-4.9), which were lower than those reported in the literature.[6] We think that our findings have a higher accuracy rate since we obtained the findings on a larger patient group. In addition, unlike the literature, we ruled out oncological diseases with CT and PET/CT findings in 10 patients and helped the clinician in terms of possible COVID-19 cases. In the light of these findings, we prevented the patient from receiving wrong diagnosis and treatment.

Indeed, PET/CT, which carries additional information about metabolic changes at the cellular level, can detect disease before being manifested in other imaging tests. It should be noted that PET/CT is neither the first-choice method for the diagnosis of COVID-19 nor a screening technique. However, in PET/CT evaluation, the diffuse bilateral multifocal increased FDG uptake in the lung should be suggestive of COVID-19 in the differential diagnosis. In these days of the COVID 19 pandemic, PET/CT evaluation should be performed together with lung window CT imaging. Thus, confusion of pathognomonic ground-glass appearances with other pathologies should be avoided. In our study, we obtained a more accurate incidence of asymptomatic patients, more realistic FDG uptake values and CT characteristic findings of viral pneumonia by screening larger numbers of patients in a longer period of time.

Thus, we wanted to emphasize the contribution of CT and PET/CT to the identification of oncology patients, who are a risky group, without threatening their own health and then the public health. In this regard, especially in oncology patients, nuclear medicine specialists, radiologists and oncologists should collaboratively work together on imaging diagnostic methods and the subsequent clinical management of the patient.

Disclosures

Ethics Committee Approval: Elazıg Fırat University Ethics Committee, The study adhered to the principles of the Helsinki Declaration of Human Rights and received Ethics Committee approval (31/12/2020, Document No. 2020/17-16).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – T.O., Y.N.; Design – T.O., F.O.K.; Supervision – T.O., F.O.K.; Materials – T.O., C.A., Y.N.; Data collection &/ or processing – T.O., C.A., Y.N.; Analysis and/or interpretation – T.O., C.A., Y.N.; Literature search – T.O., F.O.K.; Writing – T.O.; Critical review – T.O., F.O.K.

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