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ORIGINAL ARTICLE

Assessment of extra-parenchymal lung involvement in asymptomatic cancer patients with COVID-19 pneumonia detected on ^{18}F-FDG PET-CT studies

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Abstract

Background Lung involvement in patients with coronavirus disease 2019 (COVID-19) undergoing PET-CT has been previously reported. However, FDG uptake outside lung parenchyma was poorly characterized in detail. We evaluated the extra-parenchymal lung involvement in asymptomatic cancer patients with COVID-19 pneumonia through ^{18}F-FDG PET-CT.

Methods A total of 1079 oncologic ^{18}F-FDG PET-CT were performed between February 2 and May 18, 2020. Confirmed COVID-19 pneumonia was defined as characteristic ground-glass bilateral CT infiltrates and positive genetic/serologic tests. Nonmetastatic extra-parenchymal lung PET-CT findings were evaluated through qualitative (visual), quantitative (measurements on CT), and semiquantitative (maximum standardized uptake value: SUVmax on PET) interpretation. Clinical data, blood tests, and PET-CT results were compared between patients with and without COVID-19 pneumonia.

Results A total of 23 ^{18}F-FDG PET-CT scans with pulmonary infiltrates suggestive of COVID-19 and available laboratory data were included: 14 positive (cases) and 9 negative (controls) for COVID-19 infection, representing a low prevalence of COVID-19 pneumonia (1.3%). Serum lactate dehydrogenase and D-dimers tended to be increased in COVID-19 cases. Extra-parenchymal lung findings were found in 42.9% of patients with COVID-19, most frequently as mediastinal and hilar nodes with ^{18}F-FDG uptake (35.7%), followed by incidental pulmonary embolism in two patients (14.3%). In the control group, extra-pulmonary findings were observed in a single patient (11.1%) with ^{18}F-FDG uptake located to mediastinal, hilar, and cervical nodes. Nasopharyngeal and hepatic SUVmax were similar in both groups.

Conclusion In cancer patients with asymptomatic COVID-19 pneumonia, ^{18}F-FDG PET-CT findings are more frequently limited to thoracic structures, suggesting that an early and silent distant involvement is very rare. Pulmonary embolism is a frequent and potentially severe finding raising special concern. PET-CT can provide new pathogenic insights about this novel disease.

Keywords ^{18}F-FDG · PET-CT · COVID-19 · SARS-CoV-2 · Cancer · Extra-parenchymal lung

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing the coronavirus disease 2019 (COVID-19) was isolated during December 2019 in Wuhan, China [1]. In a few weeks, this novel coronavirus spread all over the world, turning into a public health emergency. At the beginning of the pandemic, Italy and Spain were the most affected countries after China. Many patients infected with COVID-19 present as asymptomatic or with nonspecific symptoms like fever, cough, dyspnea, fatigue, myalgia, headache, odynophagia, diarrhea, anosmia, or dysgeusia. Although most of them have mild presentations, a considerable proportion develops severe

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complications (acute respiratory distress syndrome, serum viral load, cardiac injury, and secondary infection). Reverse-transcriptase polymerase chain reaction (rRT-PCR) from respiratory tract samples is the gold standard for diagnosis of COVID-19 [2]. However, some imaging techniques as chest computed tomography (CT) may strongly suggest the infection until laboratory results are available [3].

Cancer is a high-risk factor for viral infections [4, 5], and patients with cancer usually demonstrate an indolent clinical course in response to several coronavirus infections as Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV [6–8]. The clinical evidence provided by Zhang et al. in China [9] and Onder et al. in Italy [10] confirmed the higher risk of this subpopulation during COVID-19 outbreaks. In particular, oncologic patients older than 60 years have an excess risk of infection, deserving special diagnostic attention [11]. Sites suffering from a high prevalence of the novel disease optimized the allocation of resources with preventive, diagnostic, and management recommendations of scientific societies. In this unique clinical context, it was proposed that shortening the course of onco-specific interventions could provide an optimal therapeutic strategy in cancer patients, reducing the exposure and the risk of infection [12]. However, some diagnostic and therapeutic processes were still being carried out in selected cancer patients despite the current situation of healthcare system.

Fluorine-18 fluorodeoxyglucose (^{18}F-FDG) positron emission tomography-computed tomography (PET-TC) is an imaging technique playing an important role during the evaluation, follow-up, and monitoring of treatment response in several oncological and inflammatory lung diseases [13]. Although this image modality is not routinely used in the management of COVID-19 patients, it could contribute to give complementary information to other laboratory and radiological data in selected cases. In addition, whole-body PET-CT allows evaluating not only the lung tissue but also other organs that could help to detect a multi-organ involvement, providing new insights about pathogenic and host response against SARS-CoV-2 infection. Although most available data suggests that COVID-19 is mainly a localized respiratory disease, a distant organ involvement has been reported in some patients. In addition, a deeper knowledge about the shift in cellular metabolism produced in the lungs and other tissues could have specific diagnostic, prognostic, and therapeutic implications. This research was aimed to evaluate the extra-parenchymal lung involvement in asymptomatic cancer patients with COVID-19 pneumonia derived to ^{18}F-FDG PET-CT.

Materials and methods

Patient selection

Although first outbreak of SARS-CoV2 infection in Spain was detected in the Canary Islands at the end of January 2020 [14], it was on February 25 when the first case was confirmed in Madrid [15]. On March 26, 12 days after the national state of alarm was decreed, Madrid registered the peak of new cases [16]. On April 2, Spain suffered the highest number of deaths per day due to this pandemic [17].

All PET-CT scans performed between February 2 and May 18, 2020, were reviewed ($n = 1157$). After excluding the PET-CT studies performed with radiotracers different from ^{18}F-FDG, localized brain studies and non-oncological indications, a total of 1079 oncologic ^{18}F-FDG PET-CT were included. According to current practice recommendations of Nuclear Medicine centers [18], all patients with any clinical evidence of respiratory tract infection did not undergo PET-CT study. In fact, the day prior the PET-CT study, a nuclear medicine physician contacted the patients and screened respiratory symptoms, delaying the scan in case of the presence of these symptoms.

Study design and data collection

A single-center retrospective observational, analytical, transversal study was performed. PET-CT scans were retrospectively reviewed to identify those with CT findings suggestive of COVID-19 pneumonia. Also, CT and FDG uptakes suggestive of non-parenchymal lung involvement of SARS-CoV-2 were characterized in detail. Clinical and demographic variables, ^{18}F-FDG PET-CT indications, presence of metastatic disease, previous oncological treatment, and blood test data (lymphocytes and monocytes count, liver transaminases, C-reactive protein, lactate dehydrogenase, and D-dimers) were analyzed.

Diagnosis of COVID-19 pneumonia and clinical referral after PET scan

CT images were reviewed and categorized using COVID-19 Reporting and Data System (CO-RADS) criteria [19]. The gold standard diagnostic technique was rRT-PCR from nasopharyngeal swabs. We defined confirmed COVID-19 pneumonia as those cases with CO-RADS categories 4 and 5 in CT scan of each PET-CT study plus a positive result of rRT-PCR test. Since the low sensitivity of rRT-PCR test could cause the diagnosis to be missed or delayed, we also consider the positive results of serum serological enzyme-linked immunosorbent assay (ELISA) test for IgM or IgG as confirmed cases. Because negative rRT-PCR results carry a very low false negative rate and CO-RADS criteria were not broadly validated for the diagnosis of COVID-19 pneumonia in asymptomatic cancer patients, we considered that this approach seems reasonable to correctly differentiate between both groups of patients. All patients with suspected COVID-19 pneumonia on CT were derived by a nuclear medicine physician to the

emergency department (ED), immediately after contacting the oncology team.

^{18}F-FDG PET/CT protocol

Intravenous 5 MBq/kg ^{18}F-FDG dose was administrated after 6 h fasting in nondiabetics or 4 h in diabetic patients, assuming a physical and sensory rest during 40–60 min prior to image acquisition. Blood glucose levels less than 200 mg/dL were required before radiotracer injection. All studies were acquired in the same equipment (Biograph 6 True Point; Siemens) following the European Association of Nuclear Medicine guidelines. An intravenous (IV) iodinated contrast agent (130 ml of Iohexol, 300 mgI/mL) was administered in all patients, in the absence of contraindications. An inspirational chest CT study was performed with a slice thickness of 2.5 mm, 60 mAs and 110 KV, with a tube rotation time of 0.6 s and a pitch of 1.2. Then, another body CT study was performed from the base of the skull to the midthigh in craniocaudal direction during free breathing. Finally, the PET study was performed in the same locations as the CT study, in caudo-cranial direction, during free breathing.

Image interpretation

All PET scans were reviewed by at least two experts (a nuclear medicine physician and a radiologist). We also reviewed the FDG uptake patterns through the whole-body in maximum intensity projection images (MIP) and axial, coronal, and sagittal PET views. Abnormal CT data in extra-parenchymal lung tissues was also reported (Table 1). The SUVmax values obtained in the nasopharyngeal and liver parenchyma were compared with normal values. Finally, experts reported an etiologic judgment about extra-parenchymal lung involvement (tumoral vs. COVID-19 related) by consensus.

Statistics

Continuous data were expressed as mean ± standard deviation (SD) or median (IQR 25–75%), and discrete variables were presented as absolute and relative frequencies (*n*, %). A Fisher exact test was used to compare discrete variables. Mann-Whitney test was applied to compare continuous clinical and analytic variables and SUVmax among patients with positive (confirmed cases) and negative rRT-PCR (controls). SUVmax of nasopharyngeal and liver parenchymas were compared between both groups through unpaired *t* test. A p value < 0.05 was considered significant (two tailed).

Table 1 Criteria applied for labeling positive extra-parenchymal lung findings on PET and CT

PET criteria	CT criteria
Lymph nodes FDG uptake	Lymph nodes enlargement (> 1 cm)
Increased liver FDG uptake†	Thrombus on CT with contrast
Increased nasopharynx FDG uptake‡	

†Considering the physiological hepatic SUVmax 5.0 ± 0.8 [20]

‡Considered physiological activity (SUVmax: 3.9 ± 1.4) [21]

Results

Clinical and biochemical profile

From a total of 1079 consecutive oncological ^{18}F-FDG PET-CT examinations, 89 patients exhibited pulmonary infiltrates on CT. Only 23 of them exhibited CT findings classified as CO-RADS 4–5 categories and underwent rRT-PCR after ^{18}F-FDG PET-CT (Table 2). While this confirmatory test was positive in 13 and negative in 9 patients, an additional single patient was confirmed by specific immunoglobulin G (IgG) test ($n = 14$ cases), representing a low prevalence of COVID-19 pneumonia (1.3%). RT-PCR and ELISA tests were performed in the first 3 days after PET-CT and between 1 and 46 days after PET-CT, respectively, in accordance with the clinical judgment of in-hospital staff. This study population consisted of 12 women and 11 men, mean age: 66.0 (34–88 years). Weight and height were 70.7 ± 11.0 kg and 166.6 ± 8.1 cm, respectively. Primary tumor location, oncological treatments, and metastatic disease are detailed in Table 2. Breast, lung, and head and neck cancer were the most frequent indications for ^{18}F-FDG PET-CT (52.2% of the patients). Both cases and controls were comparable in terms of the proportion of male gender ($p > 0.99$), age ($p = 0.11$), weight ($p = 0.46$), height ($p = 0.83$), and metastatic disease ($p = 0.39$). Almost half (47.8%) of our sample had received oncological treatment before PET-CT. Metastatic cancer was observed in 34.8% ($n = 8$); 3 of these patients also have extra-parenchymal lung findings suggestive of COVID-19. Serum C-reactive protein and lactate dehydrogenase were similar in the confirmed and control groups (2.56 ± 3.53 vs. 1.38 ± 1.17, $p = 0.35$; 559 ± 205 vs. 470 ± 145, $p = 0.28$; respectively). D-dimers tended to be higher in COVID-19 confirmed cases compared with controls (1919 ± 1533 vs. 832 ± 547, $p = 0.09$) although the differences did not reach statistical differences. Other analytical values were very similar between both groups (Fig. 1).

Lung parenchyma involvement

Lung CT findings detected in most confirmed cases were characterized by bilateral, ground-glass infiltrates with well-defined borders, predominantly peripheral and in lower lobes. In contrast, patients in the control group exhibited bilateral infiltrates

Table 2 Baseline demographic, extra-parenchymal lung PET-CT findings, oncological characteristics, and COVID-19 diagnosis results

Patient No.	Sex (F/M) †	Type of cancer	Oncological therapies ‡	Extra-parenchymal lung PET findings	Extra-parenchymal lung CT findings	Metastatic cancer	rRT-PCR
1	M	Lung cancer	–	–	–	No	Negative
2	M	Head and neck cancer	CTX/RT	–	–	No	Positive
3	F	Head and neck cancer	CTX/RT	Subcarinal ($n = 1$), bilateral hilar ($n = 2$) and pulmonary aortic window ($n = 1$) lymph nodes	Segmental PE	No	Positive
4	F	Head and neck and breast cancer	CTX/RT/IT	–	–	No	Positive
5	F	Breast cancer	–	Subcarinal ($n = 1$), bilateral hilar ($n = 2$) and bilateral cervical ($n = 2$) lymph nodes	–	No	Negative
6	M	Kidney cancer	–	Subcarinal ($n = 1$), bilateral hilar ($n = 2$) and low pretracheal ($n = 1$) lymph nodes	–	Yes	Positive
7	F	Cervix cancer	–	Subcarinal ($n = 1$) and bilateral hilar ($n = 2$) lymph nodes	–	No	Positive
8	F	Colon cancer	CTX/RT/IT	–	–	No	Positive
9	M	Ampullary cancer	–	–	–	No	Positive
10	F	Breast cancer	CTX/RT	–	–	Yes	Negative
11	F	Lung cancer	–	Subcarinal ($n = 1$), left hilar ($n = 1$), right paratracheal ($n = 2$) and bilateral supraclavicular ($n = 2$) lymph nodes	–	No	Positive
12	M	Urothelial cancer	–	–	–	Yes	Positive
13	F	Lymphoma	CTX	–	–	Yes	Negative
14	M	Head and neck cancer	–	–	–	No	Positive
15	F	Ovarian cancer	–	Subcarinal ($n = 1$) and right hilar ($n = 1$) lymph nodes	–	Yes	*
16	F	Breast cancer	CTX/RT	–	–	No	Negative
17	F	Lung cancer	CTX/RT	–	–	No	Negative
18	M	Lymphoma	–	–	–	No	Negative
19	M	Pancreatic cancer	CTX	–	–	No	Negative
20	M	Lung cancer	–	–	–	Yes	Positive
21	M	Multiple myeloma	CTX/RT	–	–	No	Negative
22	F	Breast cancer	CTX/RT	–	–	Yes	Positive
23	M	Melanoma	IT	–	Segmental PE	Yes	Positive

†*F* female, *M* male

‡*CTX* chemotherapy, *RT* radiotherapy, *IT* immunotherapy

*Patient with confirmed diagnostic by serologic IgG test for COVID-19

that tended to be less well defined, with a patchy distribution, located mainly in the middle and lower lung fields. SUVmax of ground-glass infiltrates were similar in confirmed cases than in controls (5.2 ± 3.3 vs. 4.4 ± 2.3, $p = 0.50$).

PET-CT findings outside lung parenchyma

Extra-parenchymal lung findings were found in 42.9% (6/14) of confirmed COVID-19 patients (Fig. 2). The most frequent sites exhibiting an increased ^{8}F-FDG uptake outside lung parenchyma were mediastinal and hilar nodes (35.7%, 4/14; SUVmax 5.8 ± 1.4) with a size less than 1 cm in all cases, except for a single subcarinal node with a size greater than 1 cm (Table 2, Fig. 3). These findings were interpreted as reactive inflammatory by experts.

Pulmonary embolism (PE) was incidentally detected in two COVID-19 patients (14.3%), located in the right and left inferior lobar segmental artery, respectively (Fig. 4). These patients presented the highest D-dimer values (4306 and 4221 pg/mL, respectively).

One patient with squamous cell lung cancer exhibited focal and intense ^{18}F-FDG uptake in pericardium, in the presence of

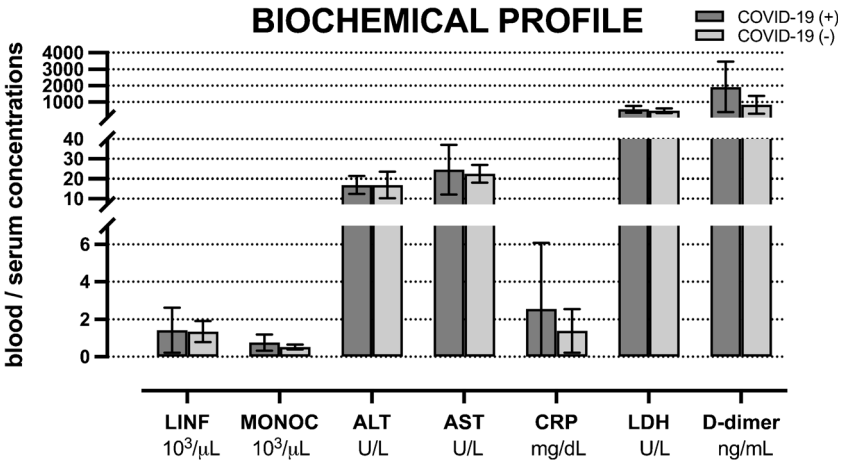

Fig. 1 Comparison of analytics between positive and negative COVID-19 patients referred to PET-CT. There were no statistical differences between both groups. *LINF* lymphocytes blood count, *MONO* monocytes blood count, *ALT* serum alanine aminotransferase, *AST* serum aspartate aminotransferase, *C-RP* serum C-reactive protein, *LDH* serum lactate dehydrogenase

normal serum troponins. After interpreting the CT images and the qualitative and semiquantitative molecular changes, the experts suggested a tumoral etiology in this case that was later confirmed by histopathology.

In the controls, extra-parenchymal findings were observed in a single patient (11.1%), with an increased ^{18}F-FDG uptake located in mediastinal, hilar, and cervical lymph nodes. We found no differences between both groups in nasopharyngeal (4.5 ± 0.9 vs. 3.9 ± 0.9, $p = 0.16$) and liver SUVmax (3.7 ± 0.4 vs. 3.5 ± 0.5, $p = 0.31$) (Fig. 1).

Discussion

Frequency of COVID-19 pneumonia in asymptomatic cancer patients

While pulmonary infiltrates were found in 8.2% of asymptomatic oncologic patients derived to ^{18}F-FDG PET-CT, characteristic tomographic changes and laboratory confirmation were available in 23 patients (2.1%). Pulmonary infiltrates were positive on FDG, with a variable amount of uptake. The positive confirmatory test observed in 14/23 patients represent a true prevalence of COVID-19 pneumonia of 1.3% in our sample. The prevalence reported by small case series are broadly variable (from 8 to 38%), since they are related with cancer subjects with suspicious CT findings and partial or total absence of laboratory confirmation [22–24]. Our very low prevalence could be related with more restrictive criteria applied to select the cancer patients derived to ^{18}F-FDG PET-CT and the heterogeneous, unpredictable prevalence of the disease during different study periods.

Analytical profile of COVID-19 pneumonia in cancer patients

In cancer patients with COVID-19 in Wuhan, the admission findings included several nonspecific abnormalities like

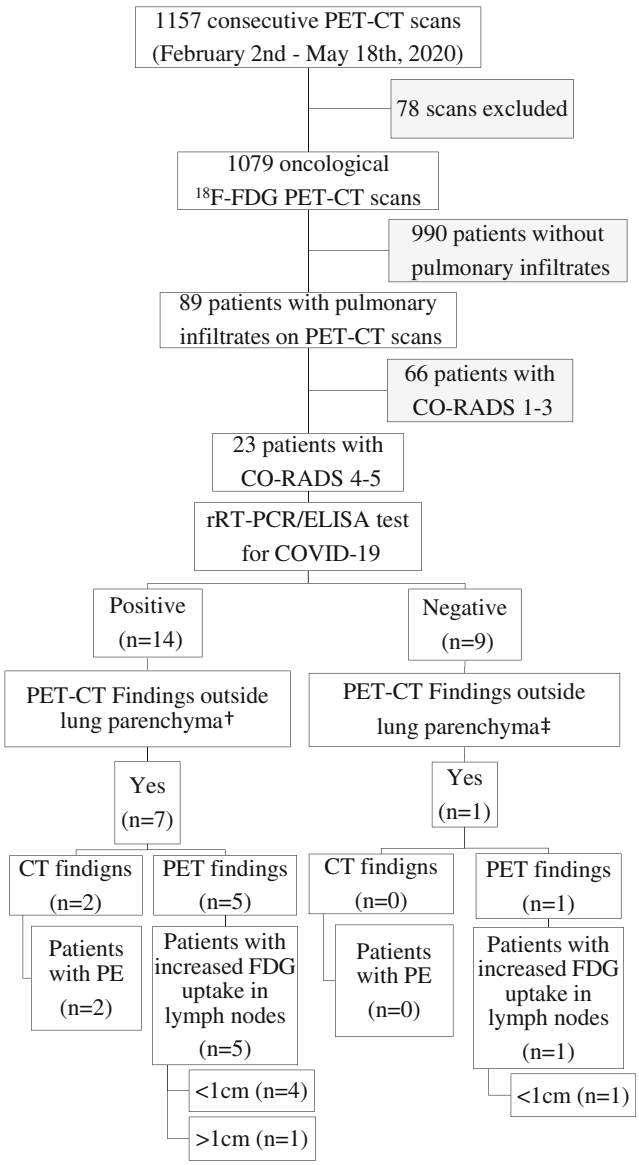

Fig. 2 Flow chart of the patient's selection and obtained results. † 11 of the 14 CT were performed with IV contrast. ‡ 8 of the 9 CT were performed with IV contrast

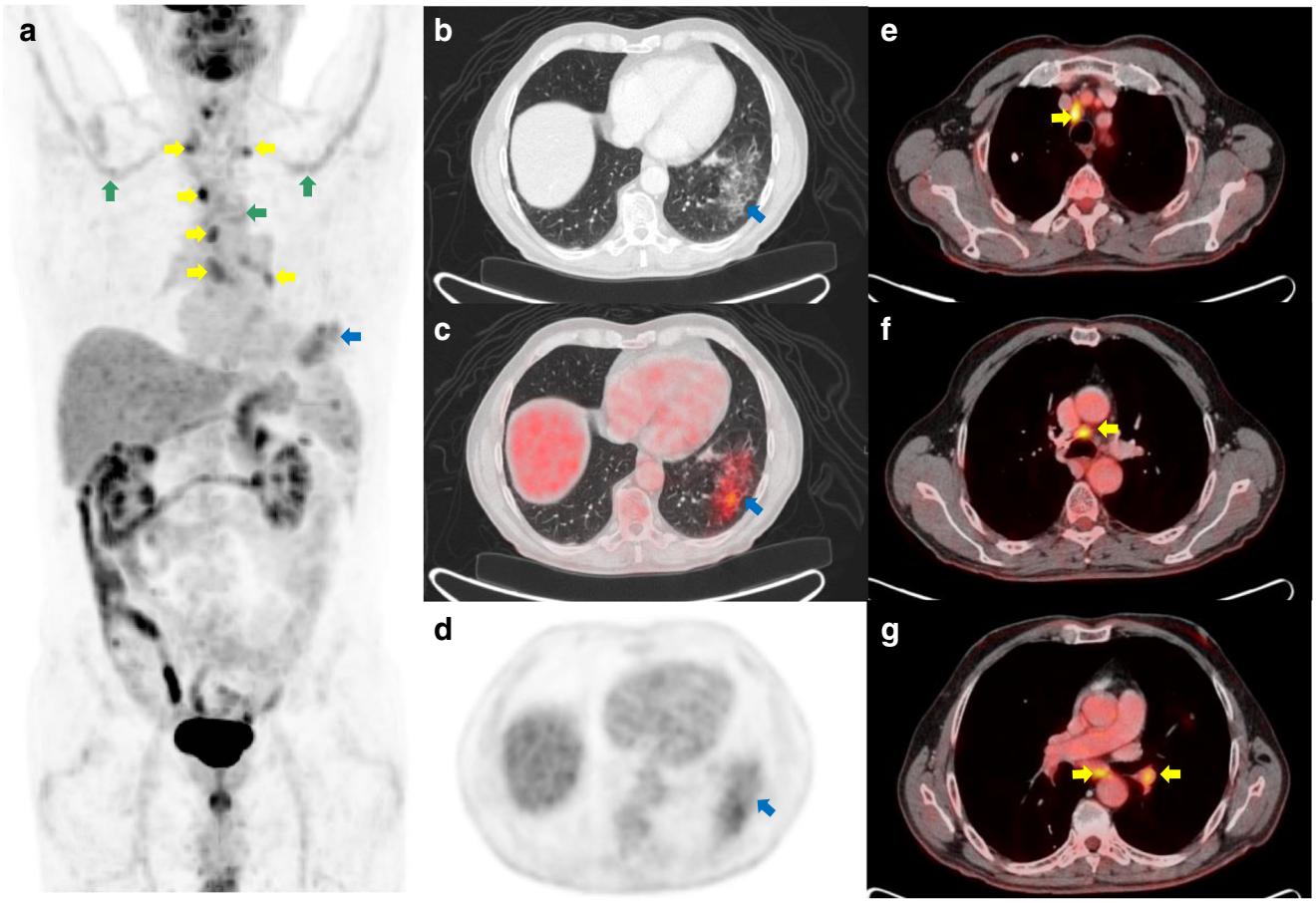

Fig. 3 A 79-year-old male with malignant ampulloma resected in 2017. PET-CT was performed due to suspicion of recurrence. (**a**) Maximum intense projection (MIP) demonstrating increased metabolic uptake in left lung base (blue arrow) and supraclavicular and mediastinal lymph nodes (yellow arrow). Axial views of (**b**) CT, (**c**) fusion, and (**d**) PET images showing ground-glass lung infiltrates in the left lower lobe with intense FDG uptake (blue arrows). (**e**, **f**, **g**) Fusion axial views showing right paratracheal, pretracheal, left hilar, and subcarinal lymph nodes (yellow arrows), all with intense FDG uptake and < 1 cm except the subcarinal node, which measures 1.3 cm. rRT-PCR confirmed COVID-19 at the ED

anemia, leucopenia, lymphopenia, low levels of albumin, and raised inflammatory reactants as lactate dehydrogenase, sensitive C-reactive protein, and erythrocyte sedimentation rate [9]. These profiles may be related to the underlying cytokine storm, with progressive activation of neutrophils, monocytes, and T-helper cells [25, 26]. However, it is well-known that acute phase reactants could be elevated in cancer patients without infections, in relation to the types, subtypes, and stages of cancer and even with oncologic therapies. On the other hand, it cannot be discarded that biochemical changes observed in non-confirmed COVID-19 could be caused by other viral agents causing pneumonia in cancer patients [27].

We found a trend toward higher levels of D-dimers in our sample of patients with confirmed COVID-19 pneumonia, with no statistical significance, in line with the results of a recently published meta-analysis [28]. Chen et al. described that 36% of patients with COVID-19 pneumonia have increased D-dimer levels [29], possibly as a consequence of an imbalance between procoagulant and anticoagulant homeostatic mechanisms. Remarkably, the two highest values of D-dimers in our sample corresponded to patients with COVID-19 pneumonia and incidental PE detected on CT.

CT findings and FDG uptake in the thorax

SUVmax of lung infiltrates was heterogeneous in previous case series reports of COVID-19 pneumonia, with means (range) of confirmed cases of 6.0 (4.3–11.3) [22] and 4.4 (2.0–6.9) [23]. Moreover, due to the small number of subjects, these authors could not compare the SUVmax of pulmonary infiltrates between patients with confirmed and suggestive COVID-19 pneumonia. Furthermore, they could not assess any tracer avidity suggesting viral spread and/or cellular inflammatory response outside lung parenchyma. We did not found differences in lung SUVmax associated with COVID-19 pneumonia, suggesting that semiquantitative FDG uptake could be a nonspecific marker of different viral pneumonia in cancer patients. This hypothesis must be confirmed in larger, multicenter series.

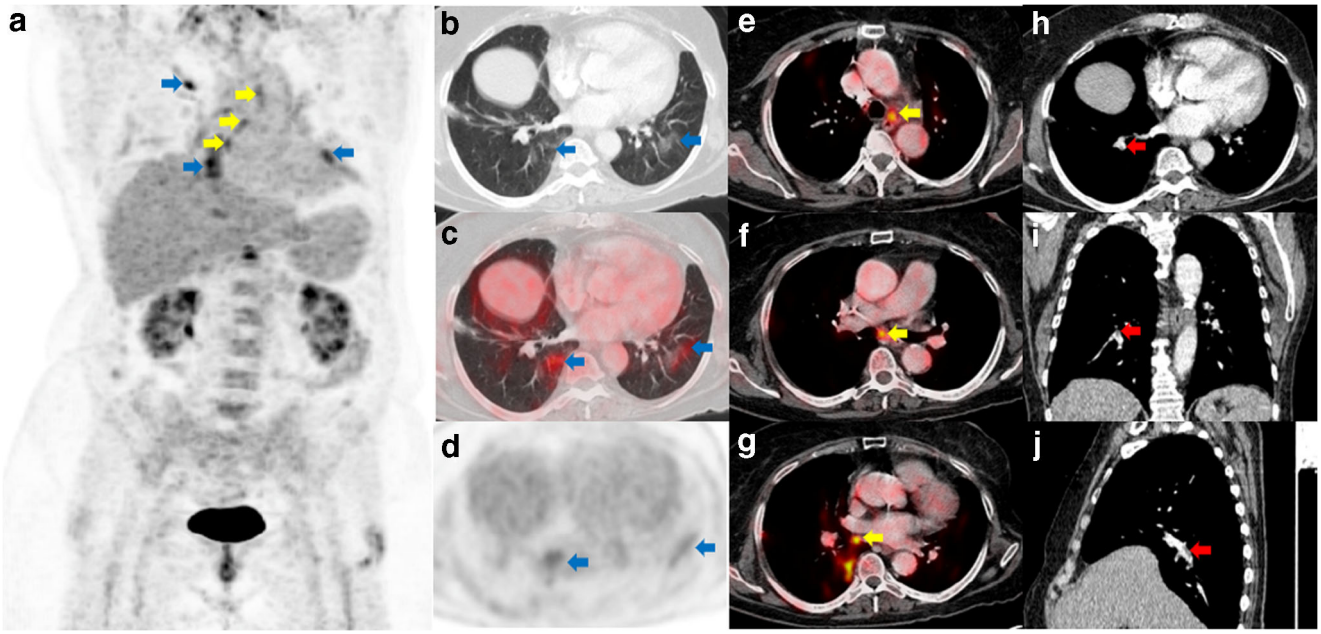

Fig. 4 A 70-year-old woman with head and neck cancer treated with surgery, chemotherapy and radiotherapy, MIP follow-up PET-CT (**a**) showing FDG uptake in lung infiltrates (blue arrows) and thoracic lymph nodes (yellow arrows). We can also observe intense FDG uptake in both subclavian arteries and mild uptake in thoracic aorta (green arrows). CT (**b**), fusion (**c**), and PET (**d**) axial views demonstrating bilateral ground-glass opacities in lungs with FDG uptake (blue arrows). (**e**, **f**, **g**) PET-CT axial views showing lymph nodes < 1 cm (yellow arrows) in (**e**) aortopulmonary window, (**f**) subcarinal, and (**g**) left hilar with intense FDG uptake. (**h**) Axial, (**i**) coronal, and (**j**) sagittal CT slices showing a filling defect, suggesting thrombus in the segmental right lower lobe artery (red arrows). As interstitial pneumonia was located in the same affected lobe, an in situ thrombosis mechanism was suggested. The patient was referred to the ED, where rRT-PCR confirmed COVID-19

After assuming several strict criteria to diagnose COVID-19 pneumonia, FDG uptake observed in lung parenchyma secondary to other inflammatory process with an indolent course seems highly improbable. So, our results suggest that CO-RADS 4–5 categories, although suggestive, could be less specific of COVID-19 pneumonia in cancer patients than previously reported. It was a predictable finding, since the sample of subjects in which CO-RADS diagnostic criteria were validated included patients with moderate/severe symptoms and a percentage of 21% patients with cancer [19]. Tian et al. described the histopathological findings of two patients surgically treated by lung lobectomies for adenocarcinoma with COVID-19 at the time of surgery. In them, the pathologic examinations revealed edema, proteinaceous exudate, focal reactive hyperplasia of pneumocytes with patchy inflammatory cellular infiltration, and multinucleated giant cells, apart from usual neoplastic findings. Since both patients did not exhibit any respiratory symptom at the time of surgery, these changes were interpreted as early silent pathologic hallmarks of COVID-19 pneumonia [30]. Chefer et al. observed that the host response against MERS-CoV pneumonia increases monocytes in lymphoid tissue of an experimental model, causing an abnormal pulmonary FDG uptake [31]. 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.

Regional lymph node involvement is frequently observed in several viral pneumonias. However, the metabolic activity has been poorly described in patients with COVID-19 pneumonia. As CT became the most widely imaging technique used for pulmonary assessment of COVID-19, it was expected that the real percentage of patients with inflammatory lymphadenopathy were higher than expected. And since PET-CT provides anatomic and metabolic information in the same study, this technique would be more sensitive to detect inflammatory and tumoral lymph nodes, mainly in the small ones. We found an increased ^{18}F-FDG uptake in mediastinal and hilar lymph nodes in 26.1% of patients (6/23) and in 35.7% (5/14) of confirmed COVID-19 patients, much more than the 1% previously reported in cases studied by chest CT [32]. Five of this 6 patients exhibited small lymph nodes (< 1 cm). The results obtained by previous case series applying ^{18}F-FDG PET-CT were heterogeneous; Albano et al. found mediastinal adenopathies in 1/5 confirmed patients [23], and Rasilla et al. did not report lymphoid FDG uptake [24].

As far as we know, the incidental and simultaneous association of lung infiltrates and PE in cancer patients with COVID-19 has not been documented, raising special concern from the diagnostic, prognostic, and therapeutic points of view. Thrombotic complications are frequently observed in critical patients with COVID-19, with a venous thromboembolism incidence of 27% and an arterial thrombotic event

incidence of 3.7% [33]. Both events are associated with poor outcomes [34]. Some researchers have described the prothrombotic state associated with SARS-CoV-2 infection with high levels of serum D-dimers and variable risk of thromboembolic events [35]. The addition of high-risk thromboembolic factors as age and cancer and the lack of prospective information in our sample make it more difficult to discern between both pathophysiological situations. Whatever the mechanism, it seems reasonable to consider these findings as new markers of poor prognosis, a question that should be explored in the next prospective, multicenter studies. Although limited, this data advocates raising the suspicions of a PE event in asymptomatic cancer patients with COVID-19 pneumonia and high D-dimers.

As previously observed in other viral pneumonias, our findings supports the idea that, at least in cancer patients, COVID-19 is an inflammatory disease limited to the lungs and its nearby tissues in most cases. The etiological diagnosis of molecular involvement outside lungs always needs to be highlighted as a clinical challenge in predisposed cancer patients. In fact, a correct and early differentiation of SARS-CoV-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. It requires a cautious balance of relevant clinical, analytical, imaging, and therapeutic data and a rigorous review by nuclear medicine experts, radiologists, and oncologists during image interpretation and subsequent clinical management.

It is well-known that the immune cell subpopulations involved in the acute response against virus infections depend mainly on each specific agent and the stage of infection. Because the activation of neutrophils is highly dependent on the anaerobic glycolysis requiring an increase in glucose, a high FDG avidity is considered a nonspecific marker of activity in several infections but usually fails to reflect the response produced by other specific cells. Even when the extrapulmonary findings were not evident, the results of our study could also suggest the potential value of ^{18}F-FDG PET-CT in the assessment of viral infections associated with known chronic pathologies as cancer, aiding to diagnose the regional involvement and to discard the presence of severe complications outside lung parenchyma since early phases of infection. This hypothesis should be assessed in future prospective investigations.

Limitations

The main limitation of our work is inherent to a retrospective, single-center study with a small number of patients. Unfortunately, clinical practice during public health emergency resulted in that rRT-PCR was not available in many patients with CT findings suggesting COVID-19 pneumonia. As a consequence, diagnosis of COVID-19 pneumonia could be confirmed by early RT-PCR after PET-CT in cases (not obtaining the false positive rate) but was not exactly discarded through serologic test in all controls. Finally, considering that parenchymal lung changes may persist for several weeks after resolution of respiratory symptoms and the frequent silent forms of viral infections in cancer patients, the time elapsed since the beginning of SARS-CoV-2 infection and the correlation of symptoms with extra-parenchymal lung involvement could not be estimated.

Conclusions

The ^{18}F-FDG uptake related to SARS-CoV-2 infection is more often limited to thoracic structures, suggesting that an early and silent extra-thoracic involvement is very rare in cancer patients with asymptomatic COVID-19 pneumonia. Incidental pulmonary embolism is a frequent and potentially serious finding raising particular concerns in these patients. ^{18}F-FDG PET-CT could provide new insights about pathogenesis and host response of this novel disease in high-risk subpopulations.

Authors' contributions CWC and JCD designed the study. JCD supervised the study. CWC, AOC, CRR, MCM, RCC, and MGE collected the data. CWC, ABG, FFC, RVR, MPC, and MGE were involved in data analysis and interpretation. CWC, ABG, and FFC wrote the manuscript. All authors contributed to drafting the manuscript and enhancing the intellectual content. All authors have read and approved the final manuscript.

Data availability The datasets generated and/or analyzed during current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval This retrospective review study involving human participants was in accordance with the ethical standards of institutional and national research committees and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All patients signed a generic consent for PET-CT. Due to the retrospective, real-life design during COVID-19 pandemics in Spain, the Ethical Committee of Clinical Research of our center (Comité Ético de Investigación Clínica del Hospital Clínico San Carlos) approved this study and waived the need for a specific informed consent (IRB no. 20/524-E).

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