

Diagnosis challenge of suspected COVID-19 pneumonia in cancer patients with radiation-induced pneumonitis

Qi Zeng

Fifth Affiliated Hospital of Sun Yat-sen University <https://orcid.org/0000-0002-8700-6661>

Caihua Tang

Fifth Affiliated Hospital of Sun Yat-sen University

Lisi Deng

Fifth Affiliated Hospital of Sun Yat-sen University

Sheng Li

Sun Yat-sen University Cancer Center

Jiali Liu

Fifth Affiliated Hospital of Sun Yat-sen University

Siyang Wang (✉ wangsiyang2020@163.com)

Hong Shan

Fifth Affiliated Hospital of Sun Yat-sen University

Research article

Keywords: COVID-19, Pneumonia, Radiation pneumonitis, Multidetector computed tomography

Posted Date: June 7th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-22567/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background During the outbreak period of COVID-19 pneumonia, cancer patients have been neglected and in greater danger. Furthermore, the differential diagnosis between COVID-19 pneumonia and radiation pneumonitis in cancer patients remains a challenge. The study aimed to determine their clinical presentations and radiological features to familiarize radiologists and clinical teams with them in order to early diagnosis and prompt early patient isolation.

Methods From January 21, 2019 to February 18, 2020, the patients selected consecutively met the following criteria: (i) presumed COVID-19 pneumonia; (ii) patients with a history of malignancy and lung exposure to ionizing radiation. A retrospective analysis including all patients' presenting was performed.

Results 4 patients from 112 suspected individuals were selected, including 2 males and 2 females with a median age of 54 years (39–64 years). After repeated pharyngeal swab nucleic acid tests, 1 case was confirmed and 3 cases were excluded from COVID-19 pneumonia.

Conclusions Despite the comparable morphologic characteristics of lung CT imaging, the location, extent, and distribution of lung lesions between COVID-19 pneumonia and radiation pneumonitis differ significantly, further combined with clinical and laboratory findings that could facilitate early diagnosis and appropriate management.

Background

As we were writing this manuscript, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread across the world at an alarming rate and become a pandemic¹. More recent attention has focused on the diagnosis and treatment strategies of coronavirus disease 2019 (COVID-19)². Ever-growing infected and suspected individuals were bound to be isolated and a large number of medical personnel from other departments such as surgery, oncology, and medicines have been transferred to the frontline departments for coping with the disease³. Thus, treatment implementation for patients with malignant tumor has to delay due to the scarcity of sickbeds and shortage of medical staff in oncology. Unlike ordinary patients, cancer patients are susceptible to infection because of their systemic immunosuppressive state caused by cancer and related treatments, such as chemotherapy and/or radiation therapy (RT). A recent study by JX He examined 18 cancer patients in SARS-CoV-2 infection and argued cancer patients might have a higher risk of COVID-19 and poorer outcomes than individuals without cancer⁴. They also propose more intensive surveillance or treatment should be considered when patients with cancer are infected with SARS-CoV-2.

In our fever clinics, of particular concern is the differential diagnosis between radiation-induced lung injury (RILI) and radiological suspicion of COVID-19 pneumonia in patients with malignancy and a history of lung exposure to ionizing radiation. So far, however, there has been little discussion about the similarity and the difference between COVID-19 pneumonia and RILI.

Therefore, our current study was performed to retrospectively summarize and distinguish their clinical presentations and CT manifestations with the goal of familiarizing radiologists and clinical teams with them in order to early diagnosis, speed up treatment and prompt early patient isolation.

Methods

From January 21, 2019 to February 18, 2020, records for patients diagnosed with suspected COVID-19 pneumonia were reviewed retrospectively in our hospital, which is the major tertiary teaching hospital in Zhuhai (Guangdong Province) and responsible for the treatments for COVID-19 designated by local healthcare authorities. The patients selected consecutively met the following criteria: (i) presumed COVID-19 pneumonia according to the diagnostic criteria (version 5) by the National Health Commission of the People's Republic of China. (ii) patients with a history of malignancy and lung exposure to ionizing radiation. No exclusion criteria were applied. The study was approved by the hospital review board and the Medical Ethics Committee. We were granted a waiver of written informed consent because it was a retrospective study involved no potential risk to patients. To avoid any potential breach of confidentiality, no link between the researchers and the patients was made available. All patients were evaluated by the following examinations within 2 days after admission: complete patient history, clinical symptoms, physical examination, hematology inspecting such as routine blood test, blood biochemistry, arterial blood gas analysis, and detection of T lymphocyte subsets, chest CT, pathogenic examination including nose and pharyngeal swab nucleic acid test for COVID-19, influenza A and B test, if necessary, blood cultures, Sputum cultures, and high throughput screening were also performed. All patients received follow-up chest CT after treatment. The management of these patients included isolation, diagnosis, treatment according to the guideline of COVID-19 (Version 5).

Chest CT protocol

The detailed protocol has been described in our previous study⁵. To put it simple, chest CT scans were performed using 1-mm slice thickness on a UCT 760 scanner (United Imaging; Shanghai, China). To minimize motion artifacts, patients in the supine position were instructed on breath-holding; CT images were then acquired during end-inspiration without intravenous contrast.

Image interpretation

All CT images were reviewed by thoracic radiologists and oncologists [QZ, CT and HS] (with over 5 years of experience) independently and resolved discrepancies by consensus. No negative control cases were examined and no blinding occurred. The axial CT and multiplanar reconstruction images were assessed independently and freely on both lung (width, 1400 HU; level, - 500 HU) and mediastinal (width, 350 HU; level, 40 HU) settings, using terms including ground-glass opacities, consolidation, number of lobes affected by ground-glass or consolidative opacities, degree of lobe involvement, nodules, a pleural effusion, thoracic lymphadenopathy (defined as lymph node size of ≥ 10 mm in short-axis dimension), underlying lung disease such as emphysema, fibrosis, cavitation, interlobular septal thickening, reticulation, bronchiectasis, or calcification. The detailed definitions of the above CT demonstrations were

as described in the peer-reviewed literature on COVID-19 pneumonia^{5,6}. The distribution of lung lesions was documented as predominantly diffuse (continuous involvement without respect to lung segments), subpleural (involving mainly the peripheral one-third of the lung), and cross-segment (confined to radiation fields and nonconformity to anatomic boundaries)⁷.

Follow-up chest CT

Previous and follow-up chest CT scans were also reviewed by two radiologists (CT and SL) to evaluate the evolution of lung lesions rated as either no significant change, improvement, or progression. Decisions were reached by consensus.

Results

As of February 18, 2020, 112 patients with suspected COVID-19 admitted to our hospital. Of them, 98 cases have been confirmed COVID-19 via repeated swab testing and 1 death. Another 14 patients were excluded from COVID-19 (Fig. 1).

In total, 5 individuals have a history of malignancy, but only 4 cases received radiation therapy were included in this present study (Fig. 1), with a median age of 54 years (39–64 years). In them with 2 males and 2 females, 1 case was confirmed and 3 cases were excluded from COVID-19. Two patients with nasopharyngeal carcinoma had completed their concurrent chemoradiotherapy without any signs of tumor recurrence, whereas another 2 patients with advanced thoracic tumors present unsatisfactory outcomes to anti-tumor systematic therapies including palliative chemotherapy, radiotherapy, or target therapy et al.

The detailed description of 4 patients with suspected COVID-19 at admission was presented below (Table 1, Table 2):

Table 1
Clinical characteristics at admission and clinical outcomes

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4
Age, years	53	55	64	39
Sex	male	female	female	Male
Histopathology	esophageal SCC	lung adenocarcinoma	NPC	NPC
TNM stage	T4aN2M1	T4N3M1	T3N2M0	T2N2M0
Exposure history	N	N	Y	Y
Comorbidities	gastric ulcer	N	sicca syndrome	hyperthyreosis
PS	3	3	1	0
Symptoms				
Fever	-	-	+	-
Maximum temperature, °C	-	-	39.5	-
Fatigue	+	+	-	-
Cough	+	+	+	-
Sputum	+	+	-	-
Chest distress	+	+	-	-
Myalgia	-	-	-	-
Dyspnea	-	+	-	-
hemoptysis	+	-	-	-
Diarrhea	-	-	-	+
Sore throat	-	-	-	-
Vomiting after eating	+	-	-	-
Headache	-	-	+	-
TIME1(days)	10	6	2	10
TIME2(months)	12.6	13.6	5.2	77.9

Note: **SCC:** squamous cell carcinoma; **NPC:** nasopharyngeal carcinoma; **PS:** performance score; **TIME1:** The time interval between the onset of initial symptoms and the first CT scan at admission; **TIME2:** The period between the onset of initial symptoms and the first CT scan at admission; **Tazocin:** Piperacillin-Tazobactam

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4
Treatment	Tazocin + Moxifloxacin +Arbidol	Tazocin+ Methylprednisolone	Sulperazone + Arbidol +Thymosin α1 + Albumin injection	Resochin
Outcomes	Transferred and discharged	Transferred and death	Transferred and discharged	discharged
<p>Note: SCC: squamous cell carcinoma; NPC: nasopharyngeal carcinoma; PS: performance score; TIME1: The time interval between the onset of initial symptoms and the first CT scan at admission; TIME2: The period between the onset of initial symptoms and the first CT scan at admission; Tazocin: Piperacillin-Tazobactam</p>				

Table 2
Laboratory Findings at Admission

Parameter, unit, (normal value)	Patient 1	Patient 2	Patient 3	Patient 3
WBC, ×10 ⁹ /L, (3.5–9.5)	6.37	10.8↑	7.87	6.42
Neutrophil, ×10 ⁹ /L, (1.8–6.3)	5.22	9.51↑	7.25↑	3.99
Hemoglobin/L, g/L, (130–175)	124↓	138	119↓	144
Lymphocyte, ×10 ⁹ /L, (1.1–3.2)	0.43↓	0.73↓	0.10↓	1.96
Platelet, ×10 ⁹ /L, (125–350)	43↓	338	96↓	270
PT, s, (9.4–12.5)	15.40↑	12	11.90	11.30
APTT, s, (25.1–36.5)	27.60	26.80	30.30	31.80
INR, (0.8–1.15)	1.34↑	1.11	1.03	0.98
D-dimer, mg/L, (0–243)	1120↑	11535↑	482↑	46
CK, U/L, (39–308)	183	67	29	141
CK-MB, U/L, (0–25)	20.10	2.6	8.10	6.4
LDH, U/L, (120–250)	259↑	721↑	153	153
ALT, U/L, (9–50)	11.80	28.10	34.60	26.3
AST, U/L, (15–40)	34.50	34.70	36.30	25.6
Total bilirubin, μmol/L, (3–24)	41.44↑	4.7	10.10	5.42
BUN, mmol/L, (3.1–8.0)	10.50↑	5.7	6.3	2.9↓
Creatinine, μmol/L, (57–111)	82.80	65	90.30	74.9
CTNI, μg/mL, (0–0.0229)	∅0.01	∅0.01	∅0.01	∅0.01

Note: WBC: white blood cell; INR: International Normalized Ratio; PT: Prothrombin time; APTT: Activated partial thromboplastin time; CK: Creatine kinase; LDH: Lactate dehydrogenase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; CTNI : Troponin I; NT-BNP: N-terminal-pro hormone brain-type natriuretic peptide; PCT: Procalcitonin; CRP: C-reactive Protein; NR: no report. *The numbers in the brackets represent the number times of swab tests.

Parameter, unit, (normal value)	Patient 1	Patient 2	Patient 3	Patient 3
NT-BNP, pg/ml, (0-125)	2160↑	641↑	208↑	29
PCT, ng/mL, (0-0.5)	9.09↑	0.10	4.62↑	0.10
CRP, mg/L, (0.068-8.2)	202.78↑	88.79↑	136.56↑	0.26
T lymphocyte subsets test				
CD4 + T cell, (550–1440)	NR	NR	13↓	342↓
CD8 + T cell, (320–1250)	NR	NR	39↓	245↓
CD4+/CD8+, (0.71–2.78)	NR	NR	0.69↓	1.4
pathogenic examination	NR	Sputum cultures(-); Blood high throughput screening(-)	Escherichia coli (+) in blood culture; influenza A and B(-)	Influenza A and B (-)
Swab nucleic acid tests of SARS-COV-2 *	Negative(3)	Negative(2)	Negative(5)	Positive
Note: WBC: white blood cell; INR: International Normalized Ratio; PT: Prothrombin time; APTT: Activated partial thromboplastin time; CK: Creatine kinase; LDH: Lactate dehydrogenase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; CTNI : Troponin I; NT-BNP: N-terminal-pro hormone brain-type natriuretic peptide; PCT: Procalcitonin; CRP: C-reactive Protein; NR: no report. *The numbers in the brackets represent the number times of swab tests.				

Patient 1

A 53-year-old male was admitted to the hospital with sputum production and cough of more than ten days duration and a little bit hemoptysis of two days duration on January 28, 2020. He also felt fatigued, chest distress, vomiting after eating, but no fever, neither from the infected area nor contact with infected peoples. The physical examination revealed coarse breath sounds during auscultation, and laboratory studies showed normal leukocyte, but lymphopenia and serious thrombocytopenia. Marked elevated concentrations of D-dimer, Procalcitonin (PCT), C-reactive protein (CRP), and N-terminal-pro hormone brain-type natriuretic peptide (NT-BNP) were observed at admission. In September 2016, Patient was diagnosed with middle and lower esophageal squamous cell carcinoma with multiple bone metastases staged with T4aN2M1 and began to receive palliative concurrent chemoradiotherapy on September 29, 2016. The radiotherapy dose using intensity-modulated radiation therapy (IMRT) for GTV (esophageal tumor lesions) was 49.4 Gy / 26Fr, and the paclitaxel/Carboplatin regimen concurrently was administered intravenously every three weeks for two cycles, then patients received palliative chemotherapy with

paclitaxel monotherapy for only one cycle because of intolerance of side effects. On December 12, 2018, patients began to receive a second palliative concurrent chemoradiotherapy for recurrence lesions (GTV 44 Gy/22Fr plus nedaplatin), after that, regular reviews were performed.

Serial CT scans showed pericardial effusion, multiple enlarged lymph nodes in the mediastinum, scattered, multiple, similar round thin wall/no wall transparent areas (Fig. 2:A2, B2, C3), smooth or nodular interlobular septal thickening (Fig. 2:A1, B1), and multiple nodules in the dorsal segment of the lower lobe of both lungs with spotted calcifications and adjacent pleural thickening (Fig. 2:A2, A3). These above lung lesions were approximately the same as before. Compared with the previous CT scan 1 year before, chest CT images performed at the 10th day after symptom onset showed the following lung lesions obvious progressively, including patchy areas of consolidation co-existed with ground-glass opacities (Fig. 2:A3), or linear scarring with discrete consolidation (Fig. 2:A2), air bronchograms (Fig. 2:A1), and irregular intralobular or interlobular septal thickening (Fig. 2:A1, A2, A3) predominately in the lower lobes of both lungs adjacent to the mediastinum conforming completely to the irradiated area. These lesions suggest the possibility of RILI, interstitial pneumonia or viral pneumonia. After 3 days of anti-infective therapy with tazocin, moxifloxacin, and arbidol, combined with aggressive supportive care, follow-up CT demonstrated partial improvement (Fig. 2: B1) but primarily increment in the extent and density of lung lesions (Fig. 2: B2, B3), continued segmental consolidations and atelectasis were observed in the lower lobe of both lungs (Fig. 2: B3). Repeated three times of swab nucleic acid test for the COVID-19 were negative. Afterward, the patient was transferred to the department of oncology to continue treatment to reduce the burden of the frontier department.

Patient 2

A 55-year-old female was admitted to the hospital with dyspnea for 1 week and exacerbation for 1 day after more than 1-year targeted therapy for lung adenocarcinoma on January 23, 2020. Fatigue, chest distress, and sputum production with cough were also present. He had no fever, neither from the infected area, nor contact with infected peoples. The physical examination revealed disappeared breath sounds of the left lung during auscultation, and laboratory studies showed slightly elevated white blood cell and neutrophil, but lymphopenia. Elevated concentrations of D-dimer, CRP and NT-BNP were displayed at admission. Sputum culture examination revealed normal flora growth, neither Hemophilus influenza nor fungal growth. In April 2018, the patient was diagnosed with left lung adenocarcinoma with intrapulmonary metastases and multiple bone metastases staged with T4N3M1 and received palliative comprehensive treatment based on target therapy of EGFR inhibitor. On November 14, 2018, the patient began to receive palliative radiotherapy for C6-T2 vertebral metastasis (GTV 30 Gy/10Fr) and left supraclavicular metastatic lymph nodes(45 Gy/15Fr).

Compared with the previous CT scan ten months before, chest CT images performed on the 6th day after symptom onset showed enlarged mass with calcification in the left upper lobe and lung hilum with the maximum section of about 79mm*48 mm, and multiple mediastinal lymph node metastases. The boundary between them is obscure with atelectasis. Magnified irregular nodules scattered in both lungs.

Metastatic tumors of the left pleura increased in the extent and quantity, so did the left pleural effusion and pericardial effusion (Fig. 3: A1, B1, C1), All these lung lesions indicated a progressive left central lung cancer after systematic therapy. There were bilateral diffused ground-glass opacities with partial consolidation (Fig. 3: B2), and a reticular pattern associated with bronchiectasis and intralobular or interlobular septal thickening (Fig. 3: B2), which indicated the possibility of viral pneumonia. After 9 days of anti-infective therapy with tazocin, combined with aggressive supportive care and glucocorticoid therapy(methylprednisolone), follow-up CT demonstrated continuous development in the scope and extent (Fig. 3:C1, C2). Repeated two times of swab nucleic acid test for the COVID-19 were negative, and blood high throughput screening for pathogenic microorganisms or viruses was also negative. The patient's disease continued to progress and died on February 6, 2020 in the department of oncology.

Patient 3

A 64-year-old woman who worked in Beijing presented to the hospital with a 1-day history of fever and cough on February 17, 2020. The maximum body temperature was 39.5 °C (103.1°F). She also had a little cough and headache. The patient traveled to Zhuhai and lived in her community where several patients were confirmed COVID-19. At admission, both lungs were clear on auscultation. Laboratory studies showed normal white blood cell and higher neutrophil, but serious lymphopenia. The concentrations of PCT and CRP increased significantly, and so did those of D-dimer and NT-BNP. The T lymphocyte subsets test showed a sharp drop in CD4 + and CD8 + T cell counts. Screening for influenza A and B were negative. In July 2019, the patient was diagnosed with nasopharyngeal carcinoma(T3N2M0) treated with definitive concurrent chemoradiotherapy followed by adjuvant chemotherapy. By September12, 2019, the patient received IMRT for nasopharyngeal tumor (GTVnx 70 Gy/33Fr), neck metastatic lymph nodes (GTVnd 66 Gy/33Fr) and lymphatic drainage of the neck (CTV 54 Gy/33Fr).

Chest CT images obtained on the second day after symptom onset showed there were minimal ground-glass opacities with partially rounded consolidation (Fig. 4: A1) in the apexes of both lungs, conforming completely to the irradiated area of low exposure. Multiple ill-defined patchy ground-glass opacities (Fig. 4: A2) were observed in the middle lobe of the right lung, considering the possibility of COVID-19 pneumonia. After 3 days of antiviral therapy with arbidol, antibiotic treatment with sulperazone, and supportive treatment with albumin injection et al, Follow-up CT demonstrated no obvious changes of lung lesions (Fig. 4: B1, B2). But the patient's symptoms improved significantly. Repeated four times of swab nucleic acid test for the COVID-19 were negative. Finally, blood culture suggested an Escherichia coli infection. Then the patient was transferred to the department of oncology.

Patient 4

A 39-year-old male was admitted to the hospital with a positive result of the swab nucleic acid test for COVID-19 a half of the day on February 14, 2020. The patient had transient diarrhea ten days ago and no other symptoms afterward. The patient traveled to Zhuhai from the infected area (Wuhan) and had close contact with the confirmed COVID-19 patient, his aunt. At admission, both lungs were clear on auscultation. Laboratory studies showed normal blood routine results. Screening for influenza A and B

were negative. The T lymphocyte subsets test showed a slight drop in CD4 + and CD8 + T cell counts. In June 2013, the patient was diagnosed with nasopharyngeal carcinoma(T2N2M0) treated with radical concurrent chemoradiotherapy. By August 18, 2013, the patient received IMRT for GTVnx 70 Gy/33Fr, GTVnd 66 Gy/33Fr and CTV 54 Gy/33Fr.

Chest CT images obtained on the 10th day after symptom onset showed there were multiple ground-glass opacities of the lower lobes of both lungs peripherally and subpleurally (Fig. 5: A2); A few linear opacities presented in upper lobe lower lingual segment of the left lung (Fig. 5: A3) within the ionizing radiation area, indicative of radiation fibrosis. After 8 days of antiviral therapy with resochin and supportive treatment, Follow-up CT scans demonstrated significant improvement in the extent and density of the ground-glass opacities (Fig. 5: B2), but a new focal ground-glass opacity of the upper lobe of right lung appeared (Fig. 5: A1, B1). Treatment continued until the result of the swab test became negative.

Discussion

This subject was conceived during my time working for the department of infectious disease. As a radiation oncologist, I was committed to the frontline to deal with COVID-19 due to the shortfall of medical staff from January 23, 2019 to March 5, 2020. During the pandemic period, it is utterly imperative to discern and distinguish COVID-19 pneumonia from other lung pathologies for further isolation and appropriate treatment as early as possible. Particularly, the differential diagnosis remains as a challenge between RILI and radiological suspicion of COVID-19 pneumonia in patients with malignancy and a history of lung exposure to ionizing radiation.

Radiation therapy is one of the most common treatments for cancer, especially lung cancer, esophageal carcinoma, and nasopharyngeal carcinoma⁸⁻¹⁰. The advances in radiation delivery techniques make a global decrease in normal tissue exposure, however the lung is one of the most sensitive tissues to radiation, RILI is one of the most clinically challenging toxicities secondary to lung radiotherapy or head and neck radiotherapy with an extended field including upper lobes of the lungs¹¹. The incidence of RILI is estimated to be 15–40%¹². Based on the time interval after the completion of radiotherapy, RILI is typically divided into radiation pneumonitis (RP), occurring within 6 months following radiotherapy (most often within 12 weeks), and pulmonary fibrosis, occurring over 1 year after radiotherapy^{11,12}. Although pulmonary fibrosis ensues from RP, they cannot be split up due to the presence of other underlying patient and treatment-related factors^{7,13}.

The severity of RILI varies from CT imaging abnormalities with no obvious symptoms to life-threatening diseases. Ordinarily, the classic symptoms of RILI include low-grade fevers, non-productive cough, dyspnea on exertion, and hypoxemia¹⁴. Likewise, prior studies have shown that mild to severe symptoms from COVID-2019 patients included fever, fatigue, dry cough and shortness of breath, and some patients may have dyspnea, productive cough, hemoptysis, myalgia, headache, sore throat, and rhinorrhea^{2,15,16}. This distinction proves particularly difficult because clinical presentations can be very similar. In our

study, three patients with RILI presented with fever, cough, sputum production, dyspnea, or hemoptysis respectively. By contrast, one patient with confirmed COVID-2019 presented with only transient diarrhea. In a word, no specific symptoms can definitively identify COVID-19.

Laboratory findings in the early stage of COVID-2019 included normal or higher white blood cells, slight or marked lymphopenia and normal infection-related biomarkers (PCT, CRP), then elevated PCT and CRP may appear in the acute stage¹⁵. As the disease progressed, the levels of D-dimer, creatine, creatinine kinase and blood urea progressively increased before death¹⁶. Likewise, because of the impact of the tumor itself and treatment-related factors, laboratory tests of patients with RILI may show signs of inflammation, such as an increased white blood cell, marked lymphopenia, CRP and PCT¹². The results in our study seem to be coherent with those of previous researches. In addition, it is noteworthy that time course is important for laboratory tests, such as elevated PCT, CRP and D-dimer level always appears in malignancies, RP or bacteria infective pneumonia, whereas no obvious changes in the early stage of COVID-2019¹⁷.

Further laboratory studies are warranted to evaluate for alternate etiologies, including screening for influenza A and B, blood cultures, and the swab nucleic acid tests. Nevertheless, blood cultures and swab tests are a little bit slow and cumbersome, and the previous study showed the sensitivity of chest CT for COVID-19 was higher compared to swab test sensitivity (98% VS. 71%, $p < .001$) for insufficient cellular material and improper extraction of nucleic acid from clinical materials^{18,19}.

As mentioned above, chest CT scans keep a vital component in the diagnostic algorithm for patients with presumed COVID-19 pneumonia. The previous researches^{5,17,20} have established that typical chest CT imaging abnormalities of COVID-19 pneumonia showed unilateral, multifocal, predominantly ground-glass opacities in the incubation period, with lesions mainly located peripherally and subpleurally, followed by the rapid development of bilateral, diffuse disease in the acute stage (Fig. 5), with GGO progressed to or co-existed with consolidations. Subsequently, consolidation continued to increase with GGO further declined, and finally, crazy paving pattern, air bronchograms and irregular intralobular or interlobular septal thickening appeared progressively. These interstitial changes indicated the development of fibrosis. Other findings included pleural effusion, lymphadenopathy, and round cystic changes¹⁷. However, none of the imaging characteristics of COVID-19 pneumonia seem specific and diagnostic, which bear some resemblance to those of other viral infections and non-infectious conditions.

In the current study, the appearance of RILI on chest CT imaging often correlates with the stage of lung injury, evolving from GGO in the initial phase (Fig. 4), subsequently patchy areas of consolidation roughly within the areas of the high-dose radiation treatment fields and likewise does not conform to normal lobar anatomy (Fig. 2, 3)¹². As the disease progresses to pulmonary fibrosis, the chest CT imaging may show scarring (Fig. 5) with consolidation and a defined area of volume loss¹¹. There are a number of similarities of CT findings between COVID-19 pneumonia and RILI, but serial chest CT imaging of patients

could help to continuously monitor the progression or improvement of lung lesions during treatment, sensitively reflecting the differences.

To the best of our current knowledge, this is the first study that regarding differential diagnosis between COVID-19 pneumonia and RILI. Our findings will facilitate the correct diagnosis of COVID-19 pneumonia early. However, there were several limitations to our study. Firstly, this was a retrospective analysis and lack of enough patients due to the scarcity of patients with suspicious COVID-19 pneumonia and a history of radiotherapy. Secondly, follow-up CT scans were available only two times and long-term radiological follow-up is warranted to confirm our results. Finally, bacterial pneumonia may be present in some patients in spite of the sputum cultures.

Conclusion

In conclusion, there are many similarities of clinical symptoms, laboratory findings and CT imaging features between COVID-19 pneumonia and RILI, in particular radiation pneumonitis, consequently, it remains as a challenge to differentiate COVID-19 pneumonia from radiation pneumonitis in the absence of pharyngeal swab nucleic acid test. Nevertheless, due to relatively low sensitivity, repeated swab tests for confirmation are needed, which delays the process of accurately diagnose COVID-19 pneumonia. Undoubtedly, elucidating key differences between COVID-19 pneumonia and radiation pneumonitis through a comprehensive evaluation of imaging characteristics combined with clinical and laboratory findings could facilitate early diagnosis and appropriate management. As a final note, several differences are summarized below based on previous research and our study:

1. Epidemiological history and past medical history

Patients with COVID-19 pneumonia tend to have the epidemiological links, such as travel history to endemic areas or contact with potential confirmed cases. Likewise, patients with radiation pneumonitis had a history of thoracic radiotherapy.

2. laboratory findings

In the early stage, patients tend to present higher PCT, CRP and D-dimer levels due to radiation pneumonitis and/or recurrence cancer itself, whereas no obvious changes in patients with COVID-2019 pneumonia.

3. Thoracic CT imaging tests

Radiation pneumonitis tends to present on serial lung CT scans as GGO with partial consolidation within 6 months after the completion of irradiation, evolved into fibrosis in the late stage, including linear scarring with discrete consolidation, air bronchograms and irregular intralobular or interlobular septal thickening. Lung lesions are usually considered to develop slowly and confinement to radiation fields and nonconformity to anatomic boundaries, whereas typical chest CT imaging abnormalities of COVID-19 pneumonia showed unilateral, multifocal, predominantly ground-glass opacities in the early stage, with

lesions mainly located peripherally and subpleurally, followed by the rapid development of the bilateral, diffuse disease, with GGO progressed to or co-existed with consolidations within 1-3weeks after initial symptoms, and finally, crazy paving pattern, air bronchograms and irregular intralobular or interlobular septal thickening appeared progressively. Overall, in spite of the comparable morphologic characteristics of lung CT imaging, the location, extent, and distribution of lung lesions between COVID-19 pneumonia and radiation pneumonitis differ significantly.

Abbreviations

SARS-CoV-2

severe acute respiratory syndrome coronavirus 2; COVID-19:coronavirus disease 2019; RT:radiation therapy; RILI:radiation-induced lung injury; PCT:Procalcitonin; CRP:C-reactive protein; NT-BNP:N-terminal-pro hormone brain-type natriuretic peptide; IMRT:intensity-modulated radiation therapy; GTV:gross tumor volume; Gy:gray; Fr:fraction; EGFR:epidermal growth factor receptor ; RP:radiation pneumonitis; GGO:ground-glass opacity.

Declarations

Ethics approval and consent to participate

The study was approved by the fifth affiliated hospital, Sun Yat-sen University review board and the Medical Ethics Committee. We were granted a waiver of written informed consent because it was a retrospective study involved no potential risk to patients.

Consent for publication

Written consent is waived because the name and hospital number of participants were not released and the research presents no more than minimal risk of harm to participants,

Availability of data and materials

All the data and materials have been provided in the manuscript.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was funded by National Natural Science Foundation of China(No. 81701723). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the

Authors' contributions

QZ and HS conceived and designed the study. QZ and JL contributed to the literature search. QZ, CT and LD contributed to data collection. QZ, CT, and SL contributed to CT imaging analysis. SW and HS contributed to data interpretation. QZ and LD contributed to the figures. QZ and SW contributed to writing of the report. All authors have read and approved the manuscript.

Acknowledgments

I, Dr. Qi Zeng, would like to express my appreciation to my wife, Mrs. Shuang Li (Department of Human Resources, The Fifth Affiliated Hospital, Sun Yat-Sen University) for her hard work of raising our children when I worked in the isolation ward. We are also grateful to all of the emergency services, doctors, nurses, and other hospital staffs for their dedication during the pandemic of COVID-19.

References

1. Layne SP, Hyman JM, Morens DM, Taubenberger JK. New coronavirus outbreak: Framing questions for pandemic prevention. *Sci Transl Med* 2020; 12(534).
2. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020.
3. Khan S, Nabi G, Han G, et al. Novel coronavirus: how things are in Wuhan. *Clin Microbiol Infect* 2020.
4. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol.* 2020;21(3):335–37.
5. Chung M, Bernheim A, Mei X, et al. CT Imaging Features of 2019 Novel Coronavirus (2019-nCoV). *Radiology* 2020200230.
6. Xie X, Zhong Z, Zhao W, Zheng C, Wang F, Liu J. Chest CT for Typical 2019-nCoV Pneumonia: Relationship to Negative RT-PCR Testing. *Radiology* 2020200343.
7. Ghaye B, Wanet M, El HM. Imaging after radiation therapy of thoracic tumors. *Diagn Interv Imaging.* 2016;97(10):1037–52.
8. Formenti SC, Rudqvist NP, Golden E, et al. Radiotherapy induces responses of lung cancer to CTLA-4 blockade. *Nat Med.* 2018;24(12):1845–51.
9. Wong AT, Shao M, Rineer J, Lee A, Schwartz D, Schreiber D. The Impact of Adjuvant Postoperative Radiation Therapy and Chemotherapy on Survival After Esophagectomy for Esophageal Carcinoma. *Ann Surg.* 2017;265(6):1146–51.
10. Huang PY, Zeng Q, Cao KJ, et al. Ten-year outcomes of a randomised trial for locoregionally advanced nasopharyngeal carcinoma: A single-institution experience from an endemic area. *Eur J*

Cancer. 2015;51(13):1760–70.

11. Hanania AN, Mainwaring W, Ghebre YT, Hanania NA, Ludwig M. Radiation-Induced Lung Injury: Assessment and Management. *Chest*. 2019;156(1):150–62.
12. Bledsoe TJ, Nath SK, Decker RH. Radiation Pneumonitis. *Clin Chest Med*. 2017;38(2):201–08.
13. Yu TK, Whitman GJ, Thames HD, et al. Clinically relevant pneumonitis after sequential paclitaxel-based chemotherapy and radiotherapy in breast cancer patients. *J Natl Cancer Inst*. 2004;96(22):1676–81.
14. Jain V, Berman AT. Radiation Pneumonitis: Old Problem, New Tricks. *Cancers (Basel)* 2018; 10(7).
15. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497–506.
16. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395(10223):507–13.
17. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis* 2020.
18. Ai T, Yang Z, Hou H, et al. Correlation of Chest CT and RT-PCR Testing in Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. *Radiology* 2020200642.
19. Fang Y, Zhang H, Xie J, et al. Sensitivity of Chest CT for COVID-19: Comparison to RT-PCR. *Radiology* 2020200432.
20. Pan F, Ye T, Sun P, et al. Time Course of Lung Changes On Chest CT During Recovery From 2019 Novel Coronavirus (COVID-19) Pneumonia. *Radiology* 2020200370.

Figures

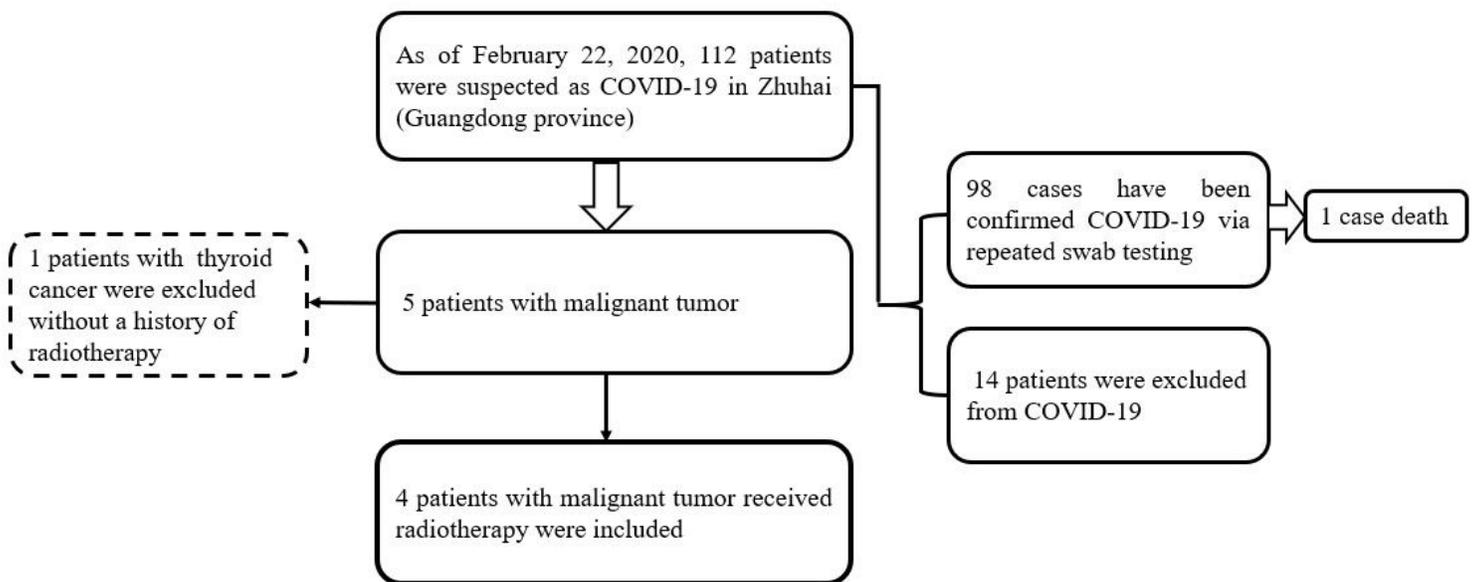


Figure 1

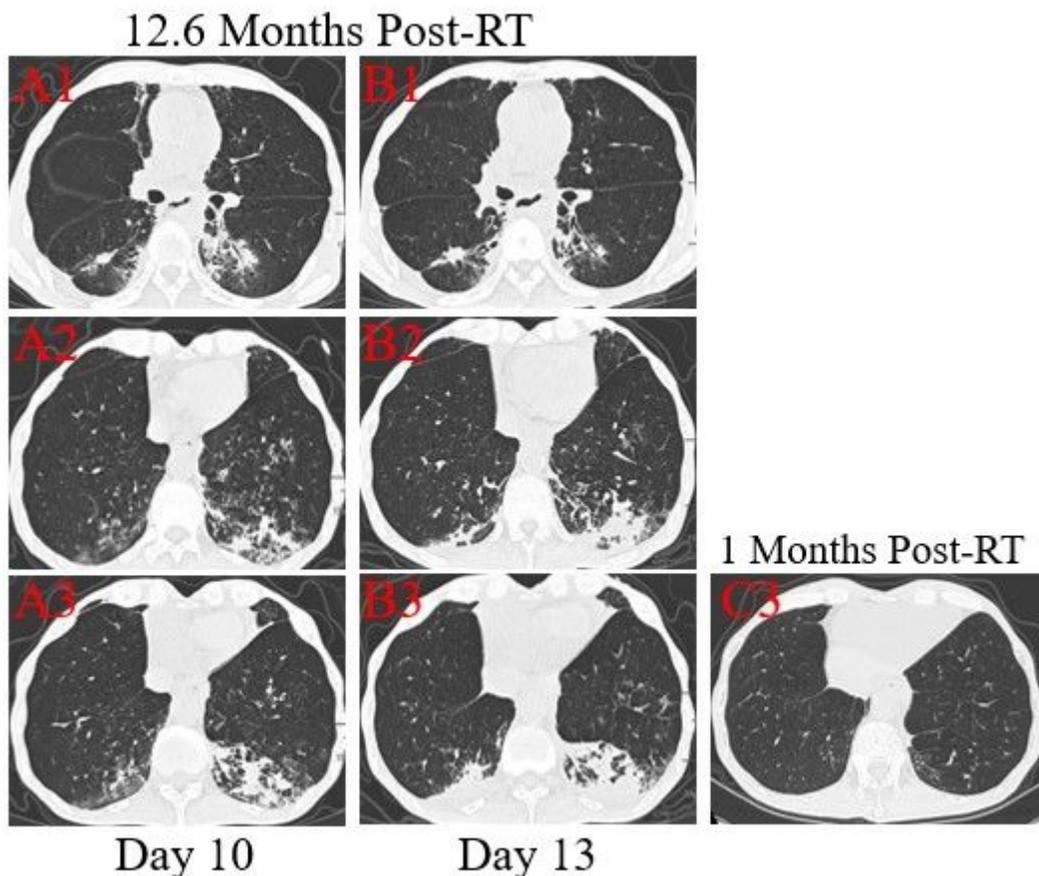


Figure 2

Transverse thin-section serial CT scans from a 53-year-old male with suspected COVID-19 pneumonia, ultimately who be excluded by repeated nucleic acid tests. He was in the 12.6 months after the completion of IMRT due to middle and lower esophageal squamous cell carcinoma with multiple bone metastases, with the middle and lower lobes adjacent to the mediastinum exposure to ionizing radiation within the target area of maximum radiation exposure. Serial CT scans showed pericardial effusion, multiple enlarged lymph nodes in the mediastinum, scattered, multiple, similar round thin wall/no wall transparent areas (Figure 2:A2, B2, C3), smooth or nodular interlobular septal thickening (Figure 2:A1, B1), and multiple nodules in the dorsal segment of the lower lobe of both lungs with spotted calcifications and adjacent pleural thickening (Figure 2:A2, A3). These above lung lesions were approximately the same as before. Compared with the previous CT scan 1 year before, chest CT images performed at the 10th day after symptom onset showed the following lung lesions obvious progressively, including patchy areas of consolidation co-existed with ground-glass opacities (Figure 2:A3), or linear scarring with discrete consolidation (Figure 2:A2), air bronchograms (Figure 1:A1), and irregular intralobular or interlobular septal thickening (Figure 2:A1, A2, A3) predominately in the lower lobes of both lungs adjacent to the mediastinum conforming completely to the irradiated area. Follow-up CT at the 13rd day demonstrated partial improvement (Figure 1: B1) but primarily increment in the extent and density (Figure 2: B2, B3),

continued Segmental consolidations and atelectasis were observed in the lower lobe of both lungs (Figure 2: B3).

3.6 Months Post-RT

13.6 Months Post-RT

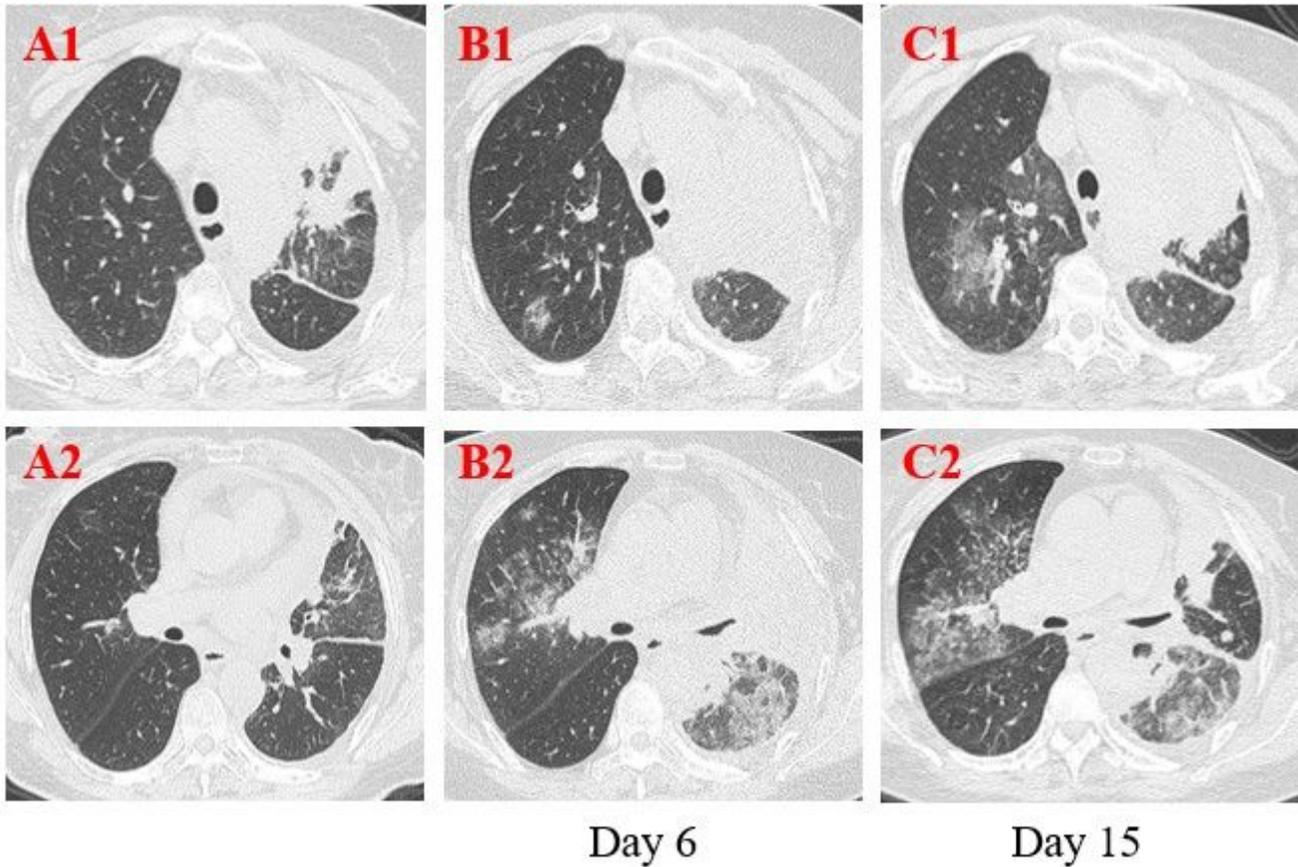


Figure 3

Transverse thin-section serial CT scans from a 55-year-old female with suspected COVID-19 pneumonia, ultimately who be excluded by repeated nucleic acid tests. He was in the 1.3 year after the completion of IMRT due to lung adenocarcinoma with intrapulmonary metastases and multiple bone metastases with the upper lung lobes exposure to ionizing radiation. Compared with the previous CT scan ten months before, chest CT images performed on the 6th day after symptom onset showed an enlarged mass with calcification in the left upper lobe and lung hilum with the maximum section of about 79mm*48mm, and multiple mediastinal lymph node metastases. The boundary between them is obscure with atelectasis. Magnified irregular nodules scattered in both lungs. metastatic tumors of the left pleura increased in the extent and quantity, so did left pleural effusion and pericardial effusion (Figure 3: A1, B1, C1), All these lung lesions indicated a progressive left central lung cancer after systematic therapy. There were bilateral diffused ground-glass opacities with partial consolidation (Figure 3: B2), and a reticular pattern associated with bronchiectasis and intralobular or interlobular septal thickening (Figure 3: B2), which indicated the possibility of viral pneumonia. Follow-up CT on the 15th day demonstrated continuous development in the scope and extent (Figure 3:C1, C2), in spite of aggressive therapy.

5.2 Months Post-RT

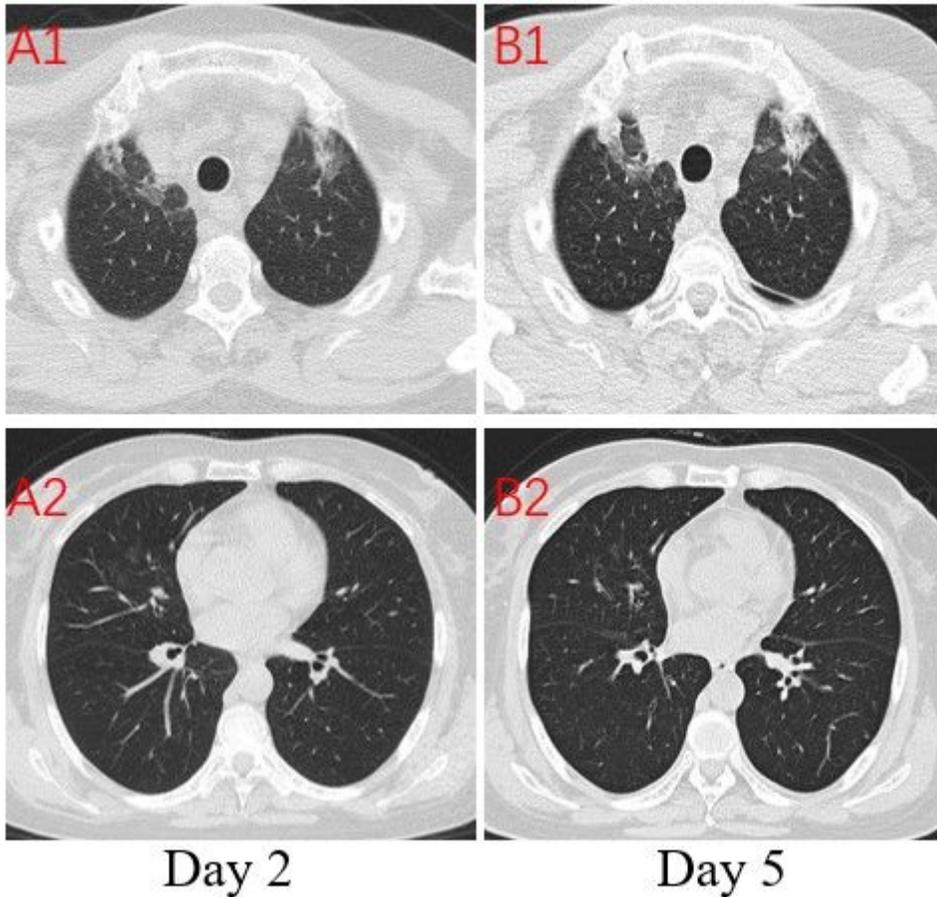
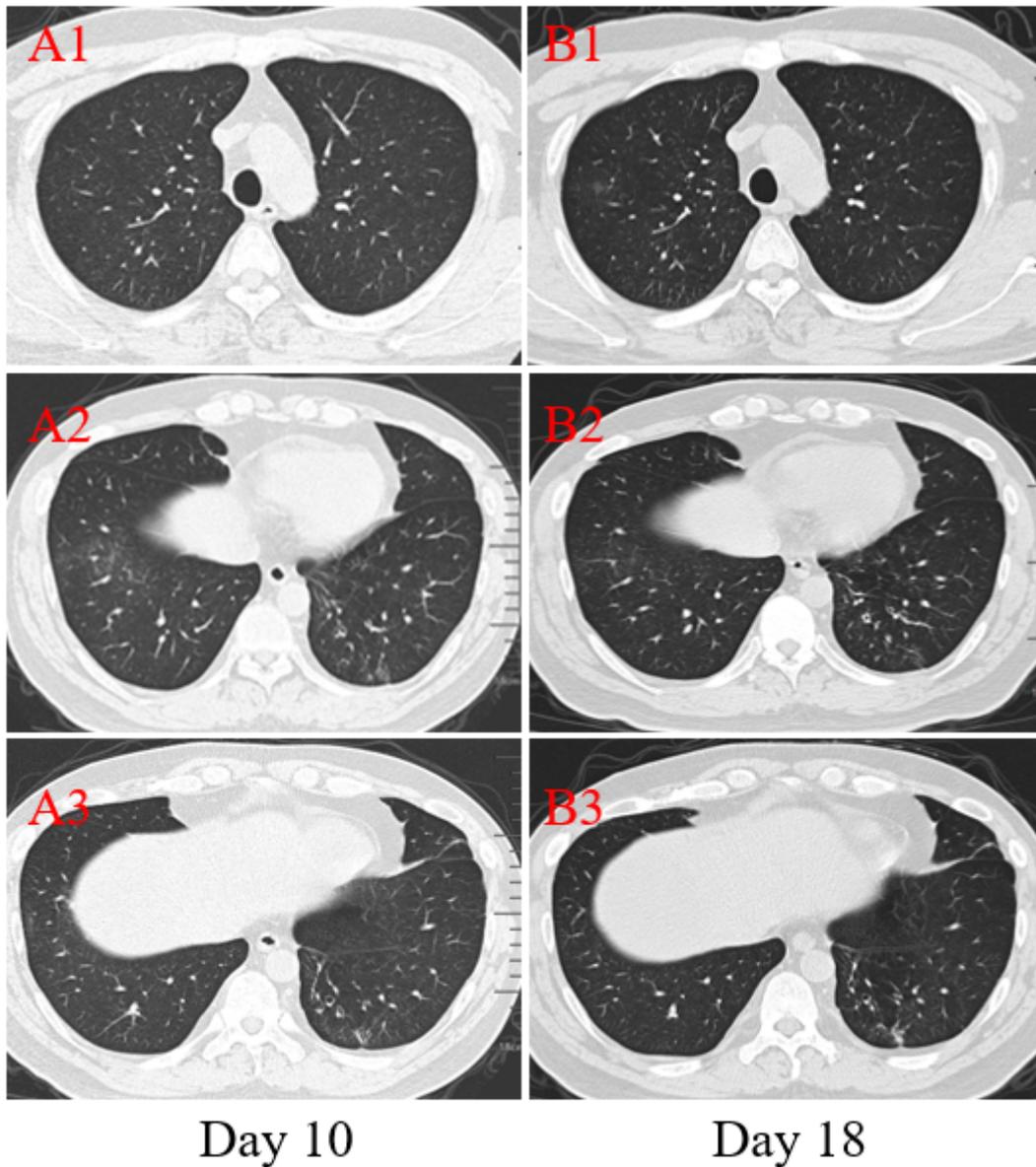


Figure 4

Transverse unenhanced thin-section serial CT scans from a 64-year-old female with suspected COVID-19 pneumonia, ultimately who be excluded by repeated nucleic acid tests. She was in the fifth month after the completion of IMRT due to nasopharyngeal carcinoma, with upper lobes of lungs exposure to ionizing radiation. Chest CT images obtained on the second day after symptom onset showed there were minimal ground-glass opacities with partially rounded consolidation (Figure4: A1) in the apices of both lungs, conforming completely to the irradiated area of low exposure. Multiple ill-defined patchy ground-glass opacities (Figure4: A2) were observed in the middle lobe of right lung. Follow-up CT on the fifth day demonstrated no obvious change of lung lesions (Figure4: B1, B2).

6 Years Post-RT



Day 10

Day 18

Figure 5

Transverse unenhanced thin-section serial CT scans from a 39-year-old male with COVID-19 pneumonia. He was in the 6th year after the completion of IMRT due to nasopharyngeal carcinoma, with upper lobes of lungs exposure to ionizing radiation due to adjacent to the treatment field. Chest CT images obtained on the 10th day after symptom onset showed there were multiple ground-glass opacities of the lower lobes of both lungs peripherally (Figure5: A2); A few linear opacities presented in upper lobe lower lingual segment of the left lung (Figure 5: A3) within the ionizing radiation area, indicative of radiation fibrosis. Follow-up CT at the 18th day demonstrated significant improvement in the extent and density of the ground-glass opacities (Figure 5: B2), but the new focal ground-glass opacities of the upper lobe of right lung appeared (Figure 5: B1).