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Clinical and Radiographic Presentations of COVID-19 among Patients Receiving Radiation Therapy for Thoracic Malignancies

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ABSTRACT

The 2019 novel coronavirus disease (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to a pandemic affecting healthcare centers across the globe. Patients with cancer have been reported to be particularly vulnerable to infection, morbidity, and severe events. Given the high proportion of asymptomatic carriers and concerns regarding speed and availability of laboratory testing, novel detection strategies are necessary to supplement traditional screening methods and facilitate mitigation of viral transmission. Recent data support the diagnostic consistency and potential value of computed tomography (CT) scans to aid early diagnosis of COVID-19. Volumetric CT image-guidance is commonly employed in patients undergoing radiotherapy and presents a unique opportunity to screen for COVID-specific lung changes. This case series describes the presentation of SARS-CoV-2 infections among three patients undergoing thoracic radiotherapy across multiple institutions. We highlight their clinical symptoms, imaging findings, potential confounders, and clinical workflow to triage these patients to the next level of care.

INTRODUCTION

The 2019 novel coronavirus disease (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to a pandemic affecting healthcare centers across the globe. With an estimated case fatality rate of 3.5% (1, 2) and a wide range across age groups, providers are rapidly adjusting their patterns of care to mitigate this impact. In particular, oncologic patients have been reported to be at increased risk of infection and at a greater risk of severe events (1). As such, patients undergoing active cancer therapy are considered more vulnerable to significant morbidity from COVID-19 (3, 4).

The current management for COVID-19 is maximum supportive care, and early diagnosis may help minimize adverse outcomes among patients (5). However, asymptomatic carriers may represent up to 42% of all infected patients (6), confirmed by the observation of high viral titers in the absence of symptoms (7, 8). In addition, RT-PCR laboratory testing has raised concerns regarding processing speed, sensitivity, and availability (9). Thus, novel detection strategies are necessary to supplement traditional screening methods and facilitate early diagnosis and mitigation of viral transmission.

Indeed, recent data support the diagnostic consistency and potential value of diagnostic computed tomography (CT) scans to aid early diagnosis of COVID-19. Sensitivity with CT has been reported to be as high as 97% (9)—significantly higher than that of RT-PCR alone, particularly during early phases of disease (10). A direct comparison of the two detection methods among 1,014 Wuhan patients resulted in positive confirmations among 88% with CT imaging versus 59% with RT-PCR, and up

to 93% of patients are deemed positive on CT before confirmation via RT-PCR testing (9). That being said, specificity of CT was 25% alone (9); thus, imaging serves as more of a complement for rapid detection, prior to RT-PCR confirmation.

Volumetric imaging with CT-on-rails (CTOR) or cone-beam CT (CBCT) is commonly employed in patients undergoing radiotherapy as part of daily alignment. Previous reports have shown that imaging as part of a radiotherapy treatment course may identify non-oncologic findings such as effusion, post-obstructive atelectasis, or infection. Likewise, post-treatment imaging after radiotherapy often identifies well characterized imaging changes such as radiation pneumonitis (11-13). Such imaging findings may often be confounded with infection and may be particularly problematic when assessing patients at risk for COVID-19.

This case series describes the presentation of SARS-CoV-2 infections among oncologic patients undergoing radiotherapy from a multi-institutional group of radiation oncology centers in the United States. In this article, we highlight the clinical symptoms, daily imaging findings, potential confounders, and clinical workflow to triage these patients to the next level of care.

CASES

Case 1

63-year-old woman, a former smoker without significant comorbidities, with recurrent adenocarcinoma who presented for definitive stereotactic ablative radiotherapy to 50-Gy in 4-fractions for a 7-mm tumor of the left upper lobe (14). CTOR, obtained for image-guidance and patient set-up prior to treatment delivery, revealed new multifocal ground

glass opacities (GGOs) of the bilateral lungs, as compared to her CT-simulation scan obtained just 20 days beforehand for treatment planning (shown in Figure 1). The treatment was held (prior to first of four planned fractions), and she was referred to the Emergency Department, with the CTOR images uploaded into the patient's electronic health record for provider review. Although the patient was asymptomatic without fever or acute respiratory symptoms and her examination was unremarkable, she tested positive for SARS-CoV-2 via nasopharyngeal swab RT-PCR. Upon notification, the patient was instructed on home quarantine precautions, and treatment was subsequently deferred as per departmental policy. All staff members involved in her treatment were rapidly notified, screened, and cleared without quarantine. Of note, a repeat test 18 days later again returned as positive, despite the absence of symptom development. She has been tentatively rescheduled for another CT-Simulation for treatment re-planning 14 days following this second positive test, assuming she remains asymptomatic during this interval.

Case 2

64-year-old woman that presented in early February with a diagnosis of cT1bN0M0 left upper lobe non-small cell lung cancer (NSCLC), diagnosed after surveillance lung CT demonstrated growth of a nodule. The patient's past medical history was significant for COPD (FEV1% predicted 63%, DLCO% predicted 42%). She had a history of being a former smoker, with a 70-pack year history. Based on the nodule's growth on surveillance lung CT, and FDG-avidity on PET/CT (30.3) a clinical diagnosis of NSCLC was made. After the patient was deemed to be a high-risk operable candidate, she was recommended for SBRT was recommended for definitive management. She underwent

CT simulation in mid-March for SBRT (55Gy/5 daily consecutive fractions), and her first treatment was delivered 10 calendar days later. However, at the time of her on treatment visit the patient reported increased severity of her baseline cough and shortness of breath, several episodes of post-tussive emesis and increased fatigue not relieved by rest. On review of her CBCT imaging, it was found that she had new GGOs in the right lower lobe (Figure 2). Based on these symptoms and findings, the institution's COVID hotline was immediately notified on 4/1/2020. However, because the patient did not meet the criteria at that time for COVID-19 screening (lack of fevers, sick contacts, or travel), she was not recommended for testing. Given the continued clinical concern for both her symptoms and new findings on CBCT, a direct communication was made with an infectious disease physician at the institution, who recommended she be treated as a presumed COVID-19 positive patient and she was approved for testing. She was given a mask and instructed to start home quarantine. Three days later her test returned as negative for SARS-CoV-2 RNA. However, given the continued high index of suspicion for COVID-19, the patient remains in quarantine, with a plan to complete her final two fractions of SBRT once she has been asymptomatic for 3 days. The new imaging findings are still attributed to her potential COVID-19 diagnosis, in the absence of any confirmed alternative.

Case 3

66-year-old woman with T1bN2M0, Stage IIIA, small-cell lung cancer of the right upper lobe. The patient's past medical history includes emphysema, obstructive sleep apnea, and non-specific pulmonary nodules that had been followed on chest CT, ultimately leading to the current diagnosis. The patient was a former smoker who quit over a

decade ago but had a 74-pack-year smoking history. The patient was treated with curative intent twice-daily thoracic radiotherapy concurrent with carboplatin and etoposide. All institutional radiation dose-volume parameters were within tolerance, the mean lung radiation dose was 9.3Gy, and the volume of lung receiving ≥ 20Gy was 19.8%. Chemoradiation was well tolerated with acute toxicities including grade 1 cough and grade 1 esophagitis. Approximately 9 weeks after radiotherapy, the patient called reporting a two-day history of a new non-productive cough with increased dyspnea and increased use of albuterol. The patient denied fever, fatigue, or a decreased appetite. The patient asked if her current symptoms could be toxicities from her radiation treatment. At the time of her call, there was an intensification of the local COVID-19 epidemic. The patient was counseled on radiation pneumonitis (RP) and the potential need to start treatment with a high-dose corticosteroid taper. No repeat imaging was obtained at the time. However, out of caution she was recommended to undergo testing for COVID-19. The COVID-19 qualitative RNA test returned positive. The patient was not treated for RP, but rather, referred for COVID-19 management.

DISCUSSION

Radiation oncology clinics around the world are currently working diligently to protect both patients and staff from the morbidity and mortality of COVID-19 (15, 16). However, this pandemic has presented at a time when many patients are either beginning or currently receiving cancer treatment. There continues to be a fine balance between triaging patient symptoms (which for thoracic patients may have some overlap with COVID-19 symptoms) and not introducing delays in oncologic care. In this series of teaching cases, we presented a range of presentations of COVID-19. While the cases

here represent patients that had both positive and negative COVID-19 testing, it should be noted that even patients with negative testing were still clinically managed as presumed positives with home quarantine and symptom surveillance.

Incidental imaging findings suspicious for COVID-19 on diagnostic chest CTs have been increasingly reported (17). Early features described to date include bilateral peripheral GGOs, which can be multifocal and/or multilobar in appearance (18-20). With increasing clinical severity, imaging demonstrates increased extent, density, and number of these GGOs (21,22). Resolution is accompanied by decrease and resorption of nodular opacities bilaterally.

The use of CT image-guidance for patients receiving radiation therapy to the chest or thorax for lung, esophageal, and breast malignancies presents a unique opportunity to screen for COVID specific lung changes. This was recently highlighted as a case study on the Radiation Oncology Incident Learning System (RO-ILS) (23). Recommendations from RO-ILS included having radiation therapists, physicists, dosimetrists, and physicians become familiar with and screen for these characteristic COVID-19 findings daily and triage patients with findings for further evaluation. It was also recommended that clinical practices report these events to RO-ILS to help determine the prevalence of these findings.

Note that a prudent differential is still necessary, as patients being treated for thoracic malignancies may have significant baseline pulmonary comorbidities. Additionally, patients that have a history of systemic therapy, particularly immunotherapy, may also have pulmonary parenchymal changes over time (24). However, as shown in the cases presented here, the rapidity of infiltrate appearance on

treatment should prompt immediate attention by the treating physician for symptom screening, vital signs, and appropriate triage to institutional COVID testing. Conversely, negative CBCTs should not be used to clinically 'clear' patients that are having other COVID associated symptoms, such as fever, new or worsening cough, new or worsening shortness of breath, and pleuritis. In a retrospective series of more than 120 COVID-19 positive patients across 4 medical centers in China, diagnostic CT images were compared by duration of time between symptom presentation and imaging (25). For patients receiving CT imaging 0 – 2 days from initiation of symptoms, 56% of these "early scans" were negative, while only 10% of intermediate scans at 3-5 days from symptoms and 4% of late scans at 6-12 days from symptoms were negative. Therefore, pre-screening of patient symptoms via nursing staff prior to CT simulation study and daily screening questions prior to treatment still represent a crucial part of clinical practice.

Another clinical scenario presented here illustrates the need to have a high index of suspicion for COVID-19 for patients who are weeks to months out from the time of completion of thoracic radiotherapy. During this pandemic, patient with a history of thoracic radiotherapy who are now suspected to have RP require attention. The characteristics symptoms of RP include progressive shortness of breath, cough, and fatigue, with or without a low-grade fever occurring weeks to several months after thoracic radiation. These symptoms overlap with those of COVID-19. Given the increasing prevalence of COVID-19, patients who present for RP evaluation should be tested for COVID-19, especially if they are to be started on empiric high-dose corticosteroids. Data indicate that corticosteroid therapy can worsen COVID-19-

associated lung injury (26). Additionally, careful review of chest CT imaging, if available, is recommended given that the diffuse and multi-lobar radiographic features of COVID-19 (27) contrast with the classic CT appearance of RP that is mostly limited to the radiation field.

Patients actively undergoing radiotherapy should have treatment paused upon suspicion for COVID-19, pending screening test result. For those who test positive, robust data are lacking regarding the appropriate timeframe for radiotherapy resumption. The CDC has provided guidelines on non-testing strategy criteria for ending transmission-based precautions in the healthcare setting (28, 29), which may be adopted for these scenarios pending stronger evidence. A test-based strategy is also outlined requiring two consecutive negative test results (collected at least 24 hours apart), although implementation may be limited due to lack of test availability and capacity. Per non-testing strategy for symptomatic patients (Case 2), CDC requirements entail the passage of: (a) ≥7 days since first appearance of symptoms; and (b) ≥3 days since recovery (defined as resolution of fever and improvement of respiratory symptoms). However, these guidelines are admittedly specific to isolation. Thus, more stringent criteria and timeframes may be warranted for active cancer patients. As for asymptomatic patients (Case 1), our institution requires ≥14-days to pass from first positive COVID-19 result (typically without need for re-testing), although this 14-day timeline was cautiously re-applied towards the patient's second positive test date (ordered through her local provider).

Although usual treatment volume has decreased at many radiation oncology centers during the COVID-19 pandemic, there are still many patients who have recently received treatment or are currently on treatment. While measures such as screening questions and temperature measurements prior to department check-in certainly play a crucial role in appropriate patient triage, we are in a unique position to use an additional resource to monitor our high-risk patients with on-treatment daily CT imaging. Although this manuscript described three scenarios for patients with thoracic malignancies, we would recommend that both the initial simulation CT and on-board CTs acquired as part of daily image-guidance of any patient where the imaging field of view encompasses the chest be reviewed for new or increasing infiltrates, particularly in patients with new symptoms. The entire image set should be reviewed, superiorly-to-inferiorly, to assess for potential changes. Due to the observations that radiologic changes may precede physical symptoms, and considering a false negative rate ranging from 10% to 30% (9), this routine part of our daily cancer care gives us an additional tool to monitor our patients during this unprecedented time.

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FIGURE CAPTIONS

Figure 1. The reference image on the right represents the CT simulation study obtained 20 days before the start of SBRT to a left upper lobe NSCLC. The daily CTOR imaging from the first fraction of treatment demonstrated new bilateral multifocal ground glass opacities concerning for COVID-19 infection (14).

Figure 2. The first image is an axial image from the CT simulation study of Case 2, obtained 9 days before start of SBRT to the left upper lobe lesion (not shown). The second image was the CBCT taken prior to the first fraction of treatment. On day 2, the patient began to experience increasing shortness of breath and cough. On the third fraction of treatment, peripheral ground glass opacities were seen in the right upper lobe, out of the treatment field, that were new compared to first two images shown here.

Figure 1

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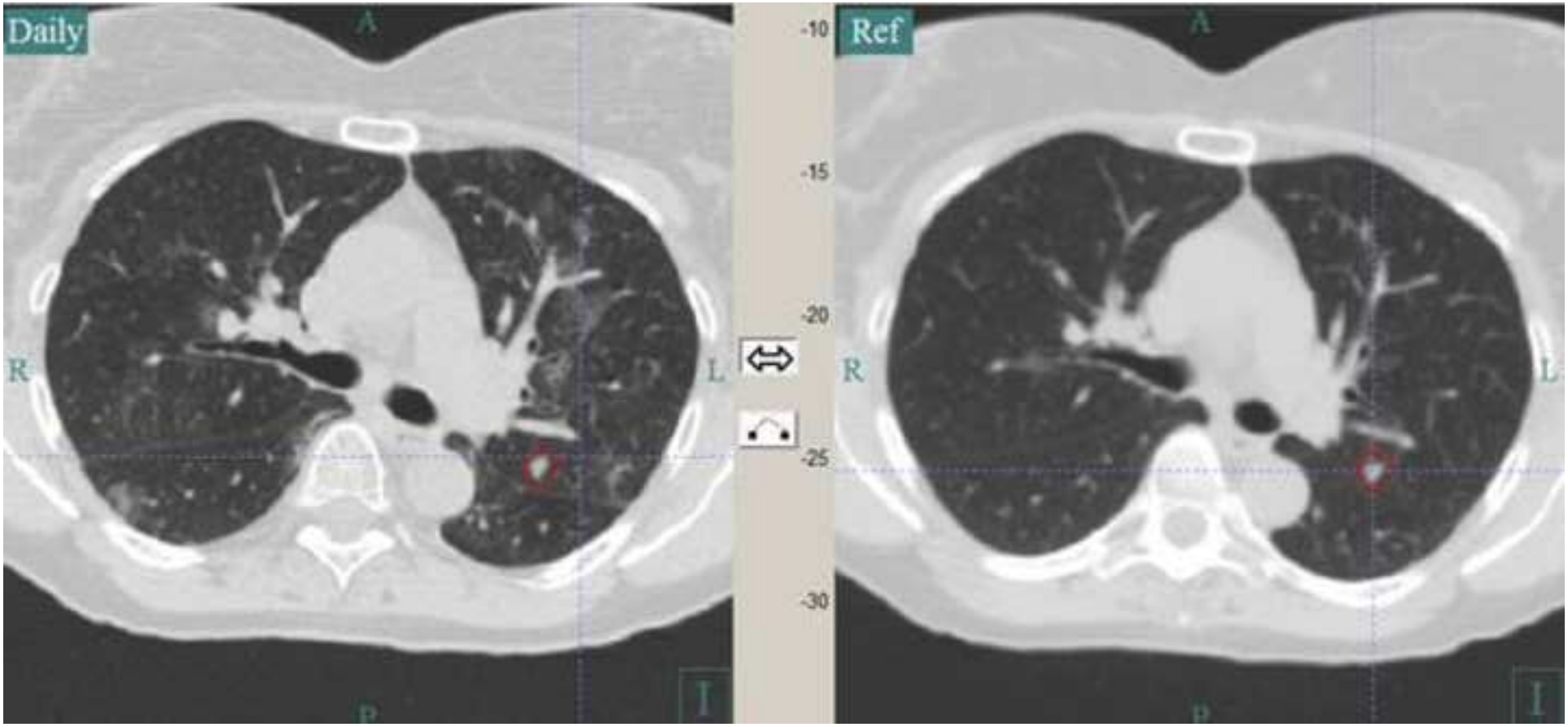

Figure 2

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