Cancer Imaging and Patient Care during the COVID-19 Pandemic

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Essentials

- Preliminary reports indicate SARS-CoV-2 infections in patients with cancer have a higher case fatality rate than individuals without cancer, and certain cancers may pose more of a risk than others.
- The US National Cancer Institute conservatively estimates 10,000 excess deaths from colon and breast cancer alone within the next ten years due to delays in screening and treatment as a result of the COVID-19 pandemic.
- Certain imaging features associated with COVID-19 may overlap with cancer imaging features and could confound future cancer imaging findings.

Summary Statement

Patients with cancer are at an increased risk of severe SARS-CoV-2 infection, and new research is continually becoming available to help clinicians understand the impact of COVID-19 illness in these patients.

Abbreviations
COVID-19 = coronavirus disease 2019, NCI = US National Cancer Institute, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

Abstract

Patients with cancer have been negatively impacted during the coronavirus disease 2019 (COVID-19) pandemic, as many of these individuals may be immunosuppressed and of older age. Additionally, cancer follow-up or imaging appointments have been delayed in many clinics around the world. Postponement of routine screening exams will result in delays in new cancer diagnoses. Clinics are continuing to monitor and adapt their appointment schedules based on local outbreaks of COVID-19. Studies on COVID-19 in patients with cancer are limited, but consistently indicate that this population is at risk for more severe COVID-19 illness. Data from recent studies also suggest that pediatric patients with cancer have a lower risk of severe COVID-19 illness compared to adults. Certain features of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection detected by lung, brain, and gastrointestinal imaging may confound radiologists’ interpretation of cancer diagnosis, staging, and treatment response. Lastly, as clinics begin to re-open for routine appointments, protocols have been put in place to reduce SARS-CoV-2 exposure to patients during their visits. This review details different perspectives on the impact of the COVID-19 pandemic on patients with cancer and on cancer imaging.
Introduction

The coronavirus disease 2019 (COVID-19) pandemic is currently (as of September 1, 2020) affecting 188 countries with 25.8 million confirmed cases and 858,000 deaths worldwide (1). Throughout 2020, COVID-19 outbreaks have emerged in different geographical areas at different times and have resulted in varying stay-at-home orders and business closures. Responses to COVID-19 also included closure of many cancer clinics, and hence postponed or cancelled patient appointments (2) resulting in a decrease in new cancer diagnoses and a delay in treatments. Patients with known cancer, suspected cancer, or at risk for cancer are particularly vulnerable during this pandemic for two main reasons: (a) postponement of screening or treatment follow-up appointments negatively impacts long-term outcomes and (b) these individuals have a higher risk for more severe COVID-19 illness because of age and immunosuppression (3–5).

During the early period of the pandemic (spanning from March to May 2020), many institutions developed guidelines on how to safely resume patient imaging appointments. Additional guidelines have been published for determining routes of care for different types of cancer (6–8). More recently, many institutions or groups of care systems have implemented marketing campaigns to encourage persons to re-enter the health care system for elective procedures, such as mammography and lung cancer screening (9). Although plans were specifically designed to mitigate potential for viral transmission, there will still likely be many individuals who will choose not to reschedule appointments during this year (and potentially into 2021) due to fears of becoming infected with severe acute respiratory syndrome coronavirus 2
(SARS-CoV-2). Others may not reschedule due to unemployment and loss of health care insurance, which threatens to amplify existing ethnic and socio-economic disparities in cancer screening and mortality (10). Models indicate that in late 2020 there could be a resurgence of COVID-19 illness, which will in part be dependent upon the ability of communities to comply with non-pharmaceutical interventions, such as physical distancing and universal masking (11,12); a resurgence would likely result in further delays in cancer diagnosis and treatment.

As the COVID-19 pandemic continues to unfold with unpredictability, it is essential to assess how the pandemic is impacting all facets of cancer monitoring and care so the longer term impacts in this patient population can be understood. In this review we will provide an overview on how the pandemic has affected patients with cancer, specifically focusing on COVID-19 illness progression in patients with cancer, long-term impacts of postponed cancer imaging and procedural appointments, potentially confounding imaging manifestations from COVID-19 during cancer imaging, and future implications for cancer imaging practices during the pandemic.

**SARS-CoV-2 Infection in Patients with Cancer**

As clinicians are challenged with determining the appropriate course of clinical care and management during the COVID-19 pandemic, it is essential to understand the impact of this disease in patients with cancer. Given the recency of this disease process, there are only limited data with modest sample sizes reporting the effects of COVID-19 in patients with cancer. Preliminary studies show that there is an increased risk of morbidity and mortality in patients with concomitant COVID-19 infection and cancer. For example, one early report from China (13) demonstrated that 1% (18 of 1590) of patients admitted to the hospital for COVID-19 illness had
cancer, which is higher than the population incidence of cancer (0.29%). The same study also demonstrated that patients with cancer were at a higher risk for developing severe events (admittance to an intensive care unit, ventilation, or death) from COVID-19 illness (39%; 7 of 18) than those without cancer (8%; 125 of 1572)(13). Another study from New York City (5), which included 218 individuals with a diagnosis of COVID-19 and cancer (164 solid tumors and 54 hematologic malignancies), reported a significant increase in COVID-19-related case fatality rate in patients with cancer as compared to individuals without cancer (28% [61 of 218] vs 6% [6182 of 104185], \( P < 2.2 \cdot 10^{-16} \) [5]). Although limited by small sample size, additional analysis from this study revealed that patients with certain solid cancers had higher COVID-19 related mortality rates than other cancers (ie lung [55%, 6 of 11] and colorectal [38%, 8 of 21] versus genitourinary [15%, 7 of 46] and breast [14%, 4 of 28] cancers). Interestingly, active chemotherapy, radiation, or immunotherapy were not associated with an increased case fatality rate in this group of patients (5).

Increased mortality and morbidity were also observed in another study which included 928 patients (mean age 66 years; interquartile range, 57-76) with COVID-19 and cancer (14). In this study, older age (per 10 years, odds ratio [OR], 1.84; 95% confidence interval [CI]: 1.53, 2.21), male sex (OR, 1.63; 95% CI: 1.07, 2.48), former smoking status (OR, 1.60; 95% CI: 1.03, 2.47), number of comorbidities (ie two comorbidities; OR, 4.50; 95% CI: 1.22, 15.28), and active cancer (OR, 5.20; 95% CI: 2.77, 9.77) were all associated with an increased 30-day mortality due to COVID-19 (14). In another study, Warner et al reviewed 1018 patients with COVID-19 and cancer, in which 30-day mortality and severe illness were significantly higher than that of the general population, and tumor type or type of cancer therapy were not significant factors for mortality.
Another recent study by Rini et al, which included 2749 patients with COVID-19 and cancer, demonstrated high rates of mortality, approaching 16% at 30 day follow-up, with increased risk of intensive care unit admission or intubation (15). This rate of mortality from COVID-19 in patients with cancer was higher than the global 1-5% mortality rate from COVID-19 for an unselected general population (16).

In contrast, numerous studies have concluded that pediatric patients have lower risk for infection with SARS-CoV-2 and less severe manifestations of disease compared to adults (17). Children are approximately 50% less susceptible to infection, comprising less than 5% of total infections, with approximately 20% or fewer developing clinical symptoms (18,19). In the United States, children represent approximately 22% of the population but less than 2% of SARS-CoV-2 infections, and only 5% of infected children require hospitalization (20). A study in Switzerland reported similar findings (21). Some of these statistics may change as schools reopen in the Fall of 2020 (22).

Reinforcing this difference between children and adults, researchers at Memorial Sloan Kettering Cancer Center determined that children in New York City with cancer did not have increased risk for infection or severity of COVID-19 as compared with children without cancer (23). Reasons underlying why children typically do not experience more severe manifestations of COVID-19 remain unclear. One hypothesis is that healthier blood vessels in children as compared with adults, particularly adults with underlying cardiovascular disease, protect against complications of COVID-19 related to thrombosis (24). However, following SARS-CoV-2 infection, a small proportion of children develop multisystem inflammatory syndrome in children (called MIS-C), a rare but sometimes life-threatening hyperinflammatory condition (25).
As the number of infected individuals increases worldwide, and with longer follow-up data, long-term assessments of patients with cancer that have tested positive for SARS-CoV-2 are being initiated in a clinical trial called COVID-19 in Cancer Patients Study (NCCAPS, ClinicalTrial Identifier: NCT04387656). The main objectives of this clinical trial are to characterize different factors related to COVID-19 and cancer outcomes, such as other comorbidities, demographics, and types of cancer treatments (26). This study also aims to assess how cancer treatments were modified in response to the SARS-CoV-2 infection. Lastly, images from recruited participants will be collected, and thus this clinical trial will enable clinicians to gain a better understanding of confounding imaging findings between cancer, treatment response, and SARS-CoV-2 infection.

**Impacts of Postponed Cancer Imaging, Treatment and Procedural Appointments**

The impact of the pandemic resulting in government mandated shut-downs, shortages of personal protective equipment, insufficiencies of healthcare organizations, social distancing mandates, and generalized fear and anxiety of the public, essentially led to a near complete halt in all outpatient elective activity, including cancer screening and follow-up. Due to these modified activities, many diagnoses, initiation of treatment plans, modifications to treatment plans, and surgeries for resection did not occur during this time. Additionally, many clinical centers converted patients undergoing cancer therapy from intravenous to oral medications and/or to less aggressive regimens (monotherapy rather than combination therapies) to reduce risks of complications, hospitalizations, and visits to treatment facilities (9). The long-term impacts on delayed cancer imaging and treatment, as well as delayed follow-up appointments, during this pandemic will not be evident for some time.
Clinics continue to adapt to daily changes by instituting different protocols based on geographic COVID-19 outbreaks (27,28). Many major cancer organizations, including the American Society for Clinical Oncology and the American College of Chest Physicians recommended delaying screening studies such as screening mammograms, colonoscopy, and surveillance for lung cancer (29,30). Some experts proposed delaying screening for cervical and prostate cancer given that they are slow growing malignancies in which screening often aims to detect precancerous lesions, such that outcomes will likely be minimally affected (31,32). However, delay in diagnosis of rapidly growing malignancies such as breast and lung cancer can result in adverse outcomes (33). An expert panel also developed consensus statement to guide clinicians on the management of lung cancer screening programs and previously detected lung nodules encompassing various scenarios (eg baseline and annual lung cancer screening, management of previously detected nodules stratified by risk, and management of clinical stage 1 non-small cell cancer [6]). The consensus was to defer imaging and management in several situations, recognizing that individualized decisions may be necessary depending on patient preferences and other local factors.

In the United States, shut downs related to COVID-19 will result in a substantial backlog of screening evaluation, with a projected delay of more than 22 million screening tests for cancer and a 20% reduction in oncology visits (10). Additionally, even as clinics reopen, patients may still choose to postpone appointments in fear of COVID-19. Avoidance of health care procedures due to COVID-19 is highlighted in one study in Italy that compared the rate of procedure and surgical refusal in women with breast cancer or suspected breast lesions before and after March 18, when Italian COVID-19 cases were on the rise. Women were more likely to refuse procedures
(such as core needle biopsies or vacuum assisted biopsies \( P = .0208 \)) and surgical procedures \( P = .0065 \) after March 18 (34). Another study evaluated patient visits to clinics for cancer care in a multiple clinics throughout the United States by comparing patient encounters between January-April 2019 and January-April 2020 (35). These clinics usually experience 28 million patient care visits; however, during the aforementioned time frame, there was a substantial decline in the number of patient encounters for new cancer diagnosis in 2020. Decreased new cancer diagnoses were documented for lung cancer \((-46.8\%)\), breast cancer \((-50.5\%)\), prostate cancer \((-46.8\%)\), colorectal cancer \((-54.2\%)\), hematologic cancers \((-46.6\%)\), and melanoma \((-67.1\%)\) (32). Additionally, this study showed substantial reductions in breast \((-89.2\%)\) and colorectal cancer \((-84.5\%)\) screenings. (35). Early estimates from the National Cancer Institute suggest that there could be an excess of 10,000 deaths from breast and colorectal cancers due to altered appointment scheduling from the pandemic within the next 10 years (36). Considering the lower overall mortality rate of COVID-19 compared to some cancers, such as breast, lung or prostate cancer, healthcare teams must formulate thoughtful mechanisms to circumvent prolonged delay in cancer diagnosis and treatment.

In addition to the delay in screening and clinic appointments, there is also a large impact on delayed treatment. Treatment options vary widely depending on cancer type, but can include surgical resection, chemotherapy, immunotherapy, radiation therapy, locoregional interventional therapies, or a combination of any of those therapies. With the delay in all ‘elective non-essential surgeries’, it is critical to identify which cancer-related surgeries are essential and which are not. Some modifications, such as the addition of radiation therapy to chemotherapy, can help to delay surgery (37). Delay in surgical resection must outweigh the risk
of tumor progression, although additional considerations include the potential added burden on hospital resources, case complexity, and risk of COVID-19 exposure (38,39). Nonetheless, neoadjuvant therapy, which requires multiple clinic visits and direct clinician-patient contact, or that is immunosuppressive, also adds potential risks for the patient that must be considered.

One confounding factor for cancer therapy is the use of immunotherapy for cancer treatment. Studies have shown that patients who receive corticosteroids while on immunotherapy have a lower overall response rate (7% versus 18%) and worse progression-free and overall survival than those not receiving steroids. Furthermore, in patients who stopped taking steroids 1-30 days before immunotherapy administration, there was intermediate reduction in progression free and overall survival compared to those on steroids (40). This concept is important, as many emerging studies show that corticosteroids may improve outcomes for patients with severe manifestations of COVID-19 (41). Insufficient data exist to evaluate the effect of short term corticosteroid use in patients with cancer who are infected with SARS-CoV-2. Additional considerations are that immunotherapy can cause treatment-related pneumonitis, which can mimic the imaging appearance of COVID-19 infection (42) (Figure 1). Frequent in-person visits are also necessary for medication administration. Thus, a tailored approach to treatment is necessary for these patients, after weighing the possible risks and benefits.

**Delayed and Postponed Cancer Clinical Trials**

Most facilities in the United States and worldwide only continued interventional clinical trials for cancer that could provide direct benefit to participants, such as testing a new therapy
for a malignancy or stage of disease with no known cure. Patient enrollment in NCI sponsored trials decreased as COVID-19 cases rose in the United States in April 2020 (43). Recognizing some geographic variations based on extent of COVID-19, most institutions typically paused all other trials, including many observational trials testing new imaging methods, probes, or sequences. For imaging studies tracking progression of cancer and response to therapy, the pause in clinical studies resulted in irrecoverable loss of data (2). Institutions generally have adopted a phased transition to resuming clinical research based on somewhat subjective assessments of direct benefits to participants versus risks of COVID-19. To help investigators continue their trials during this period, guidance was provided for minor and alternative protocol deviations for NCI sponsored clinical trials by the Department of Health and Human Services (26,44). Protocol deviations that were allowed consisted of expanding to virtual telehealth visits for patient follow up, as well as treatment or imaging delays to avoid potentially exposing patients unnecessarily within a clinic.

Observational studies, which include many imaging studies in cancer and other diseases, frequently fall under the lowest priority category of having no direct benefit to participants, even though such trials may have great benefits to future diagnosis and treatment of cancer. Cancer also commonly impacts older people who are at greater risk for severe COVID-19, have other underlying clinical conditions, and often have varying degrees of immunosuppression from therapy. Beyond institutional restrictions, clinical studies in cancer generally rely on the tremendous generosity and dedication of participants to enroll and continue on a clinical study for little or no financial compensation. It is unclear to what extent future enrollment may decline
based on perceived risks to participants and increased telehealth visits that do not bring patients to a central facility with imaging equipment.

**Imaging Manifestations from SARS-CoV-2 Infection that Could Impact Cancer Imaging**

SARS-CoV-2 infection can result in a cascade of pathophysiologic events that results in hyperstimulation of the inflammatory system producing a cytokine storm. Unmitigated inflammation causes extensive cell damage and necrosis, including activation of the clotting cascade, and can affect many different organ systems (45–47), with the potential to confound cancer imaging in certain patients. This section describes different imaging manifestations associated with COVID-19 that overlap with radiologic findings seen in a variety of cancers. If present, these mimics may confound cancer staging or assessment of treatment response.

*Lung Imaging*

Special attention will need to be given to those patients that are being screened for lung cancer or monitored for treatment responses. An expert consensus statement on reporting of chest CT findings related to COVID-19 has categorized the findings into negative, atypical, indeterminate, and typical appearance for COVID infection (6). Typical features of COVID-19 on chest CT include peripheral bilateral ground-glass opacities (GGO) with or without consolidation or septal thickening (crazy paving), multifocal GGO with rounded morphology (with or without consolidation or crazy paving), and reverse halo sign (6,48,49). CT has high sensitivity (> 95%) but low specificity (~50%) for SARS-CoV-2 infection (49–51). Asymptomatic individuals may still exhibit radiologic abnormalities in the lung (52,53), indicating that attention will be required in cases where patients may not have known they contracted COVID-19. However, it is also
important to realize that the typical COVID-19 appearance can mimic therapy-associated pneumonitis and other viral infections. Hence, when findings consistent with a typical pattern for COVID-19 are encountered, discussion with the clinical service, careful history, and appropriate evaluation for infection should be considered.

Case reports of SARS-CoV-2 infection detected incidentally on fluorine-18 fluorodeoxyglucose (\(^{18}\text{F}\))-FDG PET studies in cancer patients show accumulation of radiotracer in areas of lung with GGOs (54–56). These characteristic CT findings of COVID-19 occur in both symptomatic and asymptomatic patients with cancer. \(^{18}\text{F}\)-FDG uptake in mediastinal lymph nodes in a patient with COVID-19 has been described, which is consistent with active inflammation (54). In a case study from Italy, six of 65 patients that were undergoing PET/CT for various oncologic indications showed signs of pneumonia on CT and high \(^{18}\text{F}\)-FDG uptake in these areas. Four of these patients were then tested positive for SARS-CoV-2 infection; the other two patients were quarantined, but not tested (57). It is not uncommon that patients with incidental imaging findings suggestive of COVID-19, encountered during cancer follow-up \(^{18}\text{F}\)-FDG PET/CT, have negative PCR testing for SARS-CoV2 (Figure 2). Highly variable false-negative rates have been reported for SARS-CoV-2 RT-PCR testing (58,59), which can make diagnosis difficult. In those situations, it is imperative to compare to recent chest CT findings, if available, (eg presence and distribution of ground glass lesions versus solid nodules) as well as closely follow-up those patients with imaging to assess for temporal change and the etiology of \(^{18}\text{F}\)-FDG uptake. This is of utmost importance if treatment plans are to be modified based on suspicion of tumor progression rather than a diagnosis of COVID-19. Given the overlap in imaging findings of
infection and some cancers, such as adenocarcinomas, that can have patchy ground glass pattern, interpretation of studies can be challenging in this context (60) (Figure 2 and 3).

Besides differentiation of COVID-19 imaging findings from tumor progression, differentiation from other infectious processes is also very important. In fact, several other infections like influenza and those that occur in immunocompromised cancer patients, such as aspergillosis, may have imaging features similar to those associated with COVID-19. For example, ground glass lesions and CT halo sign are commonly observed in early invasive pulmonary aspergillosis or mucomycosis, presumably reflecting alveolar hemorrhage due to the angio-invasive nature of the pathogen (61–64). In cases of invasive pulmonary aspergillosis, early initiation of anti-fungal treatment is important to decrease mortality and morbidity. While subsequent signs such as air crescent sign can point towards the diagnosis of fungal infection(63), these are usually encountered late and have less impact on management. Apart from the overlap of imaging findings, invasive pulmonary aspergillosis has also been described as a secondary infection in COVID-19 patients.

Taken together, imaging findings in patients with lung cancer or lung metastasis should be interpreted very carefully in order to distinguish cancer-related findings from those associated with COVID-19 and other clinically-relevant infectious processes.

**Neurological Imaging**

Neurologic symptoms have been reported in patients with COVID-19. A study from Wuhan, China reported neurologic abnormalities in 36% of hospitalized patients, typically in patients with more severe disease. Patient presentations included dizziness, loss of taste and
In another study, 21% (50 of 235) of patients in the intensive care unit developed neurological symptoms (66). A few symptoms seem to raise questions about central nervous system involvement with the virus, such as anosmia, which could be caused by congestion, but also by retrograde neuronal viral extension along the olfactory nerve, bulbs, and/or tracts. Two studies have already described abnormal asymmetrical hyperintensities on fluid-attenuated inversion recovery (FLAIR) imaging along the olfactory bulbs and tracts in patients who tested positive for SARS-CoV-2 and presented with severe anosmia (67,68).

Multiple other findings have been described in patients with COVID-19, ranging from ischemic and hemorrhagic complications (69,70), likely related to hypercoagulable and/or prothrombotic states, to meningoencephalitis, demyelinating lesions, and a variety of often symmetric abnormal white matter changes on FLAIR (71–75). More pertinent imaging findings have been described in patients in whom SARS-CoV-2 was detected in the cerebrospinal fluid, including abnormally high signal intensity lesions on FLAIR and diffusion weighted imaging in the mesial temporal lobes, brainstem, and thalami (71,72). Although the majority of those changes are not commonly confused with primary brain tumors or brain metastatic disease, there can be some similarities to MRI findings in patients presenting with immunotherapy-associated autoimmune and/or limbic encephalitis, with involvement of mesial temporal lobes and/or basal ganglia (76,77). Assessing the exact etiology of brain imaging findings in patients on immunotherapy and COVID-19 is thus warranted.

Cardiovascular Imaging
The vascular system has been implicated as one of the primary targets of SARS-CoV-2 and causes of morbidity and mortality in patients with COVID-19 (78). Recent reports now suggest that pulmonary embolism may be a large contributing factor to mortality from COVID-19 (79). Endothelial cells lining blood vessels express angiotensin-converting enzyme 2, the receptor for SARS-CoV-2, making these cells a target for infection (80–82). Heart damage and arrhythmia, likely from viral infection, commonly occur in patients with COVID-19 (83). COVID-19 greatly increases risk of blood clots, with pulmonary emboli detected by CT pulmonary angiography in 20-30% of patients (84–86). In one case study, a 59-year-old man with metastatic lung cancer was suspected of having cardiac arrest secondary to pulmonary embolism with symptoms of COVID-19 illness. A CT pulmonary angiogram showed a pulmonary embolism; subsequent testing documented infection with SARS-CoV-2(87). Since patients with cancer already have elevated risk of blood clots and emboli, SARS-CoV-2 infection likely would elevate this risk, although no cohort studies have addressed that possibility. Microvascular thrombi have been proposed as a possible explanation for COVID-19-related hypoxemia (88). Even in absence of pulmonary emboli on CT, perfusional lung abnormalities have been described in patients with COVID-19 on dual energy CTs. These abnormalities consist of pulmonary vascular dilatation with decreased peripheral perfusion corresponding to GGO consolidation and a halo of increased perfusion surrounding the lung airspace disease (89).

**Abdominal Imaging**

Gastrointestinal symptoms such as diarrhea, abdominal pain, and nausea are commonly reported in COVID-19 patients. Reports suggest up to 15% of patients have gastrointestinal symptoms (90). One study found that approximately 18.6% (38 of 204) of patients admitted to
the intensive care unit exhibited gastrointestinal-specific symptoms (91). Studies show COVID-19 can affect multiple organs in the abdomen, including liver, pancreas, bowel, and biliary system. The pathogenic mechanism of action is likely related to the expression of angiotensin-converting enzyme 2 by biliary epithelial cells (45), pancreatic islet cells (92), gastrointestinal enterocytes (93) and vascular endothelium throughout the abdomen (80). Additionally, the microembolic effect from activation of the clotting cascade secondary to the severe systemic inflammatory response can result in multi-organ ischemia and infarction.

Bowel wall abnormalities on contrast-enhanced CT include small and large bowel wall thickening, pneumatosis, portal venous gas (from ischemia), and fluid-filled bowel loops in the setting of diarrhea (94). Pathologic evaluation of the bowel has shown inflammatory infiltration in the bowel wall on histology and discoloration of the bowel secondary to ischemia (47). Infarction of the bowel wall has led to segmental stenosis and dilatation of focal segments of bowel (95), which could be a mimic for obstructing apple-core bowel cancer.

Additionally, US has shown findings of cholestasis by evidence of gallbladder sludge and distension in 54% (20 of 37) of patients that underwent imaging (94). In a case study of a 79-year-old woman who displayed typical COVID-19 pneumonia on chest CT, unenhanced images of the upper abdomen showed arterial and venous thrombosis of mesenteric vessels (96). Although SARS-CoV-2 infection is associated with a hypercoagulable state and resultant emboli, these findings are not specific for COVID-19 and could occur due to other causes in patients, including patients with cancer who may have a hypercoagulable state related to their underlying disease.
In another interesting case, a 49-year-old man presented with ARDS secondary to COVID-19, along with additional complications that were likely the result of a hypercoagulable state induced by COVID-19. Imaging revealed bilateral pulmonary emboli, bilateral common femoral and external iliac deep vein thrombosis, bowel ischemia, abdominal compartment syndrome, and intra-abdominal fat necrosis from mesenteric vascular thrombosis (Figure 4). These imaging findings demonstrate multiple intra-abdominal findings of SARS-CoV-2 infection that mimic metastatic cancer. Bowel ischemia, which resulted in abnormal wall thickening and peri-colonic mesenteric infiltration, mimicked the appearance of a colon cancer with infiltration into the adjacent peri-colonic fat, peritoneal carcinomatosis, and malignant ascites with deep vein thrombosis secondary to a hypercoagulable state, all of which can be seen in patients with cancer.

While there are many abdominal manifestations in patients with COVID-19, only some will result in imaging findings, most of which are non-specific. Thus far there is limited literature and anecdotal evidence suggesting that COVID-19 imaging findings may mimic cancer. The main concern in COVID-19 patients with a cancer diagnosis is the delay in imaging and treatment resulting in progression of disease, which can sometimes affect treatment options if the cancer has progressed. (Figure 5)

*Liver Imaging*

While elevations of liver enzymes occur commonly in patients with COVID-19, reported at 40-43% in some studies(97), available data suggest that clinically significant liver injury is rare (98). Most findings include elevations in alanine aminotransferase and aspartate
aminotransferase levels, but rarely elevated total bilirubin (99). However, liver injury likely occurs more frequent secondary to sepsis and systemic inflammatory response syndrome; drug toxicity from antipyretics, analgesics, antivirals, and other drugs (100–102); COVID-19-related hypercoagulation; or damage of bile duct cells (103). Microembolic changes from hypercoagulability may lead to abnormal geographic arterial hyperperfusion on arterial phase imaging, which normalize by the portal venous phase of imaging. However, despite the prevalence of liver function abnormalities detected in COVID-19 patients, clinically significant abnormal liver imaging findings are not typically seen in these patients.

One consideration in liver imaging is management of hepatocellular carcinoma in the time of COVID-19. Modifications in management algorithms are necessary in order to ensure timely and adequate treatment of these patients, particularly since this group of patients is often undergoing evaluation for liver transplantation. Tumor progression, including size of lesion, number of lesions, or distant metastasis, can render the patient ineligible for transplant. Thus, proper risk stratification of these patients using Child-Pugh scoring, Barcelona Clinic Liver Cancer staging, tumor evaluation using American Association for the Study of Liver Diseases guidelines, and multidisciplinary discussion can help prevent progression of cancer secondary to delayed treatment from the pandemic. As one example, Figure 5 depicts a patient for whom delay in care resulted in a clinically significant increase in the size of his tumors.

**Implications for Cancer Imaging and Treatment Appointments Moving Forward**

Groups of cancer centers and medical organizations have issued guidelines for managing cancer therapy and imaging during the pandemic (6). van de Haar et al gathered information
from seven cancer centers about prioritization of cancer appointments and potential modifications to treatment regimens (9). One recommendation was to consider de-escalating cytotoxic chemotherapy and other immunotherapies to minimize immunosuppression that might increase COVID-19 severity. Additionally, guidelines were proposed to determine the urgency of different appointments for prioritization. Clinics will need to be prepared for potentially rapidly increasing or decreasing capacity for the duration of this pandemic (9).

Mazzone and colleagues presented a set of guidelines for lung cancer screening and managing patients with newly diagnosed stage I lung cancer during the pandemic (6). Recommendations included delaying onset of screening, and even considering delaying treatment for patients with newly diagnosed stage I non-small cell lung cancer (6). Akula et al reported on risk factors for multiple different cancer subtypes (breast, colorectal, gastrointestinal, glioblastoma, gynecological, head and neck, hepatocellular, and lung cancer), and suggested management guidelines during the pandemic (104). Multiple other groups have also released management guidelines during the pandemic for patients with cancers such as breast (105), lung (6), head and neck (7), as well as gastrointestinal cancers (39). Management of these patients is likely best made in a virtual multidisciplinary setting to ensure patients are receiving optimal care without affecting overall survival during this pandemic.

Care is also being taken with regards to minimizing the potential of SARS-CoV-2 exposure during appointments. The use of telehealth (ie, virtual visits) has expanded substantially over the course of the pandemic. However, different geographical regions may have limited access to resources that would facilitate these types of visits (106). If patients do need to enter the clinic, mask mandates and other infection prevention measures are being implemented across the
In cases where patients need to undergo surgery, patients should be assumed to be potential carriers of SARS-CoV-2 and undergo routine testing prior to surgery (107). Depending on specific institutional guidelines, patients may undergo SARS-CoV-2 polymerase chain reaction testing and/or antibody testing prior the surgery. Because some individuals infected with SARS-CoV-2 are asymptomatic, these tests are important in preventing potential viral exposures in healthcare settings.

Concluding Remarks

Through the beginning of the pandemic, much has been discovered about the disease course of COVID-19 and how new practices will need to be implemented throughout the course of the pandemic. As outlined here, there are challenges with maintaining scheduled appointments and treatments for patients with cancer that existed prior to the pandemic. One campaign that has recently been launched is the Return to Care initiative, which is aimed at continuing medical care appointments through the pandemic and emphasizing the measures that have been taken for patient safety (https://www.returntocarecampaign.org/). Clinicians and researchers have rapidly learned much about COVID-19, and protocols have been developed to transition to a new normal in healthcare. Outbreaks of SARS-CoV-2 infection are likely to continue for at least the next two years (108), and communities will need to continue to work together to adapt and help slow the spread of infection and COVID-19. In addition to the effect on cancer diagnosis and treatment from delay in care and changes in practice patterns, it is also important to understand overlapping imaging features of cancer and COVID-19 complications to accurately distinguish cancer progression from infection and ensure appropriate patient management. New research and evolving literature on radiographic manifestations of COVID-19 will continue to
shed light on strategies for surviving and overcoming the current pandemic. Hopefully knowledge and protocols from this pandemic will prepare researchers, clinicians, and radiologist to better manage and overcome the next global infectious disease threat.
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Figure 1. A 57-year-old asymptomatic man with renal cell cancer receiving immune checkpoint inhibitor (Nivolumab) underwent a chest CT for routine surveillance during the COVID-19 pandemic. A, B Axial and C, coronal chest CT showed rounded areas of ground glass opacities in
the lungs bilaterally. This organizing pneumonia pattern can be seen with COVID-19 infection and drug-induced pneumonitis (given history of treatment with Nivolumab). The patient was asked to report to the emergency department if respiratory symptoms developed. A follow-up CT showed persistent opacities at $D$, one month and improving opacities with reverse halo sign at $E$, 2.5 months from baseline scan. The clinical course in this asymptomatic patient was consistent with Nivolumab induced pneumonitis.
**Figure 2.** Fluorine-18 fluorodeoxyglucose (¹⁸F-FDG) and CT imaging in a 62-year-old man with a history of peripheral T-cell lymphoma presenting for follow-up. *A,* Ground glass opacities in the left lung show associated increased ¹⁸F-FDG uptake and were *B,* observed on axial CT. A SARS-CoV-2 test performed on the same day was negative. *C,* Resolution of ground glass opacities on axial chest CT obtained four weeks later. Images courtesy of Dr. Milijković, Milos (Center for Cancer Research, National Cancer Institute, National Institutes of Health).

![Image](image_url)

**Figure 3.** A 58-year-old woman with idiopathic pulmonary fibrosis presenting with shortness of breath during the COVID-19 pandemic. *A,* CT for pulmonary embolism assessment showed no pulmonary embolism, but focal round peripheral air space opacities in an organizing pneumonia pattern. The patient tested negative for COVID-19 infection on PCR and the lung opacities persisted on follow-up *B,* CT and *C,* fluorine-18 fluorodeoxyglucose PET scan performed one month later. The patient subsequently underwent a biopsy (given lack of change, negative SARS-CoV-2 test and underlying idiopathic pulmonary fibrosis as a risk factor for malignancy). This was pathologically proven to be lung adenocarcinoma.
Figure 4. A 49-year-old man presenting with severe respiratory distress secondary to COVID-19 infection. The patient developed many complications, including septic shock, acute respiratory distress syndrome, heart failure, bilateral pulmonary emboli, bilateral common femoral and external iliac deep vein thrombosis, bowel ischemia, abdominal compartment syndrome and intra-abdominal fat necrosis from mesenteric vascular thrombosis. A, Contrast-enhanced CT show diffuse ascending colon wall thickening, with submucosal edema and a featureless appearance (arrows) with stranding and nodularity in the peri-colonic fat (*). B, Contrast-enhanced CT shows diffuse peritoneal and mesenteric nodularity (*) with ascites (blue arrows). C, Coronal contrast-enhanced CT shows bilateral common deep vein thrombosis of the femur (arrows). These imaging findings demonstrate multiple intra-abdominal findings that can be seen with SARS-CoV-2 infection. These findings in particular, mimic that of metastatic cancer. The abnormality in the ascending colon also has the appearance of a colon cancer, with infiltration into the adjacent peri-colonic fat, peritoneal carcinomatosis and malignant ascites with deep vein thrombosis secondary to a hypercoagulable state which can be seen in cancer patients.
**Figure 5.** A 65-year-old man with chronic hepatitis presented for screening MRI. **A,** Arterial phase MRI reveals no cancer in December 2019. The 3-month follow-up MRI, which should have occurred at the beginning of March 2020, was delayed secondary to suspension of outpatient imaging during the pandemic shut down. MRI was obtained 6 months later (June 2020) instead. **B and D,** T2-weighted and **C,** arterial phase MRI shows two lesions measuring 1.9 cm (**B, C**) and 1.4 cm (**D**). The patient’s case was discussed at multidisciplinary liver tumor board and recommendation for microwave ablation of only the larger lesion was made. However, due to further delay in care secondary to the pandemic, the patient was scheduled 2 months later for microwave ablation. **(E, F)** Contrast-enhanced US performed prior to microwave ablation reveals clinically significant interval increase in size of both lesions. The largest lesion was greater than the 3.5 cm threshold for curative microwave ablation. However, imaging was performed after the patient was already under general anesthesia. After discussion with the ordering clinician, the decision was made to biopsy and treat both lesions. Post-ablation contrast-enhanced US shows adequate ablation zones with margins greater than 1 cm larger than the tumor size.