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## Delayed access to lung cancer screening and treatment during the COVID-19 pandemic: are we headed for a lung cancer pandemic?

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On March 11 2020, the World Health Organization declared the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or COVID-19) to be a global pandemic. Since then, significant re-organisation of healthcare provision has occurred to deal with the increasing burden of patients requiring hospitalisation and to minimise infection of healthcare workers. As a result, delays in diagnosis and treatment have been reported across all cancer types. However, lung cancer may be one of the most impacted due to a number of factors including overlapping symptoms with COVID-19 and shared needs from respiratory medicine services.

Prior to the pandemic, lung cancer was the leading cause of cancer diagnosis and mortality worldwide, accounting for 11.6% of new cases and 18.4% of deaths.<sup>1</sup> The poor prognosis is largely attributed to the majority of patients being diagnosed at an advanced stage. The pandemic has seen a sharp drop in referrals to lung cancer services, with concerns of a surge of late-stage presentations followed by a rise in mortality rates.<sup>2</sup>

Screening programs targeting asymptomatic at-risk populations aim to detect cancer at an early stage where curative treatment remains an option. However, with measures to relieve the burden on the healthcare system, operation of lung cancer screening programs has been largely suspended. Consensus statements from expert multidisciplinary panels conclude that it is appropriate to defer enrollment in screening and modify lung nodule evaluation due to the risks of COVID-19 exposure and the need for resource reallocation.<sup>3</sup> Indeed, a recent study reported a 72% decrease in the annual low-dose CT study volume performed for screening purposes when compared with the pre-COVID-19 period.<sup>4</sup> However, the consequences of delayed detection have the potential to erode recent gains made by screening. In a population-based modelling study from the UK assessing the impact of delays in cancer detection on survival outcomes, it was estimated that 1235 to 1372 additional deaths could be expected, equating to an increase of 5.8-6% five years after diagnosis.<sup>5</sup>

In symptomatic patients, a number of factors impact the timeliness of lung cancer diagnosis in the COVID-19 era. The overlap in manifestations between lung cancer and COVID-19, including cough and breathlessness, has led to patients self-isolating due to concerns of being infectious. Furthermore, public health advice to remain home if possible has resulted in general reluctance to attend healthcare services. Additionally, telehealth consultation with the inability to examine patients creates opportunity for missed diagnosis of lung cancer. Lastly, reduced access to radiology, nuclear medicine, and tissue acquisition procedures due to prioritization of COVID-19 cases has contributed to the delay in diagnosis. Interpretation

of CT chest findings and distinction between features of COVID-19 and lung cancer can also be challenging where both conditions may present with ground glass opacities, nodules, consolidation, lymphadenopathy and effusion. Minimally invasive procedures for tissue diagnosis such as bronchoscopy and endobronchial ultrasound have been particularly affected due to their aerosol-generating nature and the risk of infection transmission. Furthermore, the prolonged duration of each procedure due to personal protective equipment protocols, requirement for closed circuit ventilation, and room cleaning between patients, has resulted in limited capacity on procedure lists.

The significant impact of COVID-19 in thoracic malignancy has been demonstrated by the TERAVOLT study which described hospitalisation and mortality rates of 76% and 33% respectively.<sup>6</sup> There have been reports of increased mortality in the event of COVID-19 infection following surgery, rising up to 40-50%.<sup>2</sup> Furthermore, patients undergoing surgery or chemotherapy within the month preceding COVID-19 diagnosis have been shown to bear a higher risk of severe infection-related complications.<sup>7</sup> Importantly, in patients receiving chemotherapy or the newer molecular and immunotherapy agents, the clinical and radiological manifestations of drug-related pneumonitis are similar to those of COVID-19, posing a major management challenge for oncologists. As such, lung cancer patients have experienced treatment delay or interruption in order to minimise the risk of exposure of vulnerable immunocompromised patients to COVID-19 and to alleviate the demands on healthcare staff, hospital beds, operating theatres and intensive care units.

However, the corollary is the adverse impact upon prognosis. A delay to surgery beyond 6 months is associated with a 5-35% decline in 5-year survival depending on patient age and tumour stage.<sup>8</sup> Similarly, postponement of radiotherapy by more than 24 days is associated with a risk of up to 30% disease progression for lung cancer patients with regional nodal spread at presentation.<sup>9</sup> Lung cancer oncology clinical trials and research have been critically affected by the pandemic, with a demonstration of 40-50% fall in enrolment in trials conducted by the SWOG Cancer Research Network with implications for patients who would benefit from receiving novel agents.<sup>10</sup> Lastly, reduced access of visitors to palliative care services have added to the psychological distress felt by lung cancer patients and families.

While there is no doubt of the detrimental effects of COVID-19 upon lung cancer, there are opportunities for improvement emerging from the response to the pandemic. Increased efficiency of digital consultation may advance equity of access for patients in remote settings. Similarly, the ability for specialists to join virtual multidisciplinary meetings may improve attendance at such forums. Lastly, the use of non-invasive modalities for diagnosis of lung cancer, such as liquid biopsies for molecular analysis, may rationalise the need for invasive testing in frail patients.

With over 66 million cases and 1.5 million deaths at the time of writing, the trajectory of the COVID-19 pandemic remains uncertain. However, the aggressive nature of lung cancer does not allow for diagnosis or treatment to be delayed. Approaches such as systematic testing for COVID-19 in patients suspected or confirmed of having lung cancer may be of value in decision-making processes. Furthermore, decision analysis modelling of the likelihood of disease progression and the probability of acquiring COVID-19 infection may help guide triaging of diagnostic and treatment procedures.<sup>11</sup> Lastly, alternative management options should be considered for patients with locally advanced disease who may be effectively treated with non-surgical and less immunosuppressing therapies.<sup>12</sup> Ultimately, a careful balance will need to occur to avoid a surge in lung cancer cases in the wake of this pandemic.

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