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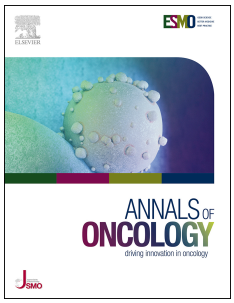

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EDITORIAL

Testing for COVID-19 in lung cancer patients

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Coronavirus disease 2019 (COVID-19), is a respiratory tract infection caused by the severe acute respiratory syndrome (SARS) coronavirus (COV), also named SARS-CoV-2. COVID-19 was first recognized in Central China (Wuhan, the capital of Hubei province) at the end of December 2019, later becoming a pandemic, spreading rapidly in multiple countries worldwide.[1] According to data from China and Italy, the first two countries with the highest incidence, the majority of patients infected by SARS-CoV-2 were asymptomatic or presented with mild upper respiratory tract symptoms. However, about 14-24% of patients developed pneumonitis and required hospitalization and oxygen support. About 5% of patients developed acute respiratory distress syndrome (ARDS) or sepsis-related acute organ dysfunction, requiring admission to intensive care units (ICUs).[2,3]

The case fatality rate (CFR = %), defined as number of deaths in COVID-19 positive patients divided by number of those tested positive, is significantly higher for those with underlying concomitant disease, such as cardiovascular disease, diabetes, chronic respiratory disease and cancer, as well as older age. This phenomenon is observed in both Chinese and Italian populations, but it appears to be more pronounced in the Caucasian population.[3,4] The overall CFR in China was reported at 2.3% compared to 7.2% in Italy. A stratified analysis showed that the CFR in Italy and China was very similar in patients who are younger (<70 years), but higher in Italy for patients who are 70 years or above. This includes 687 patients who were older than 90 years, where the CFR was 37.6% and 11.9% in Italy and China, respectively.

Different approaches towards SARS-CoV-2 testing could partly explain the difference in incidence and CFR. Initially, Italy adopted a non-discriminative testing strategy that included both symptomatic and asymptomatic patients. But after 6 days, when large numbers of patients suffered from severe SARS-CoV-2-related ARDS, the Italian Ministry of Health decided to allow testing only in symptomatic patients who were potential candidate for hospitalization, and this decision may have resulted in a biased selection and delayed treatment for these patients. In this editorial, we would like stress the identification of lung cancer patients as a specific population for testing prioritization for COVID-19.

Based on available data, smoking history has been correlated with a higher incidence and severity of SARS-CoV-2 infection[4,5]. Comparing smokers and non-smokers, the risk of severe symptoms is 1.4 times higher (RR=1.4, 95% CI: 0.98–2.00), and risk of ICU admission, mechanical ventilation or death is 2.4 times higher (RR=2.4, 95% CI: 1.43–4.04).[9] Structural and immunologic-induced modifications are the two main tobacco-related damages accounting for susceptibility to infections. Peribronchiolar inflammation and fibrosis facilitate pathogen adherence and potentially amplify pulmonary inflammation.[6] In addition, changes in humoral, macrophage and cell-mediated immune response may aggravate the immunosuppressive effect.[7,8] It has been postulated that prior tobacco-related lung damage, including chronic obstructive pulmonary disease (COPD) and lung cancer, additionally predispose to more severe COVID-19 complications.[5].

While all types of malignancies seem to be associated with high COVID-19 prevalence, morbidity and mortality, lung cancer represents a specific scenario of cumulative risk factors for COVID-19 complications, including older age, significant cardiovascular and respiratory co-morbidities, smoking-related lung damage, as well as the unavoidable addition of treatment-related immune impairment or suppression. [10,11]

Defective pulmonary architecture from mechanical tumor obstruction or previous lung surgery may also predispose to infection. Changes in the anatomy of airway and pulmonary tissue lead to intra- and peri-tumoral microenvironment alteration, which may secondarily affect immune cell infiltration characterized by an increase in macrophages and inflamation.[12] The presence of macrophage infiltration in lung tissue poses a higher risk for cytokine release. During SARS-CoV-2 infection, massive cytokine release has been postulated to be the major step in leading to the development of ARDS.[13,14] Considering that lung cancer patients show similar clinical symptoms including cough, fever and dyspnea with SARS-CoV-2 infection compared to other individuals, an accurate COVID-19 screening model could allow for early detection and potentially reduce the risk of severe complication and mortality.

A significant proportion of lung cancer patients need corticosteroids for prophylaxis, treatment and symptom control related to cancer or chronic obstructive pulmonary disease.[15] It is well established that steroids may reduce inflammation and immune cellular activity, including lymphopenia and impaired T-cell function. Corticosteroids are possibly deleterious in the management of COVID-19 ARDS[15] and they may mask some of the early symptoms of SARS-CoV-2 infection, arguing for routine SARS-CoV-2 testing in patients receiving steroids.[16]

To date, many concerns are shared within the thoracic oncology community on the predisposing risks of immunosuppression by cancer therapy including chemotherapy, immunotherapy and molecularly-targeted therapy. These concerns are supported by recent findings by Liang *et al* that surgery or chemotherapy within the month preceding SARS-CoV-2 diagnosis were associated with higher risk of complications.[10] This may impose specific consideration on the schedule and dose of cytotoxic chemotherapy for lung cancer patients in epidemic areas such as the Lombardy region in Italy.

While the impact of immune checkpoints inhibitors or tyrosine kinase inhibitors on the risk and course of COVID-19 remains unknown, radiological features of lung cancer or related to these treatments may be characterized by ground-glass opacities, mimicking COVID-19 radiological characteristics. Recently, data about higher sensitivity of radiologic imaging compared to nasopharyngeal/oropharyngeal swab are emerging[17] and, considering that lung cancer patients periodically undergo CT scans, an emerging amount of COVID-19-suspicious imaging, even in the absence of new symptoms, is likely to increase in the next upcoming weeks.

In the era of COVID-19, the optimal management of patients with lung cancer remains unknown and the oncology community should have increased awareness to prevent the emergence of an increase in cancer-related and infectious mortality. While suspending or delaying cancer treatment delivery seems logical in some cases, the risks/benefits and final outcomes of these deviations remain to be measured.

With this in mind, a novel global registry (TERAVOLT - Thoracic cancERs international coVid 19 cOLlaboraTion) is now in action, collecting data worldwide with the objective of developing a tailored risk assessment strategy for lung cancer patients.

Despite the current lack of robust data, it is essential to establish an international consensus on testing for SARS-CoV-2 in lung cancer patients, where the early identification of SARS-CoV-2 may result in tailored management. ESMO will soon publish on its website proposals of treatment recommendations in the era of COVID-19. In this scenario, baseline SARS-CoV-2 testing for all patients affected by lung cancer should be recommended. In addition, for those patients with a negative swab test and new ground-glass opacities detected on CT scan, with or without new respiratory symptoms, bronchoscopy should be considered to increase testing sensitivity.

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