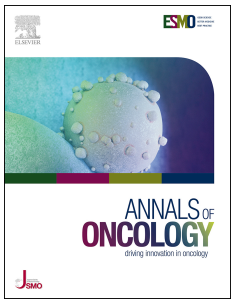
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal Pre-proof



Testing for COVID-19 in lung cancer patients

Antonio Passaro, Solange Peters, Tony S.K. Mok, Ilaria Attili, Tetsuya Mitsudomi, Filippo de Marinis

PII: S0923-7534(20)39293-0

DOI: https://doi.org/10.1016/j.annonc.2020.04.002

Reference: ANNONC 153

To appear in: *Annals of Oncology*

Received Date: 30 March 2020

Accepted Date: 3 April 2020

Please cite this article as: Passaro A, Peters S, Mok TSK, Attili I, Mitsudomi T, de Marinis F, Testing for COVID-19 in lung cancer patients, *Annals of Oncology* (2020), doi: https://doi.org/10.1016/j.annonc.2020.04.002.

EDITORIAL

Testing for COVID-19 in lung cancer patients

Antonio Passaro[1§], Solange Peters[2], Tony S K Mok[3], Ilaria Attili[1],

Tetsuya Mitsudomi[4], Filippo de Marinis[1]

1. Division of Thoracic Oncology, IEO, European Institute of Oncology IRCCS, Milan, Italy
2. Department of Oncology, Centre Hospitalier Universitaire Vaudois, Lausanne University, CH-1011 Lausanne, Switzerland.
3. Department of Clinical Oncology, State Key Laboratory of Translational Oncology, Chinese University of Hong Kong, Hong Kong, China.
4. Thoracic Surgery, Kinki University Faculty of Medicine, Osaka-Sayama, Japan

§ Correspondence:

Antonio Passaro, MD, PhD

Division of Thoracic Oncology
IEO, European Institute of Oncology IRCCS, Milan
Via G. Ripamonti, 435 - 20141 Milan, Italy
Phone: 0039-02-57489482 | Fax: 0039-02-94379235
Email: antonio.passaro@ieo.it

Article Type Editorial
Word count 1086 (excluding, disclosure, acknowledgements, references)
Running Title Lung cancer and COVID-19
Keywords: lung cancer; COVID-19
References: 17

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.

Acknowledgements: This work was partially supported by the Italian Ministry of Health with Ricerca Corrente and 5x1000 funds.

Disclosure: The Authors do not have any conflict of interest to declare related to topics discussed in this article.

AP served in a consultant/advisory for Astra Zeneca, Agilent/Dako, Bristol-Myers Squibb, Lilly, Merck Sharp & Dohme and Roche Genentech.

SP has received education grants, provided consultation, attended advisory boards, or provided lectures for Abbvie, Amgen, AstraZeneca, Bayer, Biocartis, Bioinvent, Blueprint Medicines, Boehringer Ingelheim, Bristol-Myers Squibb, Clovis, Daiichi Sankyo, Debiopharm, Eli Lilly, F Hoffmann-La Roche, Foundation Medicine, Illumina, Janssen, Merck Sharp & Dohme, Merck Serono, Merrimack, Novartis, Pharma Mar, Pfizer, Regeneron, Sanofi, Seattle Genetics, Takeda, and Vaccibody, from whom she has received honoraria (all fees to institution)

TSKM reports a leadership position at Hutchinson China MediTech, AstraZeneca, Sanomics Limited, International Association for the Study of Lung Cancer, American Society of Clinical Oncology, and Chinese Society of Clinical Oncology; stock ownership at Hutchinson China MediTech and Sanomics Limited; grants from AstraZeneca; personal fees from Boehringer Ingelheim; grants and personal fees from Roche/Genentech, Pfizer, Eli Lilly and Company, Merck Serono, Merck Sharp & Dohme, Novartis, SFJ Pharmaceuticals, and Bristol-Myers Squibb; personal fees from Vertex, OncoGenex Pharmaceuticals, Celgene, Ignyta, Cirina, Fishawack Facilitate, Takeda Oncology, Janssen Pharmaceutica, Hutchinson China MediTech, and GeneDecode; grants from Clovis Oncology and Xcovery LLC; and personal fees from OrigiMed, Hengrui Therapeutics, Inc., Sanofi-Aventis R&D, Yuhan Co., Ltd., prIME Oncology, Inc., Amoy Diagnostics, Loxo Oncology, Inc., ACEA Pharma, Boehringer Ingelheim, Eli Lilly and Company, Bristol-Myers Squibb, Genentech, Amgen, Spectrum Pharmaceuticals.

TM has served in a consultant/advisory role for Astra Zeneca, Bristol-Myers Squibb, Eli-Lilly, Merck Sharp & Dohme, Chugai, Taiho, Ono, Novartis and Boehringer Ingelheim, Guardant, Roche diagnostics received honoraria from Astra Zeneca, Bristol-Myers Squibb, Eli-Lilly, Merck Sharp & Dohme, Chugai, Taiho, Ono, Novartis, Boehringer Ingelheim, Johnson & Johnson and had grant support from Chugai, Taiho, Boehringer Ingelheim, Pfizer, Daiichi-Sankyo, Sanofi-Aventis, Ono.

FdM served in a consultant/advisory for Astra Zeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Merck Sharp & Dohme, Novartis, Roche Genentech, Takeda, and Pfizer. IA made no disclosures. IA report nothing to disclosure.

References

1. Carbone M, Green JB, Bucci EM, et al. Editorial: coronaviruses: facts, myths and hypotheses. *J Thorac Oncol*. 2020 Mar 5. doi: 10.1016/j.jtho.2020.02.024
2. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020. Epub 2020/02/28. doi: 10.1016/S2213-2600(20)30079-5. PubMed PMID: 32105632
3. Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. *JAMA.* March 23, 2020. doi:10.1001/jama.2020.4683
4. Wu Z, McGoogan JM. Characteristics of and Important lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for disease control and Prevention. *JAMA. 2020.* Https://doi: 10.1001/jama.2020.2648
5. Cai H. Sex difference and smoking predisposition in patients with COVID-19. *Lancet Respir Med.* 2020. doi: 10.1016/S2213-2600(20)30117-X
6. Crotty A, Shin S, Hwang, JH. Inflammatory Diseases of the Lung Induced by Conventional Cigarette Smoke. Chest.2015 148(5), 1307–1322.doi:10.1378/chest.15-0409
7. Sterzelak A, Rataiczak A, Adamiec A, et al. Tobacco Smoke Induces and Alters Immune Responses in the Lung Triggering Inflammation, Allergy, Asthma and Other Lung Diseases: A Mechanistic Review. *Int J Environ Res Public Health*. 2018;15(5):1033. doi:10.3390/ijerph15051033
8. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med.* 2020.:https://doi.org/10.1016/S2213-2600(20)30076-X
9. Vardavas C, Nikitara K. COVID-19 and smoking: A systematic review of the evidence. *Tob Induc Dis.* 2020. DOI: https://doi.org/10.18332/tid/119324
10. 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): P335-337.
11. Yu J, Ouyang W, Chua MLK, et al. SARS-CoV-2 Transmission in patients with cancer at a tertiary care hospital in Wuhan, China. *JAMA Oncol*. Published online March 25, 2020. doi:10.1001/jamaoncol.2020.0980
12. Milette S, Fiset PO, Walsh LA, Spicer JD, Quail DF. The innate immune architecture of lung tumors and its implication in disease progression. *J Pathol*. 2019;247(5):589–605.
13. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet.* 2020. DOI: https://doi.org/10.1016/S0140-6736(20)30628-0.
14. Ruan Q, Yang K, Wang W, et al. Clinical Predictors of Mortality Due to COVID-19 Based on an Analysis of Data of 150 Patients From Wuhan, China. *Intensive Care Med.* 2020. DOI: 10.1007/s00134-020-05991-x.
15. Russell CD, Millar JE, Baillie JK, et al. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet 2020; 395 (10223); P473-475.
16. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med.* 2020. doi:10.1001/jamainternmed.2020.0994
17. 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*. 2020. doi:10.1148/radiol.2020200642