

Lung cancer and COVID-19: problems and perspectives

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Abstract. – COVID-19 pandemic generated concerns about the healthcare of patients with cancer, not simply because of the formidable impact of COVID-19 patients in the public healthcare system, but also due to the overlapping pathognomonic signs of many forms of lung cancer with lung injuries associated with COVID-19. This report tries to shed light on the issue. We evaluated the great concern of people suffering from lung cancer and also infected with SARS-CoV-2 by discussing evidence and data from current literature. Lung cancer in Italy has represented more than 1 case/4 (27%) in the latest ten years and nevertheless, even due to the concurrence of many complex interplays between COVID-19 and cancer even at the immune level, a consensus protocol and expert guidelines to diagnose and treat lung cancer upon SARS-CoV-2 infection are yet lacking. New insights and consensus panels should be therefore proposed, even at the simplistic level about if priority must be either given to COVID-19 or to cancer therapy.

Key Words:

Lung cancer, COVID-19, Hospitalization, Diagnose, Patients.

Introduction

Current literature suggests that cancer-suffering individuals with SARS-CoV-2 infection exhibit a higher risk to develop a severe form of COVID-19¹⁻⁴. The consideration that any comorbidity in the infection of SARS-CoV-2 in subjects suffering from chronic inflammatory ailments such as cancer, should exacerbate the immune response to COVID-19, may be logically fore-

casted, particularly if SARS-CoV-2 infection is a major cause of the so-called “cytokine storm”. Searching for discriminating biomarkers, able to dissect the contribution of COVID-19 from the one associated to cancer, in order to improve both diagnosis and therapy, may be particularly crucial in this sense.

Actually, recent evidence⁵ was reported showing that the biomarker CTSL, i.e., cathepsin L, which is expressed in many cancerous tissues, is encoded by a lysosomal cysteine proteinase gene, which regulates both the tumoral progression and the entry of SARS-CoV-2, so resulting as a crucial biomarker to predict oncologic patients' susceptibility to COVID-19.

The concerning relationship between cancer and SARS-CoV-2 infection does not involve only immune-biological mechanisms to foresee the severity degree of COVID-19 but, fundamentally, also the diagnostic (and prognostic) relationship between lung cancer and COVID-19⁶. As a matter of fact, many aspects of the lung injury caused by carcinomas recall damages caused by the SARS-CoV-2-mediated immuno-thromboembolic and inflammatory mechanisms, so compelling the physician to wonder if cancer exacerbates COVID-19 or quite the contrary. Actually, a complex interplay exists between immunosuppression and immunotherapy in patients with cancer upon infection with SARS-CoV-2⁷.

Recent studies^{5,6} have reported a substantial decrease in the diagnostic burden of new cases of lung cancer throughout the COVID-19 pandemic emergency, alongside a significant increase in the time elapsed to reach the first, initial chemopreventive treatment. Furthermore, high expression

of the biomarker CTSL correlates to a significant short overall survival in lung cancer⁵. Is it possible, therefore, to suggest reliable biomarkers in order to better manage lung cancer in the COVID-19 era?

Whether the demonstrated heightened risk for a severe acute respiratory syndrome from coronavirus 2 (SARS-CoV-2) infection might be associated to a pre-existing form of cancer or not, is under investigation. Moreover, including other pre-existing (even co-morbid) characteristics of the patient – such as age, previous smoking lifestyle, genetic immunological changes, treatments used to fight the cancer or an underlying cardiopulmonary condition in the infected patient – the opposite circumstance if COVID-19 may exacerbate lung cancer, is still far to be fully elucidated⁸. Despite different kinds of malignancies can enhance a risk occurrence for more exacerbated forms of COVID-19 and higher prevalence of its impact in the population, besides to the well-known association with different comorbidity spectra, lung cancer specifically constitutes in itself a circumstance for which accumulating etiopathogenetic factors may enhance the rate of severe complications in COVID-19⁹⁻¹¹.

The same consideration that the microenvironment where the etiopathogenesis of COVID-19 occurs and develops, i.e., the lungs, also represents the milieu where lung tumors develop their malignancy, should raise controversial issues in the diagnostic research for lung cancer in COVID-19 patients.

Quite frequently, oncologic patients have already undergone treatments that caused immune impairment or immune suppression, which cannot be fully prevented^{6,10}. Briefly speaking, those subjects show therefore additional features that makes particularly burdensome the pathological concern, such as respiratory and cardiovascular co-morbidities, damages due to previous smoking, and often elderly^{4,12}.

Further insightful factors, which might increase the predisposition to SARS-CoV-2 infection, are previous surgeries to the lungs or also a defective lung architecture. This latter can be particularly worsened during SARS-CoV-2 infection. The presence of a tumor, which represents a mechanical stretcher¹³, can lead to sensible modifications to the airways, and changes of the pulmonary tissues can cause consequent adaptations of the microenvironment in intra-and-peri-tumoral areas. Many of these changes are quite relevant not just in themselves, but because of the secondary

and ancillary effects they can elicit on immune cells, their infiltration and activity, which can be assessed by a higher level of macrophages and by an increase of pro-inflammatory mediators¹⁴.

How can the immunity of a lung cancer affect the development of COVID-19 and vice versa? Evidence¹⁵⁻¹⁷ comes from highlighting the pathogenesis of lung cancer in the immune microenvironment caused by COVID-19.

For example, a possible interplay between lung cancer and COVID-19 in the role of ROS as signaling molecules has recently reported by Zhu et al¹⁷. The occurrence of an immune activation in both the contexts, cancer and infection, should exacerbate the inflammatory response. While in lung cancer the activation of the HIF-1 pathway may facilitate the immune escape, the concurrent activation of the NF-κB signaling increases the inflammatory mechanism, thus altering the Nrf2/Keap1/ARE system, which, in turn, by exerting an immune-suppressive action on both the pathological settings, represses the immune response in COVID-19 and allows tumor to escape from the patient's immune surveillance¹⁷.

On the other side, exacerbation due to COVID-19 induced cytokine storm in people with lung cancer is another concerning matter of debate^{18,19}.

Given that both cohorts of patients (lung cancer and COVID-infected patients) exhibit similar symptoms from a clinical perspective, such as fever, cough and dyspnea among others, it would be fine to be endowed with a proper, validated and standardized screening model, so as to avoid risks of complications and death by detecting COVID-19 promptly²⁰.

There has not been an ideal way to deal with pulmonary cancers in patients under COVID-19 pandemic²⁰: whether it is the best choice to go on in treating cancer or put patients on hold, temporarily or indefinitely, is hard to be debated. Risks and benefits in the specific situation must be undertaken into thorough consideration, but the whole context often increases the uncertainty of the final outcome^{20,21}.

The widest expert and medical community, especially in the oncology field, must be made aware of this, so to avoid an increase in mortality, either due to cancer or coronavirus infection.

The creation of a global registry (TERAVOLT – Thoracic cancerS international coVid 19 cOLlaboraTion) followed this rationale^{22,23}.

Its aim is to operate worldwide to accumulate data and to propose an *ad hoc* blueprint to assess

risks for patients with pulmonary cancer, while getting infected by SARS-CoV-2. An international consensus on protocols to test for SARS-CoV-2 in lung cancer patient is paramount. Admittedly, strong data are particularly scant to date, nonetheless early detection of the coronavirus would be essential for adjusting optimal care for patients. The ESMO (European Society for Medical Oncology) is currently working on this issue, and is collecting proposals to be published on their website, on the basis of numerous suggestions and advice about the best way to treat cancer subjects in the COVID-19 era. The first and foremost step is to test all of these patients for SARS-CoV-2. Furthermore, a bronchoscopy should be taken in consideration, when patients who resulted negative to the testing show ground-glass opacities not detected before on CT scans, even when lacking novel respiratory symptoms²⁴.

Searching for Different Options in the Treatment

Not all lung cancers exhibit the same pathological picture, so they cannot be treated in the same way. Despite this simplistic foreword, the issue tries to highlight those minimal differences in the impact led by different cancers on COVID-19, which should be soundly considered as well.

An oncologist displays a range of therapeutic options at his disposal: immunotherapy, chemotherapy, targeted therapy, supportive care. Wondering which one is best suited should be assessed by the hallmarks and typical features of the tumor itself, by the information given by biomarkers, and by the comorbidities from which the patient might suffer from the malignancy progression^{20,25}. Among such elements, which guide the physician to earn a correct evaluation, even the presence of COVID-19 constitutes a fundamental matter of debate about the evolutionary route of the cancer itself. Therefore, the concurrence of a SARS-CoV-2 infection, should not be considered as the simple adjunct of an inflammatory pathology but as a true and real comorbidity or, worst, an immunological complication²⁶.

The huge spreading of coronavirus cases has had a negative impact on already overcrowded medical care facilities. Too many patients have forced hospitals to turn their operating rooms into ICUs, usually because of lacking better options.

Personnel availability has also been a serious concern, as healthcare providers could be sick with COVID-19 themselves and forced into quarantine. To cope with the pressure of the increased

demand for care, they also had to choose which kind of treatments could go ahead as previously planned and which ones could be postponed. The chief principle to be followed was frequently ensuring an appropriate caregiving, and this encompassed timely healthcare²⁷.

Obviously, any delay in the treatment regimen could make the difference between life and death. This broad idea shapes all the processes of caring for oncologic patients^{28,29}.

Those individuals who, *via* proper biomarkers, were diagnosed with oncogenic-addicted NSCLC, possessed best survival chances, with fewer side effects and a better tolerability, when undergoing therapy with TKIs³⁰.

Further steps must be performed, considering the overall progression of the disease. If particularly burdensome and asymptomatic, a follow-up every 4-8 weeks may be sufficient. Where there is local progression, radiation therapy can be suggested. Where there is symptomatic progression or TKI-induced pneumonitis, in the presence of COVID-19, this must be treated first. The steroid use in TKI-induced pneumonitis must be evaluated on the basis of its risks *vs.* its benefits³¹. Obviously, any further component able to add its features to the correct diagnosis and therapy of cancer during the COVID-19 emergency, has been taken into account³².

Novel mutations might require new biopsies. In this circumstance, the best option is a biopsy specimen on biological fluids, as reiterating a tissue biopsy is a complex procedure that involves multiple departments.

Another treatment which comes into question because of its possible effects on COVID-19 is immunotherapy. In recent years, the best standard³³ of care for pulmonary cancer involved the use of immune checkpoint inhibitors (ICIs), which can be used by themselves or in combination with chemotherapy in stage III and IV NSCLC with no oncogenic driver.

Do immunotherapy and ICIs protect patients from COVID-19 or put them at higher risk of death, due to exacerbation linked to the cytokine storm that ensues? The question is raised by the numerous issues³⁴ related with lung cancer in COVID-19.

Up to date studies³⁵ from TERA-VOLT (The Thoracic Cancers International COVID-19 Collaboration) have not shown any evidence of impact from ICIs. Moreover, whether maintaining therapy or not in patients who have not relapsed after 2 years, should be assessed. And, if vis-

iting the hospital for therapy cycles is seen as an increased opportunity for virus exposure, scheduled appointments could be re-organized to address this concern, perhaps by opting for longer intervals between sessions (i.e., nivolumab every 4 weeks or perm-brolizumab every 6 weeks).

A different scenario is represented by patients who are undergoing chemotherapy, who must be differently evaluated to avoid discontinuance. It represents the chosen treatment in several circumstances, either as pre-operative measure, or a concurrent aid to those already undergoing chemoradiation (CCRT), or as palliative therapy for those with no or low expression of L1 and no oncogenic driver mutation. The population is frailer and more at risk of immunosuppression and the impact of a COVID-19 infection can change the result in ways that may not be determined solely by the selected therapy itself³⁶.

A case-by-case evaluation of whether is best to do adjuvant or neoadjuvant chemotherapy (NACT) or not, should be the best manner to proceed.

If the subject is young and the disease is locally advanced, adjuvant chemotherapy could be a good solution. For example, while NACT could be a better choice in those cases that will allow for a short-term postponement in those facilities that are overwhelmed by pandemic-related situations³⁷, postponing or renouncing maintenance therapy can be considered, along with patients themselves, for those who have long-standing monitoring of their disease treatment³⁸.

As a general rule, a screening for COVID-19 should be performed on all patients before any consultancy, even including pre- and post-analytical issues. This should be made in order to keep the risk for infection at the bare minimum. Patients could of course be asymptomatic but be infected by COVID-19 at the same moment; thus, in specific situations (i.e., before undergoing major surgery), it would be wise to test them routinely.

Follow-Up in the Time of COVID-19

Table I shows how lung cancer is particularly frequent in the Italian population, from an investigation referred to the period 2010-2020 from the AIRT-tum research³⁸.

Follow-up visits are affected by the COVID-19 pandemic too, and how to best provide visits depends on the point patients are set in the course of their treatment.

Patients who have freshly received their diagnosis might need more frequent visits, as well as starting their therapies right away. If patients do not show any symptom, clinic in-person visits can be postponed up to a year. If safe, chemotherapy can also be delayed. Where possible, and CT scans and imaging results are available, phone calls or virtual meetings could substitute examinations and lengthen the time between appointments, so as to reduce the risk for infection. Other strategies can be implemented to this aim. Testing and exams should be booked at the nearest laboratory, to shorten travelling time and consequent possible exposure of the patient. The choice of medication could also have a relevant impact. Oral therapies (TKI) and agents (i.e., etoposide) are preferable, and their dosing should be performed at a longer approved interval. Imaging might be scheduled every 3 cycles instead of 2, as long as it is deemed safe to do so, expanding this way the intervals between appointments.

Finally, different approaches can be entertained to reduce immune suppression: chemotherapy lacking for those who just need maintenance therapy, use of hematopoietic growth factors, use of drugs with a weaker bone marrow suppression effect, ozone therapy^{38,39}.

Cancer and COVID-19: What's New

People who died for COVID-19 were mostly elderly people with comorbidities. The recent report³⁸ from the Italian Institute of Health, on Jan 10, 2022, allows us to highlight the ratio of the different comorbidities in a sample of 8.436

Table I. Incidence of cancers in Italy (2010-2020).

Rank	Males		Females		Total	
	Cancer	%	Cancer	%	Cancer	%
1	Lung cancer	27%	Breast cancer	17%	Lung cancer	12%
2	Colorectal cancer	11%	Colorectal cancer	12%	Colorectal	7%
3	Prostate cancer	8%	Lung cancer	11%	Breast cancer	4%
4	Liver cancer	7%	Pancreas cancer	8%	Pancreas cancer	4%
5	Gastric cancer	8%	Gastric cancer	8%	Liver cancer	4%

deceases respect to cancers (Table II). The relationship between cancer and obesity is greater in males, whereas females' comorbidities regarding autoimmune disorders account for at least 2-fold the level observed in males. This should suggest that the landscapes where a physician should observe the relationship between cancer and immunity are quite different if males were mainly diagnosed respect to females

The Italian Ministry of Health, alongside with expert councils on cancer diagnosis and therapy in the time of COVID-19 pandemic, has outlined some data. According to a recent analysis⁴⁰ of the activities carried out by AGENAS during the COVID-19 pandemic in 2020, evidence reported that a decrease of about 30% occurred in the volumes of the three screenings (cervical equal to -32.20%, mammography, -30.32% and rectal colon, equal to -34.70%) and a decrease in activity volumes of tumor surgery ranging from 20% to 24% to 30%: for breast cancer -22.05%, for prostate cancer -24.02%, for colon cancer -32.64%, for rectal cancer -13.86%, for lung cancer -18.25%, for uterine cancer -13.84%, for melanoma -21.47%, for thyroid cancer -31.23%.

Furthermore, from IQVIA surveys on real prescription data, updated to December 2020, reports recorded again -17% in mammograms, -13% in lung CT scans and -13% in colonoscopies. In addition, stable or even worsening data on new diagnoses (-14%), surgical interventions (-24%) and minor hospitalizations (-37%) were obtained in the period October-December 2020 compared to the first wave, respectively at -15%, -20% and 16% compared to the period February-June 2020.

Finally, the most concerning data is that Italian oncologists, engaged in the 4th COVID-19 pandemic wave (February 2021), declared that they visited an average of 30% less patients (25-30) than during the pre-pandemic period. Briefly

speaking, there was a significant impact on the number of new diagnoses and treatments, as well as requests for specialist visits and examinations: -613,000 new diagnoses (-13%), -35,000 new treatments (-10%), -2,230,000 referrals to specialist (-31%), -2,860,000 exam requests (-23%). This was reflected above all in hospitals to a drastic reduction in the consumption of drugs⁴⁰⁻⁴⁴.

Furthermore, according to the Oncological Scientific Societies⁴⁴ in Italy, there was a great effort to ensure the timeliness of all treatments through the organization of safe routes for cancer patients, despite one million interventions were diminished in 2020 as routine surgeries. Oncological radiotherapy experienced a higher mass of excellent activities, better than other countries and this shows that when there is one adequate technology and an adequate multi-disciplinarity it is possible to treat the patient in an optimal way. There was also a notable decline in participation in clinical trials which have a real and important impact on assistance, especially in onco-hematological patients.

COVID-19 has created a situation of "cancer alarm" that must be addressed with crucial and urgent measures, including vaccination^{32,45}, since the blocking of oncological examinations and visits, the reduction of screening since the beginning of the pandemic, which was followed by hesitancy and fear of patients to access hospitals in correspondence of the different waves, have created the conditions for an increased incidence in tumors in the next few years^{46,47}. Starting from the commitments contained in the resolution of some Italian politicians, a hasty change of address, leading to the approval of a new National Plan of Oncology in line with European Directories and EU Guidelines, was considered in order to resume how carrying out oncological screening, promote patient care in a homogeneous way throughout the national territory, guaranteeing

Table II. Comorbidity ratio (%) of cancer deceased patients respect to other comorbidities.

Rank	Comorbidity		Males		Females	
			Cancer/H	27.0	Cancer/H	21.0
1	Hypertension (H)	65.8	Cancer/H	27.0	Cancer/H	21.0
2	Type 2 diabetes (T2)	29.1	Cancer/T2	57.2	Cancer/T2	52.5
3	Ischemic cardiopathy (IC)	28.2	Cancer/IC	55.6	Cancer/IC	60.5
4	Obesity (O)	11.6	Cancer/O	147.8	Cancer/O	125.3
5	Autoimmunity (AU)	4.7	Cancer/AU	221.7	Cancer/AU	495.5
6	BPCO (BO)	17.5	Cancer/BO	88.2	Cancer/BO	100.6

access to diagnostic tests and therapies of anticancer targeting, was the major objective of medicine.

In Italy, in 2021, the Senate approved a unitary scheduling plan⁴⁸ with which it was asked with insistence to the Government to approve the New National Plan for Oncology as soon as possible and the Government, apologizing, has undertaken to do so by June 2022, nevertheless now still on debate. This represented good news for all cancer patients, for their families, but also for everyone joining any associations that represent them. Cancer patients at the time of the pandemic have been left too alone with a serious impairment of their physical, emotional and psychological health. The newly approved agenda marks one decisive and courageous turning point, a real commitment to restart by being by patients' side with all means that science and technology offer, but also with a human affectivity that puts an end to the state of loneliness, at times even abandonment, of patients. In a dramatic moment like the pandemic, the European Commission has provided one important response to support the cancer burden, by funding the "Mission on cancer⁴⁸", whose goal is to save 3 million lives by 2030.

To achieve this purpose, five areas of intervention have been identified: understanding, preventing what can be prevented, optimize diagnostics and treatment, support the quality of life, ensure equal access.

Conclusions

The whole world suffered a health crisis of relevant proportions when the COVID-19 pandemic hit. As a consequence, many oncologists were forced to adapt the treatment plans for their lung cancer patients with changes that made sure that they still had adequate care according to the new guidelines, but within accepted standards. The ESMO recommendation²⁷ states: "In this environment, cancer practitioners have great responsibilities: provide timely, appropriate, compassionate, and justified cancer care, while protecting themselves and their patients from being infected with COVID-19. In case of shortages, resources must be distributed fairly".

Healthcare staff also should be protected. They can be harmed in different ways, such as infection or exhaustion, and their job can have an emotional toll on them. For both them and the patients they care for, it is essential to take this also into consideration.

Conflict of Interest

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Authors' Contribution

UT conceived the manuscript, supervised the report and research, checked and validated the manuscript; CC and MP contributed to the elaboration of literature and data; MB, supervised the paper; SC wrote, checked, revised and submitted the manuscript.

Ethics Approval

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