

Severity of COVID-19 in patients with lung cancer: evidence and challenges

Antonio Passaro ¹, Christine Bestvina,² Maria Velez Velez,³ Marina Chiara Garassino,⁴ Edward Garon,⁵ Solange Peters⁶

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AP, CB and MVV contributed equally.
MCG, EG and SP contributed equally.

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¹Division of Thoracic Oncology, European Institute of Oncology IRCCS, Milan, Italy

²Department of Hematology/Oncology, University of Chicago Medicine, Chicago, Illinois, USA

³Division of Hematology/Oncology, David Geffen School of Medicine, University of California, Los Angeles, California, USA

⁴Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

⁵David Geffen School of Medicine, UCLA, University of California Los Angeles, Los Angeles, California, USA

⁶Department of Oncology, Centre Hospitalier Universitaire Vaudois, CHUV, Lausanne, Switzerland

Correspondence to

Solange Peters;
solange.peters@chuv.ch

ABSTRACT

Cancer patients are highly vulnerable to SARS-CoV-2 infections due to frequent contacts with the healthcare system, immunocompromised state from cancer or its therapies, supportive medications such as steroids and most importantly their advanced age and comorbidities. Patients with lung cancer have consistently been reported to suffer from an increased risk of death compared with other cancers. This is possibly due to the combination of specific pathophysiological aspects, including underlying pulmonary compromise due to smoking history and the increased specific pressures on respiratory healthcare services caused by the related pandemic. Rationally and safely treating patients with lung cancer during the pandemic has become a continuous challenge over the last year. Deciding whether to offer, modify, postpone or even cancel treatments for this particular patient's population has become the crucial recurrent dilemma for lung cancer professionals. Chemotherapy, immunotherapy and targeted agents represent distinct risks factors in the context of COVID-19 that should be balanced with the short-term and long-term consequences of delaying cancer care. Despite the rapid and persistent trend of the pandemic, declared by WHO on March 11, 2020, and still ongoing at the time of writing (January 2021), various efforts were made by oncologists worldwide to understand the impact of COVID-19 on patients with cancer. Adapted recommendations of our evidence-based practice guidelines have been developed for all stakeholders. Different small and large-scale registries, such as the COVID-19 and Cancer Consortium (CCC19) and Thoracic Cancers International COVID-19 Collaboration quickly collected data, supporting cancer care decisions under the challenging circumstance created by the COVID-19 pandemic. Several recommendations were developed as guidance for prioritizing the various aspects of lung cancer care in order to mitigate the adverse effects of the COVID-19 healthcare crisis, potentially reducing the morbidity and mortality of our patients from COVID-19 and from cancer. These recommendations helped inform decisions about treatment of established disease, continuation of clinical research and lung cancer screening. In this review, we summarize available evidence regarding the direct and indirect impact of the COVID-19 pandemic on lung cancer care and patients.

INTRODUCTION

Patients with cancer have been disproportionately affected by the COVID-19 pandemic. Although data collected are heterogeneous

due to patients' demographics, variable testing availability or policy, and cancer patients' management guidelines over time, 1%–8% of patients hospitalized with COVID-19 had an history of hematological malignancies or solid tumors.¹ Available data confirm that patients with cancer are possibly more likely to be infected by SARS-CoV-2 and, more importantly, definitively prone to develop severe complications defined here as admission in an intensive care unit (ICU), the need for mechanical ventilation (MV) or death as a result of COVID-19. The mortality rate in patients with cancer has been reported to be 25%–30%.^{1–3}

Large datasets demonstrate that cancer is independently associated with mortality in hospitalized patients with COVID-19.⁴ Not all cancers appear to have equal risks of morbidity and mortality, with a mortality range from 8% to 30%.⁵

THE SPECIFIC CASE OF LUNG CANCER

Patients with lung cancer and those with hematological malignancies appear to be at the highest risk of death from SARS-CoV-2 infection.⁶ In contrast to hematologic malignancies, profoundly immunosuppressive therapy is not typical in lung cancer.

Lung cancer represents a clinical scenario characterized by an increased risk of pulmonary complications, severe lung injury and high mortality from COVID-19, due to pathophysiological, clinical and treatment-related risk factors.⁷

A significant interplay of factors frequently associated with lung cancer, including smoking-related lung damage, significant cardiovascular and respiratory comorbidities, and older age, induce higher severity of SARS-CoV-2 infection.^{7–9} Patients with lung cancer share fragility related to defective pulmonary and alveolar architecture due to previous thoracic surgery or radiotherapy and/or malignant airway obstruction that may also predispose to more severe infections.

The alterations of alveolar epithelium and pulmonary vessels lead to tumor microenvironment modifications, including an increase in immune cell and tissue-resident macrophages infiltration, critical for innate immunity and inflammation.¹¹⁰

This widespread immune component within alveolar epithelium poses a higher risk for cytokine release. In addition, the alveolar damage and fibrin deposits represent risk factors for thrombosis of small and large pulmonary vessels.¹¹¹ These two pathogenetic pillars have been postulated to be the major steps in leading to the development of severe lung injury and acute respiratory distress syndrome (ARDS) during the SARS-CoV-2 infection.¹¹¹

Smokers are five times more likely to contract influenza than non-smokers, and in particular, smoking history has been related to a higher incidence and severity of SARS-CoV-2 infection.¹¹ Structural and immunologic-induced modifications are the two main sources of tobacco-related damage that accounts for susceptibility to infections. Changes in peribronchiolar homeostasis and inflammation additionally impair the building of an efficient antiviral or bacterial immune response required for infection clearance.^{12–14} Smokers showed high risk ($\times 2.4$ times) of COVID-19 severe events (ICU admission, MV or death) compared with non-smokers (RR=2.4, 95% CI 1.43 to 4.04).¹⁴

Additionally, a cumulative risk for severe COVID-19 injury is related to long-term tobacco-related lung damage, including chronic obstructive pulmonary disease (COPD) and lung cancer.⁷

Finally, the all-cause case–fatality rate in patients with cancer after SARS-CoV-2 infection was significantly associated with increasing age, rising steadily from 65 years, encompassing the majority of patients with lung cancer.¹⁵

The interaction between these pathological and clinical factors, in addition to the complex role of antineoplastic therapy and concomitant medications, define patients with lung cancer as an extremely vulnerable patient subgroup at the time of COVID-19 pandemic, for severe illness.

Reflecting on the unmet needs characterizing the management of non-communicable diseases globally, patients with cancer, and in particular lung cancer, are additionally suffering from the disruption of healthcare service due to COVID-19, which is significantly amplifying the specific negative prognostic impact of this novel disease on our patients.¹⁶

As described across registries, the well-known dismal prognosis of lung cancer combined with reduced cancer services and simultaneously reduced ICU capacity lead to ICU triage strategies that often disadvantage patients with lung cancer and significantly augment their mortality.^{3,5,17}

MORTALITY RATE ACROSS MAIN REGISTRIES AND SERIES

During the COVID-19 pandemic, several real-world datasets investigated the risk for hospitalization, complications and death in patients with cancer. Data were

generally retrospectively collected through multicenter registry-based observational cohort studies worldwide^{6,18} (table 1).

Although the fast enrollment and the heterogeneity of patient populations are prone to potential biases, the results consistently confirmed that patients with cancer represent a significantly vulnerable group to SARS-CoV-2 infection.¹⁸

The impact of COVID-19 on patients with thoracic malignancies—and in particular lung cancer—was evaluated through two different approaches: non-disease-oriented studies including patients with or without a diagnosis of solid or hematologic tumors; and disease-specific studies, planned and developed to investigate the impact of SARS-CoV-2 infection on patients with thoracic cancer.

Registry data from China

In the largest report from China, a multicenter retrospective cohort study including 13077 patients with COVID-19, 23 had a history of lung cancer, although only five were metastatic. In this subgroup, 78% of patients showed a severe clinical outcome with a mortality rate of 39%. Overall, this series showed that patients with cancer were more likely to have severe illness. It also confirmed that ECOG Performance Status (PS) ≥ 2 , older age and advanced or metastatic stage were all associated with an increase in mortality rate.¹⁹

Dai *et al* reported a multicenter retrospective analysis including 105 hospitalized patients with cancer from 14 hospitals in Hubei Province, China, the epicenter of the first COVID-19 outbreak.²⁰ Lung cancer accounted for 20.9% (22/105) of these patients, with a death rate of 18.1% (4/22), an ICU admission rate of 27.2% (6/22), risks of severe/critical symptoms in 50% (11/22), and utilization of invasive mechanical ventilation (IMV) of 18.1% (4/22). In patients affected by lung cancer, the average time (means/SD days) from initial onset of COVID-19 symptoms to death (16.75/8.17), ICU admission (10.00/6.82), critical symptoms (8.55/5.71) and IMV (14.50/6.98) were at least a week from symptom onset. Data from this first large cohort study raised two very interesting issues: compared with all other patients, patients with primary or metastatic tumors in the lungs were more prone to rapid clinical deterioration on SARS-CoV-2 infection and patients who underwent cancer surgery showed higher complication and mortality rates.²⁰

Retrospective analysis from the Veneto region of Italy

In an extensive retrospective epidemiological study, developed during the first peak of COVID-19 pandemic in the Veneto region (Northeast of Italy), investigators collected data from 84,246 consecutive Italians tested for SARS-CoV-2 to evaluate the prevalence of cancer and clinical outcomes of viral infection.²¹ Among the 9275 SARS-CoV-2 positive patients, 723 had a cancer diagnosis (7.8%), which was associated with a high rate of

Table 1 Registries and series of COVID-19 cases in patients with thoracic malignancy

Author or group (if applicable)	Location	Study characteristics	Total number of patients with thoracic malignancies	Mortality rate	Outcomes of patients with lung cancer
Tian <i>et al</i> ¹⁹	China	Retrospective analysis 13077 total patients with COVID-19.	23 patients with lung cancer.	39% (9/23)	Severe clinical outcome: 18/23 (78%).
Dai <i>et al</i> ²⁰	China (Hubei)	Multicenter study of 14 hospitals. 641 COVID-19 positive patients, of which 105 with cancer.	22 patients with lung cancer.	18% (4/22)	<ul style="list-style-type: none"> ▲ ICU admission rate: 27% (6/22). ▲ Severe/critical symptoms: 50% (11/22). ▲ Risk of mechanical ventilation: 18.1% (4/22).
Rugge <i>et al</i> ²¹	Italy (Veneto)	Regional cancer registry 9275 patients with COVID-19, of which 723 with cancer.	21 patients with lung cancer.	24% (5/21)	<ul style="list-style-type: none"> ▲ Hospitalization rate: 62% (13/21). ▲ Low ICU admission rate 5% (1/21). ▲ Lung cancer was associated with a fourfold risk of death from SARS-CoV-2.
de Joode <i>et al</i> ²² ; Dutch Oncology COVID-19 Consortium	The Netherlands	Observational cohort study of cancer patients with COVID-19 409 total subjects.	47 NSCLC patients.	47% (22/47)	
Lee <i>et al</i> ²³ , UKCCMP	UK	Observational cohort study including 1044 cancer patients with COVID-19.	111 patients with lung cancer.	39% (43/111)	Multivariable-adjusted case fatality rate not significantly different than the remainder of cancer patients: OR 1.41 (95% CI 0.75 to 2.67; p=0.29).
Various authors ^{5,24-26} ; CCC-19	Multicenter, primarily USA based	Cohort study of patients with COVID-19 who have cancer.	237 patients with lung cancer (based on interim 2749 patient analysis), ²⁴	26% (61/237)	Significantly higher mortality rate than the 16% (433/2749) for all patients with cancer.
Luo <i>et al</i> ²⁷ ; MSKCC	New York, USA	Monoinstitutional series of patients with lung cancer and concomitant positive SARS-CoV-2 RT-PCR.	102 patients with lung cancer.	25% (25/102)	<ul style="list-style-type: none"> ▲ Hospitalization rate: 62% (63/102). ▲ ICU admission: 21% (21/101). ▲ Risk of mechanical ventilation: 18% (18/100).
Various authors ²⁸⁻³⁰ ; TERAVOLT	Multicenter, international	Cross-sectional and longitudinal cohort study of thoracic malignancy patients diagnosed with COVID-19.	1012 patients with thoracic malignancies.	32% (326/1012)	<ul style="list-style-type: none"> ▲ Hospitalization rate: 72% (733/1012). ▲ ICU admission: 12% (118/1012). ▲ Mechanical ventilation, both tube assisted and non-invasive: 25% (248/1012).

CCC-19, COVID-19 and Cancer Consortium; ICU, intensive care unit; MSKCC, Memorial Sloan Kettering Cancer Center; NSCLC, non-small cell lung cancer; TERAVOLT, Thoracic cancerERs international COVID-19 cOLLABoratioN; UKCCMP, UK Coronavirus Cancer Monitoring Project.

hospitalization (56.6 vs 34.4%) and mortality (14.7% vs 4.5%) particularly for males and elderly patients. Overall, 21 patients had a lung cancer diagnosis, with a mortality rate of 23.8% (5/21) and a hospitalization rate of 61.9% (13/21). Of note, only one patient with lung cancer was admitted to ICU, while in the overall study population, ICU admission rate for COVID-19 was not associated with cancer. Lung cancer was associated with a fourfold risk of death due to SARS-CoV-2 infection, although the patient population was too small to draw robust conclusions.²¹

Dutch Oncology COVID-19 Consortium (DOCC)

The Dutch Oncology COVID-19 consortium developed the DOCC registry. Overall, 409 patients with a cancer diagnosis or cancer treatment in the past 5 years were included in this analysis. In this registry, 13.4% (n=47) patients reported a diagnosis of lung cancer, showing a mortality rate (fatal event) of 47% (22/47).²² In a multivariate analysis, de Joode and colleagues²² showed that lung cancer (p=0.003), male gender (p=0.035) and age ≥65 years (p<0.001) remained independent risk factors for a fatal outcome of COVID-19.

UK Coronavirus Cancer Monitoring Project (UKCCMP)

In contrast to previously reported findings, in a non-disease-oriented registry, the UKCCMP database did not observe an increased case-fatality rate for patients with lung cancer (0.39, 43/111 patients with lung cancer) compared with other cancers, despite 43 deaths. The authors proposed that lung cancer might not be considered as a specifically susceptible group, keeping in mind that these results may have been affected by the relatively small sample size. Lee *et al*²³ confirmed that the all-cause case-fatality rate in patients with cancer after SARS-CoV-2 infection was significantly associated with increasing age, from 0.10 in patients aged 40–49 to 0.48 in those aged 80 years and older.

COVID-19 and Cancer Consortium (CCC-19)

In addition to the Chinese and European registries, data about adults with a current or past diagnosis of cancer and COVID-19 were collected in the well-structured US-based CCC-19 cohort study.⁵ The preliminary comprehensive results of the CCC-19 was based on 928 patients, including 91 (10%) with lung cancer, demonstrated an overall mortality rate of 13%, a hospitalization rate of 50% including 14% of ICU admission, and 12% rate of mechanical ventilation.⁵ The updated analysis based on 2749 evaluable patients showed a high mortality rate of 26% for patients with lung cancer (61/237), significantly increased compared with breast cancer (8%), prostate cancer (18%), colorectal cancer (19%) or lymphoma (22%), with an updated 16% (433/2749) mortality for the whole CCC-19 cohort.²⁴

The CCC-19 data were updated step by step during the pandemic, from 928 to 3899 evaluable patients. Analysis confirmed that different independent factors are associated with 30-day mortality:

- ▶ General factors (eg, older age, male sex and number of major comorbidities (two vs none)).
- ▶ Cancer-specific factors (eg, ECOG PS >1, active or progressive cancer).
- ▶ Laboratory variables (eg, low absolute lymphocyte count, high or low absolute neutrophil count, low platelet count, abnormal creatinine, D-dimers, troponin, and C reactive protein).^{24–26}

As discussed previously, completing some non-disease-specific evaluation, several specific thoracic cancer-oriented registries or cohort study evaluated the impact of COVID-19 in this specific cancer population.

MSKCC retrospective analysis

In a USA single-center retrospective series, Luo and colleagues²⁷ investigated the thresholds of COVID-19 severity in lung cancer. Among the 102 evaluable patients, most with metastatic or active lung cancer (72%), the rate of hospitalization was 62%, and the overall mortality rate was 25%, even though deaths attributed to COVID-19 constituted only 11% of all deaths. In addition, for patients that required ICU admission (21%), 72% died. Pulmonary comorbidities (eg, COPD) or smoking history were the greatest determinants of COVID-19 severity. Cancer-specific features, including prior thoracic radiation or surgery or the presence of active/metastatic disease, did not appear to impact the severity of COVID-19.

In another report by Luo *et al*¹⁷ the authors evaluated the impact of the immunotherapy in patients with lung cancer and concomitant COVID-19 diagnosis, to investigate whether programmed death 1 (PD-1) blockade affects severity of illness from patients with COVID-19 in patients with lung cancer. The results, based on 69 consecutive patients with lung cancer, showed that PD-1 exposure was not associated with increased severity of COVID-19.

Thoracic cancerERs international COVID-19 19 cOLlaboraTion (TERAVOLT)

A structured analysis of patients with lung cancer and COVID-19 was investigated in the TERAVOLT registry. The study enrolled patients with thoracic cancer (non-small cell lung cancer (NSCLC), mesothelioma, thymic epithelial tumors and other pulmonary neuroendocrine neoplasms) with either confirmed COVID-19 infection or clinically diagnosed infection.²⁸

The updated results based on 1012 patients showed higher mortality (32%) and hospitalization rate (72%), compared with a dramatic low ICU admission (12%) and mechanical ventilation rate (7%).²⁹

As reported in the CCC-19 results, TERAVOLT confirmed the COVID-19 related general risk factors for mortality, including age and comorbidities as well as cancer-specific factors, namely PS (≥2 vs <2), and the use of steroids prior to COVID-19 diagnosis.^{28–30}

CONCLUSIONS FROM REGISTRY DATA

Although data discussed are heterogeneous by nature due to different study designs and variable medical practices at the time of COVID-19, all results consistently confirm that lung cancer predicts a worse outcome on SARS-CoV-2 infection, as described by a higher rate of hospitalization and ARDS and a significantly higher mortality rate.³¹

LUNG CANCER TREATMENT AND COVID-19

The primary goals of the treatment of patients with lung cancer during the COVID-19 pandemic are to minimize the risk of patient exposure as well as the risks of complication should they contract COVID-19, while managing lung cancer, which has a high risk of mortality.³² Early in the pandemic, when there were shortages of personal protective equipment, limited COVID-19 testing supplies, and many regions of the world saw overwhelmed health-care systems, lung cancer surgeries were delayed and systemic treatments were canceled. Fortunately, additional data have been gathered from TERAVOLT, CCC-19, and others, allowing providers and patients to make a risk–benefit analysis of proceeding with treatment versus delaying or omitting.

In this manuscript, we analyzed data from the main registries and series about the impact of specific cancer treatment for lung cancer during the pandemic. During these troubled times, different evidence-based recommendations (eg, American Society of Clinical Oncology (ASCO),³³ European Society for Medical Oncology (ESMO)^{34 35} and International Association for the Study of Lung Cancer (IASLC))³² were developed to improve the management of patients with lung cancer and to mitigate the pandemic impact on our patients.

Surgery

While surgical resection strategies for lung cancer remain the same, many logistical challenges arise in weighing the risks and benefits to delaying resection based on the severity of the COVID-19 pandemic. Limited resources including hospital beds have led to delays of non-urgent surgeries, particularly non-oncological elective interventions. Perioperative COVID-19 has been associated with mortality rates as high as 10%–24% in the overall surgery population.^{36 37} For patients undergoing surgery for lung cancer, the UK Lung Cancer Coalition's Clinical Advisory Group stated that increased mortality as high as 40%–50% has been seen in patients who contracted COVID-19 following surgery for lung cancer.^{38 39} To reduce the risk of operation during the incubation period for COVID-19, patients should receive COVID-19 testing prior to surgery.³²

The ESMO recommends keeping all NSCLC surgeries as a priority and that surgical delays should not last more than 6–8 weeks.³⁵ The ASCO, however, recommends clinicians and patients make individual determinations of risk and benefit in proceeding with surgery.⁴⁰ The American College of Surgeons has published guidelines on triaging

elective cases for surgical care during the COVID-19 pandemic and includes characteristics such as solid versus non-solid component, size of the presumed lung cancer, node positivity, and completion of induction chemotherapy.⁴¹ All of this information can help triage patients treatment, as well as help thoracic surgeons advocate for their patients in the context of COVID-19.

Radiation therapy

The European Society for Radiotherapy and Oncology and the American Society for Radiation Oncology partnered to author: 'Practice recommendations for lung cancer radiotherapy during the COVID-19 pandemic'.⁴² Treatment recommendations are given for a variety of clinical scenarios, from stage I–III NSCLC, prophylactic cranial irradiation for small cell lung cancer (SCLC), and palliative radiation for NSCLC. Recommendations are given for both an 'early pandemic scenario', where risk mitigation of both the patient and radiotherapy staff are balanced with the treatment of lung cancer, as well as a 'later pandemic scenario', where resources are limited requiring patient triage. Hypofractionated radiation schedules have been recommended to reduce the number of visits to healthcare facilities, as well as possible patient and staff exposure to COVID-19.⁴³ Additional recommendations have included avoiding twice daily radiation, the use of single fraction radiation in the palliative setting, and the delay or omission of prophylactic cranial irradiation for patients with SCLC.⁴⁴

Chemotherapy

In the original TERAVOLT analysis of 200 patients, treatment with chemotherapy alone was associated with increased risk of death (HR 2.54, 95% CI 1.09 to 6.11).²⁸ In an updated analysis of 1012 patients presented at ESMO, patients receiving chemotherapy alone or not receiving treatment had worse outcomes compared with patients receiving immunotherapy, chemoimmunotherapy, or targeted therapy (HR 1.4, 95% CI 1.02 to 2.0, $p=0.03$).²⁹ In a single center analysis of 102 patients with lung cancer treated at Memorial Sloan Kettering, no effect of recent systemic therapy was seen on COVID-19 outcomes, including chemotherapy or chemoimmunotherapy.²⁷ In the CCC-19 registry, which includes patients of multiple tumor types, the highest 30-day mortality by treatment type was chemoimmunotherapy at 30% 30-day mortality.⁵ Patients receiving chemotherapy or chemoradiation had a 30-day mortality of 18% (Wise-Draper ESMO).⁴⁵ However, it is difficult to know how to interpret these data given the inclusion of multiple tumor types and the wide variety of systemic therapies included in the analysis. In fact, 182 distinct drugs were included in the analysis. Additionally, the diseases and patients' characteristics, including comorbidities, defining each treatment opportunity in lung cancer—like for example chemotherapy without immunotherapy—will per se define a precise disease scenario that can only incompletely be accounted and adjusted for.

In addition to the risk of COVID-19 infection for patients with cancer, delays in cancer care can also negatively affect patients' cancer course. The average delay of oncologic treatment for patients in the TERAVOLT registry was 21 days.²⁹ The Centers for Disease Control and Prevention (CDC) recommends immunocompetent individuals with COVID-19 quarantine for 10 days, while those considered immunocompromised quarantine for 20 days.⁴⁶ It remains to be seen how treatment delays will affect patient's cancer outcomes.⁴⁷

Immunotherapy

Early in the pandemic, there was concern that immune checkpoint inhibitors (ICIs) may worsen the complications of COVID-19. The concern was that ICIs may increase the cytokine storm causing ARDS of COVID-19, as well as the possibility of overlapping pneumonitis from ICIs and COVID-19.⁴⁸ However, the results of multiple registries including TERAVOLT,^{28–30} the CCC19,^{5 24} as well as 102 patients with lung cancer treated at Memorial Sloan Kettering Cancer Center,^{17 27} all demonstrated that patients treated with ICIs alone, without chemotherapy, had outcomes equivalent or better to those receiving other cancer treatments. Given this information, for patients who have high PDL1 expression $\geq 50\%$, treatment with immunotherapy alone should be strongly considered over chemoimmunotherapy.³²

Alternative dosing of immunotherapy regimens, which are administered less frequently, can and should be considered. This can limit both patient and provider exposures, while retaining efficacy, thereby optimizing the risk–benefit ratio.^{32 35} Pembrolizumab 400 mg given every 6 weeks has been approved by both the European Medicines Agency (EMA) as well as the US Food and Drug Administration (FDA).⁴⁹ Nivolumab can be dosed 480 mg every 4 weeks as opposed to every other week.⁵⁰ Atezolizumab is able to be dosed every 4 weeks at 1680 mg.⁵¹ Durvalumab dosing of 1500 mg every 4 weeks was initially approved and has demonstrated efficacy in the small cell population.⁵² The every 4-week dosing can be considered for the stage III NSCLC consolidation setting as well.³²

Pneumonitis present on CT scans for patients with lung cancer has traditionally had a differential of immunotherapy pneumonitis, radiation pneumonitis, or progressive lung cancer depending on the clinical context. COVID-19 pneumonitis has also been reported on imaging and can be difficult to differentiate based on imaging alone. CT findings suggestive of COVID-19 should lead to an appropriate infectious workup for COVID-19 while taking into account the remaining differential.^{32 53}

Targeted therapy

The treatment of NSCLC with tyrosine kinase inhibitors (TKIs) has become much more common over the last decade and has led to significant improvements in the 5-year overall survival of patients with lung cancer. In the initial TERAVOLT analysis of 200 patients with thoracic

malignancies, 28 patients were on TKI alone. These patients were less likely to be hospitalized (OR 0.24, 95% CI 0.077 to 0.708).²⁸ In expanded analysis presented at both ASCO and ESMO, patients receiving targeted therapies do not have increased risk of death in multivariate analysis.^{29 30} The degree to which this relatively favorable outcome is related to the mechanisms of these therapies as opposed to the different demographics of the patients who use them (younger, non-smokers) is not fully understood.

Similar to immunotherapy, TKIs are known to cause interstitial-like pneumonitis at varying rates and can be difficult to distinguish from COVID-19 induced pneumonia. The clinical picture of new or progressive cough, dyspnea, and/or fever can also be similar. Patients should receive COVID-19 based testing if there is either radiographic or clinical concern.^{7 32 53}

IMPACT OF COVID-19 PANDEMIC ON LUNG CANCER RESEARCH

The COVID-19 pandemic has greatly affected the care of patients with lung cancer and has affected multiple aspects of cancer research.⁵⁴ Since the start of the pandemic, there has been a decrease in clinical trial enrollment, and several active trials have been placed on hold.⁵⁵ While data demonstrating the effect of COVID-19 specifically on lung cancer research is scant, several studies show that cancer research in general has been compromised.^{56–63} Cancer clinical trials have been at the focus of these studies, but it is essential to highlight that translational and observational studies have also been affected.⁵⁷ The mechanisms by which research has been compromised include decreased funding, operational concerns with tissue collection and biobanking, holds on clinical trials, reduced workforce, and reduced networking opportunities for international collaborations.^{1 61}

In an effort to help sustain cancer research during the pandemic, the National Institute of Health in the USA has implemented changes in its policies to increase flexibility around research funding, such as including administrative supplements to existing grant awards, extending deadlines for grant applications, allowing salary support through grants, and extending eligibility periods for early-stage trainees. However, other significant funding sources, such as philanthropic donations, have dramatically decreased.¹ As such, organizations that depend on these donations to allocate grant funds, like the American Cancer Society, the Canadian Cancer Society, and Cancer Research UK, have had to significantly reduce their budget for research funding.^{60 62} Despite these budget cuts, there have been ongoing efforts to continue cancer research and determine the impact of COVID-19 on patients with lung cancer (NCT04538456).

Operational challenges regarding obtaining, keeping, and processing specimens for translational and correlative studies have been profound. With the surge of COVID-19, patients requiring hospitalization have increased, leading to decreased hospital capacity and

a subsequent postponement of surgeries and procedures.^{59 64} This has compromised cancer care and has affected the acquisition of specimens for translational and correlative studies.^{58 64} Since patients with lung cancer are at a higher risk of infection with SARS-CoV-2 than the general population, there are concerns with the handling of specimens from patients that test positive for the virus.⁶⁴ These specimens are potentially infectious and require special procedures.⁵⁸ A study evaluating the effect of COVID-19 on cancer biobanks showed that NCTN biobanks saw a dramatic decrease in both biospecimen receipt and distribution of 40% and 60%, respectively. Finally, multiple cancer research laboratories have had to shut down because of local mandates, stay at home orders and to comply with social distancing strategies. This has led to the loss of experimental resources such as patient-derived xenografts, transgenic mice and cell lines. Other resources have been repurposed for COVID-19 research, like the evaluation of anticancer agents for the treatment of COVID-19.^{57 65 66} These shutdowns will lead to delays in cancer research and potentially important discoveries.^{57 67}

While the effect of the COVID-19 on lung cancer trials specifically has not been reported, cancer trials in general have been severely disrupted since the start of the pandemic.¹ For instance, cancer centers have generally prioritized certain clinical trials based on their evidence of clinical activity.⁶⁶ As such, phase I trials have been disproportionately held.⁶⁵ Suspension of clinical activities has affected the ability to recruit patients, comply with protocol-mandated visits, and has affected the acquisition of laboratory and radiological data that are essential for both trial endpoints and correlative studies.⁵⁴ Many institutions have halted research-only blood draws and tissue collection and are only collecting samples that directly affect primary trial endpoints as long as patient safety is not compromised in doing so.^{68 69} An analysis of data obtained from a combination of surveys, IQVIA, clinicaltrials.gov, and interviews revealed that only around 15%–20% of trials conducted in Europe and the USA were enrolling patients at the usual rate.⁶² Additionally, 20% of clinical trials in Asia and the US were not enrolling patients when this survey was conducted. For investigators who continued to conduct trials, the greatest barriers to enrollment included the need for in-person patient evaluation and intravenous administration of the investigational agent. Most investigators reported reaching out to their ethic committees regarding concerns around staff safety (30%) and protocol deviations (27%). Regarding new clinical trials, investigators' main concerns included patient follow-up and type (eg, target agents, chemotherapy, immunotherapy or combination of these with some investigational agents) and route of administration of the agent (oral vs intravenous or subcutaneous). Sixty per cent of interviewees rated the pandemic as having a 'moderate' or 'high' impact on their trials, and 80% of respondents anticipated protocol deviations and concerns regarding missing data. This study also reported that around 200 clinical trials were suspended during

April and May.⁶² Similarly, a survey of 64 investigators conducted by ASCO evaluated the pandemic's impact at a clinical trial level in both academic and community centers. Fifty per cent of respondents reported discontinuation of research-only laboratory collections, 60% reported halting screening and enrollment, and most reported that initiation visits had to be conducted remotely.⁷⁰

The pandemic has changed the way clinical research is being conducted. Investigators have had to develop innovative ways to continue to conduct cancer research. For instance, investigators are now using telemedicine for patient follow-up as well as electronic methods for obtaining consent remotely.⁶² Other strategies to mitigate direct patient contact have included the shipment of investigational agents to the patients' homes with administration supervision via telehealth.⁵⁴ Furthermore, both the US FDA and the EMA released guidelines to help investigators, sponsors, and institutional review boards (IRBs) navigate clinical trials during this health crisis. These guidelines address issues such as the collection and reporting of data, different modalities for patient follow-up, and risk–benefit evaluations of continuing versus halting trials.^{71 72} The US FDA requested that sponsors increase flexibility regarding protocols and authorized remote communication with patients for follow-up that should be reflected in protocol amendments.⁶⁶

To conclude, the pandemic has affected several aspects of cancer research, from preclinical studies to clinical trials. These are likely to decrease cancer discovery both in the short and long term.⁵⁷ However, investigators have circumvented some of these difficult circumstances using different strategies that could change the way cancer research is conducted moving forward.⁵⁴

CONCLUSION

The SARS-CoV-2 pandemic has severely affected patients with lung cancer and impaired the progress of lung cancer research. Patients with lung cancer are at an increased risk of becoming infected with the virus and experience higher morbidity and mortality than the general population.³ At the beginning of the pandemic, patients with lung cancer were deprioritized for the ICU admission or mechanical ventilation, as confirmed by the TERAVOLT data, with an increasing rate of death. To date, based on the acquired knowledge on the impact of COVID-19 in patients with cancer, this approach appears out of order, confirming that patients with lung cancer should not be excluded from ICU beds and should be prioritized to receive a prompt and comprehensive care, as other patients.

Despite challenges posed by the pandemic, there has been an unprecedented international effort to understand the impact of COVID-19 on this patient population. Cancer societies, including ESMO and ASCO, have released statements and guidelines to help clinicians manage patients with lung cancer during this health

crisis.^{35–40} Studies such as the TERAVOLT analysis and CCC19 have provided essential information on the effect of different treatment modalities on patients with lung cancer in the context of COVID-19.^{5–28} These analyses provide detailed guidance on the risk of different treatment strategies, with a goal to improve outcomes in patients with lung cancer infected with the virus. Regarding the continuation of clinical research, the FDA and EMA have also released guidelines for continuing clinical research during the pandemic. They have urged sponsors to increase their flexibility and allow telemedicine and remote monitoring for patient follow-up of patients enrolled in clinical trials.^{71–72}

As the number of COVID-19 cases continues to surge across the globe, it is becoming increasingly evident that the incidence of COVID-19 in patients with lung cancer will continue to rise, at least until populations are effectively vaccinated.³¹ Further research is needed to understand the mechanisms that lead to increased susceptibility and mortality in patients with lung cancer infected with SARS-CoV-2. To date, as supported by the main international worldwide oncology societies, including American Association for Cancer Research (AACR),⁷³ ASCO,⁷⁴ ESMO,^{75–76} National Comprehensive Cancer Network (NCCN) and Society for Immunotherapy of Cancer (SITC),⁷⁷ patients with cancer and in particular lung cancer should receive an approved COVID-19 vaccination, also for those undergoing treatments, including chemotherapy, target agents and immunotherapy. Furthermore, as the development of new therapies to treat or prevent COVID-19 infection increases, evaluating the efficacy and side effects of these therapies, and their interaction with anticancer agents including effects of the vaccines will be essential for continuing to care for patients with lung cancer.

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ORCID iD

Antonio Passaro <http://orcid.org/0000-0002-7575-3870>

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