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.

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Commentary

TERAVOLT: Thoracic Cancers International COVID-19 Collaboration

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Prior publications on small subsets of cancer patients infected with SARS CoV-2 have shown an increased risk of mortality compared to the general population. Furthermore, patients with thoracic malignancies are thought to be at particularly high risk given their older age, smoking habits, and pre-existing cardio-pulmonary comorbidities. For this reason, physicians around the world have formed TERAVOLT, a global consortium dedicated to understanding the impact of COVID-19 on patients with thoracic malignancies.

Background

Coronavirus disease 2019 (COVID-19), a respiratory tract infection caused by the severe acute respiratory syndrome (SARS) coronavirus (CoV), also named SARS-CoV-2, began in Wuhan, China, in 2019 followed by a rapid global spread that led the World Health Organization to declare a pandemic in March 2020, with 3,883,098 confirmed cases and 268,560 deaths as of May 7, 2020.

Initial publications describing SARS-CoV-2 were mostly from China, with small numbers of cancer patients. The National Health Commission of China reported on 1,099 patients from 552 hospitals in mainland China, noting a median age of 47 years, 58% male, and 24% had comorbidities that were associated with more severe COVID-19 illness (Guan et al., 2020); only 0.9% of patients had cancer. The median duration of hospitalization was 12 days, 5.0% required an admission to the intensive care unit (ICU), and 1.4% died. The most common presentation included fever in 44% of patients at the time of admission, increasing to 89% during hospitalization, and cough (68%). Laboratory abnormalities included lymphopenia (83%), thrombocytopenia (36%), and elevated C-reactive protein (61%).

A report from Wuhan Jinyintan Hospital identified 99 patients infected with SARS-CoV-2. The median age was 55 years, 68% were male, and 51% had comorbid disease, including cancer in only 1% of patients within the cohort (Chen et al., 2020). The most common presenting symptoms included fever (83%), cough (82%), and dyspnea (31%). Laboratory abnormalities included lymphopenia, anemia, and abnormalities in liver and kidney function tests. Seventeen percent of patients developed acute respiratory distress syndrome (ARDS), and 11% had died at the time of publication. The first two deaths were in patients with a long history of smoking.

A retrospective review of 138 patients with COVID-19 from Zhongnan Hospital of Wuhan University reported a median age of 56 years, 54% were male, and 46% had comorbid disease, including cancer in 7.2% of patients (Wang et al., 2020). Common presenting symptoms were fever (99%), fatigue (70%), cough (59%), myalgia (35%), and dyspnea (31%). Older age, hypertension, cardiovascular disease, and diabetes were risk factors for ICU admission, while cancer was not; however, this finding could be biased due to treatment decisions and/or restrictions in cancer patients. Treatments included antiviral therapy (90%), antibiotics (64%), and steroids (45%), yet the impact of such therapies on survival was not reported. High D-Dimers were identified as a negative prognostic indicator. At the time of publication, 4.3% of patients had died.

Defining Impact of COVID-19 on Thoracic Cancer Patients

While providing valuable data on this lethal illness, the majority of these reports are from single institutions, including

patients with similar ethnicity, albeit with a wide spectrum of cancer diagnoses and comorbid conditions. In a meta-analysis, the overall pooled prevalence of cancer in patients with COVID-19 was 2.0% (Desai et al., 2020). Preliminary data did not clarify whether cancer patients were at higher risk of contracting the virus compared to the general population, nor did they elucidate risk factors for developing the most severe form of the disease. However, these data did suggest the population most at risk of death from COVID-19 was those affected by cardiovascular diseases, diabetes, and hypertension as well as older age, male gender, and obesity, which collectively corresponds to a common prototype seen with a co-existent lung cancer diagnosis. Notably, a recent publication of 218 patients from Montefiore Health system in the United States reported that cancer patients with COVID-19 had a greater risk of death compared to non-cancer patients, as well as a 55% (6/11) mortality rate specific to lung cancer (Mehta et al., 2020). Albeit with small numbers (n = 22), a publication from China suggested that lung cancer patients had the second-highest risk of developing severe and critical symptoms, ICU admission, and death behind hematological malignancies (Dai et al., 2020).

Additionally, the specific impact of stage of disease, oncologic therapeutic strategy, and concomitant therapy on the severity of COVID-19 could not be addressed in these earlier reports, due to small patient numbers and heterogeneity of the cohort. One publication noted that the use of corticosteroids, which are frequently administered to thoracic cancer patients during treatment and for symptom management, may worsen the sequelae of ARDS in patients with COVID-19 (Russell et al., 2020). Markedly increased hypercoagulable profiles due to hyperfibrinogenemia were reported in a series of patients with COVID-19 admitted to the ICU for ARDS, leading to recommendations regarding prophylactic anticoagulation in patients admitted to hospital with COVID-19 (Ranucci et al., 2020). As both cancer as a disease and cancer treatments are often associated with a hypercoagulable state, it is imperative to understand how a cancer diagnosis along with concomitant therapies and existing co-morbidities affects outcomes in COVID-19 patients.

Many societies have provided treatment recommendations for patients with malignancies during this pandemic, thereby revisiting our standards of care for cancer patients and allowing for a better risk/benefit ratio. Many hospitals underwent radical reorganization, including implementing telemedicine to minimize hospital visits, identified as a contamination risk in this community (Yu et al., 2020). A series of questions started to emerge among members of the thoracic community: paramount was how to balance the risk of SARS-CoV-2 infection with the potential risk of delaying cancer care, whether we should treat patients according to the current guidelines or by adapting care, and determining the outcome of COVID-19 on patients with thoracic cancers.

About the Consortium

TERAVOLT is the first global registry aimed at understanding the impact of COVID-19 infection on patients with thoracic malignancies, including patients with non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), mesothelioma, thymic epithelial tumors, and carcinoid/neuroendocrine tumors of thoracic origin. The goals of TERAVOLT are to (1) determine in patients with thoracic malignancies who develop COVID-19 the demographic, comorbidities, and anticancer therapies that place these patients most at risk for hospitalization and death; (2) determine the clinical picture of patients with thoracic malignancies infected by SARS-CoV-2, a diagnosis made more difficult when the presentation of the illness is so similar to the daily symptoms endured by many of our patients; (3) provide practitioners with real-time data on therapies that may impact survival to COVID-19; and (4) evaluate long-term impacts on care and the delay in care to patients with both curable and incurable thoracic malignancies.

The consortium was founded on March 15, 2020, with a final steering committee and live registry available less than a week later (Figure 1A). The steering committee includes investigators from multiple academic centers and with different backgrounds (including thoracic malignancy experts, statisticians, epidemiologists, and computational biologists), all of whom are authors on this Commentary. By May 7, 2020, participation extended to both academic and community clinicians from 185 institutions and 28 countries (Figure 1B), with over 400 cases entered within the first 6 weeks. Participation in the consortium is voluntary, but database access requires approval from the institution's ethics committee. Case eligibility criteria include any patient with thoracic cancer who has a laboratory-confirmed COVID-19 infection or suspected infection due to symptoms (fever >37.5°C, decreased oximeter saturation $\geq$5%, cough, diarrhea, otitis, dysgeusia, myalgia, arthralgia, conjunctivitis, and rhinorrhea) and close contact with a patient with a confirmed COVID-19 infection, or with lung-imaging features consistent with coronavirus pneumonia.

TERAVOLT collects the following data: (1) baseline demographics including age, smoking habits, sex/gender, and country of origin; (2) patient's baseline characteristics, including co-morbidities and concomitant therapies; (3) patient's cancer diagnosis, stage, and current and previous therapies, including chemotherapy, immunotherapy, targeted therapy, surgery, and radiation; (4) patient's COVID-19 illness, including symptoms, laboratory values, imaging, and treatment measures (e.g., anticoagulation, antibiotics, and antiviral therapy), either as an outpatient or during the hospital admission; and (5) outcome from COVID-19 infection including intensive care admission, prolonged hospitalization, or death. These collected measures are being analyzed to provide clinicians with guidance on patient care in real time. Additionally, timing of cancer therapy relative to their COVID-19 diagnosis, as well as anticancer therapy interruptions following recovery, is also being collected to determine the impact this pandemic will have on the outcomes of patients with thoracic malignancies.

TERAVOLT is utilizing REDCap®, a secure web platform for building and managing online databases and surveys (Harris et al., 2019). REDCap was developed specifically around HIPAA-Security guidelines with servers housed in a local data center at Vanderbilt University Medical Center (VUMC), and all web-based information transmission is encrypted. TERAVOLT survey and database maintenance and data distribution are coordinated at VUMC, and data analysis and interpretation are performed jointly within the consortium. A unique feature of this REDCap platform is the ease of adapting the survey questions

Figure 1. Consortium Development Timeline and Global Participation as of May 7, 2020
(A) TERAVOLT was rapidly conceived and executed, with over 400 patients entered into the database within 6 weeks of being active.
(B) TERAVOLT includes participation from 28 countries across the world.

based on the evolution of this pandemic, allowing for additional measures to be collected as our understanding of the virus expands .

Harnessing the Power of a Community

The rapid development and approval of the TERAVOLT database highlights the impact of this novel virus on the global population. Fundamental to the database's success was the endorsement of scientific societies, in particular International Association for the Study of Lung Cancer (IASLC), European Society of Medical Oncology (ESMO), European Thoracic Oncology Platform (ETOP), and European Respiratory Society (ERS), which disseminated information regarding the importance of this consortium, along with a collaborative and collegial steering committee. The first data were presented just over a month after the consortium was formed, indicating a higher-than-expected mortality (33%) in the first 200 patients with data entered. The longitudinal nature of the consortium and registry will allow us to answer important questions on whether mortality was due to the severity of COVID-19 or to a patient's underlying cancer diagnosis, or rather due to decisive factors from patients, physicians, or institutions. TERAVOLT is also partnering with global advocacy groups to develop patient-specific surveys that will collect data globally on the cancer patient's perspective on the pandemic and on their illness. We envision that data from patient surveys can be combined with data from clinical registries in order to develop personalized treatment options that consider the patient's perspective along with clinically reasoned decisions. For more information on TERAVOLT, please visit http://teravolt-consortium.org/.

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