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Commentary

Supporting Clinical Decision-Making during the SARS-CoV-2 Pandemic through a Global Research Commitment: The TERAVOLT Experience

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To understand the real impact of COVID-19 on cancer patients, an entirely new data collection effort was initiated within the Thoracic Cancers International COVID-19 Collaboration (TERAVOLT). TERAVOLT reported high mortality related to COVID-19 infection in thoracic cancer patients and identified several negative prognostic factors. In this commentary, we discuss the importance and limits of patient registries to support decision-making in thoracic cancer during the SARS-CoV-2 pandemic.

In the midst of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, oncologists have had to rapidly restructure their work to optimize safe delivery of care for their cancer patients, weighing the risks of morbidity from coronavirus disease 2019 (COVID-19) against the benefit of intended cancer therapies. From the onset of the pandemic, patients with cancers appeared to be at increased risk for more serious illness with COVID-19 (Kuderer et al., 2020; Tian et al., 2020; Luo et al., 2020; Wang et al., 2020; Sica et al., 2020; Mehta et al., 2020). In such a chaotic time, with insufficient quality data available and limited knowledge of the SARS-CoV-2 infection, understanding

the real impact of COVID-19 on cancer patients had quickly become a challenge for the thoracic cancer community. To support decision-making, an entirely new data collection effort was initiated within the Thoracic Cancers International COVID-19 Collaboration (TERAVOLT) (Whisenant et al., 2020; Garassino et al., 2020).

Two months after conception, the TERAVOLT group had enrolled 200 patients from 42 institutions across eight countries (Italy, Spain, France, Switzerland, the Netherlands, USA, UK, and China). Garassino et al. (2020) reported a 33% mortality rate and a low proportion of thoracic cancer patients receiving intensive care or mechanical

ventilation. Only smoking seemed to significantly correlate with higher death rates (Garassino et al., 2020). Results from 1,000 patients were presented at the European Society of Medical Oncology (ESMO2020) virtual congress and confirmed the significantly high mortality related to COVID-19 among the thoracic cancer patients included in the registry, evaluated at 32% (N = 326; note that a large proportion of patients were diagnosed early in the pandemic in the first wave in Europe and North America). The results of the multivariate analysis (Table 1) suggested that Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2 (OR 3.6; 95% CI 2.7–5), smoking history (OR 1.8; 95% CI



Table 1. Multivariable Model of Factors Associated with Death

Clinical and Demographic Characteristics	Reference Levels	Odds	95% CI	p
ECOG at COVID-19 diagnosis	≥2 versus <2	3.6	2.7–5.0	<0.001
Stage at COVID-19 diagnosis	IV versus ≤III	1.9	1.4–2.7	<0.001
Smoker	Former or current versus never	1.8	1.2–2.7	<0.01
Prior steroids	Yes versus no	1.7	1.1–2.0	<0.01
Age	>65 versus ≤65	1.5	1.1–2.0	0.01
Oncological treatment	None or chemotherapy versus immunotherapy, chemo + immuno, or target	1.4	1.02–2.0	0.03

1.2–2.7), stage IV (OR 1.9; 95% CI 1.4–2.7), age >65 (OR 1.5; 95% CI 1.1–2.0), steroids >10 mg (OR 1.7; 95% CI 1.1–2.0), and chemotherapy or no treatment were significantly associated with negative outcomes. The role of anticoagulants and steroids at COVID-19 diagnosis is still under debate.

As of September 2020, despite differences in healthcare delivery and improvement in our understanding of how to manage patients infected with SARS-CoV-2, and timing of data collection during this lasting pandemic, mortality unfortunately remains high, and factors influencing mortality remain consistent.

The registry was important for addressing oncologists' questions about the impact of COVID-19 on the outcomes of patients with thoracic malignancies. Based on the preliminary results, we are now more confident in delivering tyrosine kinase inhibitors and immunotherapy and more careful in administering chemotherapy to patients with ECOG PS2. We are now aware that mortality is high, that we must stress self-isolation and other strategies to avoid infection, and that we must spend the necessary time to educate patients and families.

The international nature of this registry (as of September 11, 2020, 211 centers across 20 countries and six continents), with the engagement of academic and community oncological centers as well as the endorsement of key medical societies such as International Association for the Study of Lung Cancer (IASLC), European Society for Medical Oncology (ESMO), European Thoracic Oncology Platform (ETOP), and European Respiratory society (ERS), was vital to the rapid enrollment of cases. However, global

engagement required the collection of manageable and comparable data. The information recorded is based on an extensive literature review and reflects daily clinical practice at different cancer centers worldwide. The data collection focused on thoracic malignancies, mainly lung cancers, in order to guarantee the uniformity of the study population. Furthermore, to ensure the quality of the registry, TERAVOLT has established a data management system, including database managers, statisticians, and epidemiologists, to cover such aspects as data collection, data quality controls, error correction, data analyses, and reporting. A scientific steering committee has been established to ensure the timely dissemination of results and the effective, appropriate, and transparent use of data collected. Furthermore, the availability of similar or common clinical practice guidelines, the existence of standard protocols of care for thoracic malignancies accessible worldwide, and the involvement of academic cancer centers in Western countries have helped minimize possible information bias related to the treatment of the enrolled patients. Comprehensive knowledge of the predictive and prognostic factors for lung cancer ensured adjustment for known confounding factors at the time of analyses.

After over 6 months of a global pandemic, it seems clear that patient registries, such as TERAVOLT, by observing real-world clinical practice, may collect the information necessary to evaluate patient outcomes in a generalizable manner. To correctly interpret this information, however, the potential sources of bias (selection and information) that challenge observational studies need to be ad-

ressed. In this regard, TERAVOLT registry also has some limitations. It includes patients from countries with different socioeconomic levels and data from both academic and community hospitals; thus, it is not immune to generalizability issues. The first 200 TERAVOLT patients were mostly from Europe and were mostly registered from Italy, France, and Spain during the initial wave of the pandemic, which nearly overwhelmed the health care systems at that time. Thus, the geographical locations included in the initial cohort could partially explain the low number of intensive care unit admissions observed (Garassino et al., 2020). Since the first publication, the countries contributing to TERAVOLT have increased significantly, including 20 countries across Europe and North and South America and a limited number from Asia and the rest of the world. As the pandemic continues to evolve, patient enrollment has been and will continue to be clearly determined by the geographical spread of SARS-CoV-2.

As of September 2020, the majority of patients enrolled in TERAVOLT had stage IV non-small cell lung cancer and were on systemic treatment. Thus, these patients are not representative of the entire population of lung cancer patients. TERAVOLT is largely organized by medical oncologists, and therefore the patient population naturally tends to be characterized more by patients with advanced stage lung cancer. Furthermore, the initial limited and subsequently growing knowledge about the pathology and natural history of SARS-CoV-2, together with increasing experience in treatment of the infection and evolution of surveillance criteria, may have influenced the collection of data regarding SARS-CoV-2 infection.

To improve its generalizability, TERAVOLT is strengthening the collaboration between oncologists and other health care providers such as pulmonologists, surgeons, and radiation oncologists and is considering expanding the partnership with external data sources to validate key assumptions (e.g., the Observational Health Data Sciences and Informatics [OHDSI], <https://ohdsi.org/who-we-are/>; openSAFELY, <https://opensafely.org/>; the Cancer Consortium [CCC-19], etc.). In addition, TERAVOLT is envisioning long-term data collection to adequately contextualize the results of the registry

in pandemic waves and to adapt data collection over time to capture additional information. TERAVOLT investigators have also launched an international patient questionnaire to determine perceived impact of the pandemic on their cancer care. A Dutch survey showed that 30% of patients have experienced consequences of COVID-19 on their treatment and follow-up visits, which makes patients very concerned about the impact of these decisions on their cancer outcome (de Joode et al., 2020).

In our opinion, TERAVOLT is an example of global collaborative commitment which, by leveraging the exceptional professional skills, commitment, and passion of its partners, has been able to significantly support thoracic cancer care under challenging circumstances created by the COVID-19 pandemic. We hope this registry serves as a model for future collaborative cancer research, to help patients benefit from global efforts to address key issues in future research with a TERAVOLT-like approach.

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