International registry on thoracic cancer patients with COVID-19

TERAVOLT

(Thoracic cancERs international coVid 19 cOLlaboraTion)

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RATIONALE

China first, and the rest of the world subsequently, have been experiencing the outbreak of the severe acute respiratory syndrome coronavirus 2 (SARSCoV-2), namely coronavirus disease (COVID-19), since the end of 2019 [1]. Clinical pictures of COVID-19 can vary a lot, from mild flu-like forms, to severe multiple organ dysfunction syndromes rather than respiratory failure [2], which might be related to the multiple organs distribution of angiotensin converting enzyme 2, the functional receptor for SARS-CoV-2 [3, 4].

To date, the spread of COVID-19 has already reached the epidemiological criteria to be declared pandemic [5], and on March 11th, 2020, with more than 118,000 cases in 114 countries, and 4,291 deaths, the WHO have officially confirmed the pandemic [6].

By the end of February 2020 COVID-19 have already hit Europe hardly, particularly Italy, with 12462 confirmed cases according to the Istituto Superiore di Sanità as of March 11th, and 827 deaths [7]. Considering the infection rapid spread, which can affect a high percentage of each community in a short time, the mortality rate and the death risk estimation are surely related

with the breakdown of the healthcare systems. In China the estimated risk of death varied indeed from the 12% in the epicenter of the epidemic, to ≈1% in less affected regions [8] including Europe, USA, Australia, Latin America, Iran, Canada and many others.

It is well known that cancer patients are more susceptible to infection compared to healthy people and non-cancer patients; that predisposition have been historically related to the systemic malignancy-related immunosuppressive state and to active disease-oriented treatments, such as chemotherapy, radiotherapy and surgery [9-12]. Things might be different for cancer patients undergoing immune checkpoint blockade, who represents an exception from the immunological point of view. A kind of paradoxical immunological response to influenza infection/vaccination during immune checkpoint inhibitors have been already described, even suggesting improved oncological outcomes for these patients [13-15].

The first Chinese report described 18 (≈1%) out of 1590 COVID-19 cases with a history of cancer (mostly lung cancer). Despite the small sample size, the authors observed that the cohort of cancer patients had had an increased risk of developing severe COVID-19-related events compared to non-cancer population [16]. Surely the sample size and high variability of the cancer population might have affected the reliability of their results, however cancer care professionals are now called to cautiously manage this emergency, and cannot fail to consider that cancer patients have to be carefully monitored and prevented from COVID-19 development risk.

Considering this background, we propose a global registry to describe and monitor thoracic cancer patients (NSCLC, SCLC, Malignant Pleural Mesothelioma [MPM] and thymic epithelial tumours [TETs]) with COVID-19, factor associated to severe events, develop a tailored risk assessment strategy for thoracic cancer patients, develop treatment recommendations for thoracic cancer patients .

STUDY DESIGN and ENDPOINTS

This is a longitudinal multi-centre study on thoracic cancer patients (any age, sex, histology, stage, in active treatment as well as in clinical follow-up) which, experienced COVID-19. Information on clinical features, clinical course, management and outcomes will be collected for both, thoracic cancers and COVID-19 infection (see Appendix 1 including the list of data to collect). Considering the limited data available about COVID-19 evolution, the sample size will be not anticipated. However, with about 150 centers and a median of 5 patients at every center, a sample size of 750 patients approximately can produce a confidence interval for the categorical estimate of +/-2%. Clinical data will be extracted from medical records of consecutive patients from January, 1st 2020 until the end of pandemic declared by WHO.

Inclusion criteria

Any thoracic cancer patients with a COVID-19 diagnosis defined as follow:

- Laboratory confirmed (RT-PCR techniques) COVID-19.
- Suspected COVID-19 cases; diagnosed clinically based on symptoms (fever >37.5°, decrease of oximeter saturation of at least 5 %, cough, diarrhoea, otitis, dysgeusia, myalgia, arthralgia, conjunctivitis and rhinorrhea and and exposures).
- Clinically diagnosed cases; suspected cases with lung imaging features consistent with coronavirus pneumonia.
- Asymptomatic cases; diagnosed based on positive viral nucleic acid test results but without any COVID- 19 symptoms.

The following explorative endpoints will be evaluated:

- major demographic features of thoracic cancer patients with COVID-19 (e.g. age, sex, place of residence);
- prevalence of major comorbidities in thoracic cancer patients with COVID-19;
- proportion of thoracic cancer patients experiencing a severe events overall and by severe events including deaths;
- proportion of thoracic cancer patients by COVID-19 clinical course;
- proportion of thoracic cancer patients with COVID-19 who received chemotherapy, surgery, radiotherapy, immune check point inhibitors in the last 2 months before COVID-19 infection;

- predictive factors of severe events in thoracic cancer patients with COVID-19 including cancer-related treatment;
- prognostic factors of thoracic cancer patients with COVID-19 including cancer-related treatment;

Additional outcomes to consider, in a second phase of the registry implementation, could include the follow-up of the thoracic cancer patient survivors in terms of treatment (when cancer-related treatment started again, which treatment) and outcomes. This will allow to assess the impact of the COVID-19 pandemic and the decision taken with regards to thoracic cancer patients treatment on their cancer outcomes (e.g. progression, death).

STATISTICAL ANALYSES

Descriptive statistics of patients demographical (e.g. age, sex,) and clinical characteristics (e.g. comorbidities, severe events, therapy) will be provided together with 95% confidence intervals. Association with baseline factors with continuous outcome will be analysed by generalised linear models, while categorical analyses will be approached with logistical model and time-to event endpoints will be analyzed semiparametric proportional hazard model.

DATABASE MANAGEMENT

Data for this study will be collected in a REDCap® (Research Electronic Data Capture) database. REDCap is a secure web platform for building and managing online databases and surveys. REDCap's streamlined process for rapidly creating and designing projects offers a vast array of tools that can be tailored to virtually any data collection strategy. REDCap provides an intuitive user interface that streamlines project development and improves data entry through real-time validation rules (with automated data type and range checks). REDCap also provides easy data manipulation (with audit trails for reporting, monitoring and querying patient records) and an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus).
Investigators who have received appropriate institutional research approval (i.e., Institutional Review Board or Institutional Ethics Committee) will be given a web link with a survey where they can enter data about their specific patients. Guidelines about the data collection and to properly enter the data will be developed. Investigators at Vanderbilt University Medical Center in

Nashville, TN, United States (Leora Horn, MD and Jennifer Whisenant, PhD) will manage the online survey and keep records of all institutional approvals.

REDCap servers are housed in a local data center at Vanderbilt University Medical Center, and all web-based information transmission is encrypted. REDCap was developed specifically around HIPAA-Security guidelines and is recommended to researchers by both our Privacy Office and Institutional Review Board. REDCap has been disseminated for local use at ~3,100 other academic/non-profit consortium partners in 128 countries. Vanderbilt leads the REDCap Consortium, which currently supports more than 614,000 projects and 834,000 users. More information about the consortium and system security can be found at http://www.projectredcap.org/.

To comply with local regulations regarding use and disclosure of protected health information (PHI), patient identifiers (e.g., name, date of birth, medical record number) will not be collected as part of this study. Investigators will access the medical record of their patient, enter required data into the database. The database will be maintained for an infinite amount of time. The protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project. Future research, that is not defined in this protocol, wishing to access the REDcap database will need institutional review board/ethic review board approval before obtaining access to the REDcap database.

ETHICAL CONSIDERATIONS

All the study procedures will be in accordance with the precepts of Good Clinical Practice and the declaration of Helsinki. According to the regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016, the following requirements regarding personal data will be guaranteed: pseudonymisation and encryption, the confidentiality, integrity, availability and resilience of treatment systems and services, the ability to restore the availability and access of data in the event of a physical or technical accident.

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