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FRACTIONATION AND CHANGES IN PATIENT CARE

Injuries From Asymptomatic COVID-19 Disease: New Hidden Toxicity Risk Factors in Thoracic Radiation Therapy

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In the near future, among the many upheavals caused by the coronavirus disease 2019 (COVID-19) outbreak, the thoracic radiation oncology community might have to face a new unexpected risk factor for patients undergoing radiation therapy (RT) for thoracic malignancies. The major challenge will especially concern patients with asymptomatic COVID-19. Although we may expect that for symptomatic cases the RT strategy will be similar to the current management of RT patients with a pre-existing lung condition,[1] a different scenario can be envisaged for patients who have contracted COVID-19 without apparent symptoms.

Common signs of COVID-19 include fever and dry cough or respiratory symptoms; however, infection can be asymptomatic. In a study investigating the infection exposure before and after the lockdown in the population from a north Italian village, about 43% of the confirmed infections detected were asymptomatic and never developed symptoms during the survey period.[2] Similarly, a comprehensive screening of the Icelandic population conducted by the National University Hospital of Iceland and the deCODE genetics biopharmaceutical company indicated that 43% of the participants who tested positive reported having no symptoms.[3] At the time we are writing, the spread of COVID-19 has taken on pandemic proportions, with nearly 6 million confirmed cases and 350,000 persons dead (https://coronavirus.jhu.edu/map.html). It could be estimated that asymptomatic or undiagnosed infections far exceed tens of millions of people worldwide. This cumulative number is expected to increase until a vaccine for COVID-19 is developed and available for large-scale human use.

Recent studies, some in the form of case reports, refer to computed tomography (CT) imaging abnormalities, even in recovered asymptomatic COVID-19 patients. The analysis of the positive cases from the cruise ship Diamond Princess revealed that 73% were asymptomatic, of whom 54% had lung opacities on CT, usually showing a prevalence of ground glass opacity (GGO) over consolidation.[4] A comparable prevalence of abnormal chest x-ray in asymptomatic and minimally symptomatic patients was reported by a radiologic center in the first Italian COVID-19 epicenter.[5] An unsuspected COVID-19 case undergoing CT for other pathologies showed numerous foci of GGO suggestive of COVID-19; the patient was subsequently diagnosed with a nasopharyngeal swab test.[6] Another case report by McGinnis et al demonstrated bilateral GGOs detected after CT image guidance performed as part of the routine setup and delivery of curative RT treatment in a patient who was ultimately asymptomatic for COVID-19.[7]

In symptomatic patients, longitudinal CT studies showed diffuse lesions with extensive multifocal involvement; abnormalities were bilateral in most cases and progressed rapidly after symptom onset.[8,9] Lesions were particularly

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evident in the lower lobes, posterior lung fields, and peripheral lung zones. Various combinations of pure GGOs, GGOs plus reticular or interlobular septal thickening, and GGOs plus consolidation were common. These mixed patterns of GGO peaked during illness and became the second most prevalent pattern thereafter. Long-term follow-up analyses are clearly required to determine whether the reticulation represents irreversible fibrosis, thus clarifying the transient or permanent nature of CT changes noted in asymptomatic COVID-19 survivors. In addition, concerns exist for COVID-19 carriers on direct and indirect involvement of other organs, with the cardiovascular system being particularly affected.[10]

Notably, it is still controversial whether asymptomatic COVID-19 carriers are mainly young people[2,11]; 47% of the Icelandic infected persons were less than 40 years old (https://www.covid.is/data).

All these findings suggest that in the future there could be a non-negligible proportion of patients, possibly of young age, in need of thoracic RT and with undiagnosed pre-existing cardiopulmonary damage from asymptomatic COVID-19. This might represent an additional hidden comorbidity for radiation-induced injury. COVID-19 per se does not modify the dose constraints for patients receiving thoracic RT as long as pulmonary function can be considered adequate. However, future studies might provide the rationale for adjustments based on sufficient solid information. Indeed, as most clearly pointed out in a study by Defraene et al, a higher baseline lung density was prognostic for a higher susceptibility to radiation-induced damage in patients with lung cancer treated by RT.[12] As a result, dosimetric limits of standard thoracic RT practice commonly considered safe may not be equally safe for this new patient population.

Radiation-induced lung injury is the major dose-limiting factor in thoracic RT, especially for lung and esophageal cancer.[13] Radiation pneumonitis, with a clinical spectrum that may vary from no symptoms to a potentially life-threatening condition, is a common acute morbidity after RT for intrathoracic malignancies. Density changes of lung parenchyma with extended areas of GGO may be evident on posttreatment CT, even in cases of asymptomatic radiation pneumonitis. In addition, radiologic density changes are considered a relevant driver for symptomatic late lung complications, especially when the affected volume becomes important.

Similarly, a large spectrum of cardiac toxicities has been reported as an important and feared complication of thoracic RT. The most frequent types of radiation damage to the heart reported in the literature are pericarditis, valvular defects, coronary artery disease, cardiomyopathy, and a significant increase in mortality due to cardiac disease.[14] Furthermore, subclinical lung damage could be indirectly responsible for secondary cardiac damage.[15-17]

In clinical practice, radiation treatment planning is performed according to prediction models for different radiation-induced toxicities.[18] In particular, in the last decades, research efforts have aimed at determining factors that contribute to radiation pneumonitis development. Age, cardiac comorbidities, the concomitant or sequential use of chemotherapeutic agents, and irradiation of the heart or inferior part of the lungs are some of the factors found to significantly increase the risk of lung toxicity.[13,19] Furthermore, the analysis of cardiac events identified age, cardiac comorbidities, and chemotherapy as concomitant risk factors for heart toxicity.[14]

A new risk factor is henceforth likely to emerge for a nonnegligible percentage of patients in the already complex scenario of the identification of patient-specific susceptibility to radiation-induced toxicity. Notably, the identification of areas of GGO on thoracic planning CT possibly caused by asymptomatic COVID-19 should be an additional issue to take into account in RT planning optimization for thoracic malignancies in the post−COVID-19 era.

Hence, radiation-related research is called to focus effort on identifying the interplay of the effects of COVID-19 with radiation-induced injury by disentangling established pathophysiological pathways from the influence of new subclinical damage induced by asymptomatic COVID-19. A reasonable approach would imply a comprehensive, interinstitutional strategy of data collection in the near term to gather data about mixed interactions between COVID-19−related and −unrelated conditions. Such information could be obtained from both quantitative imaging studies (eg, treatment planning CT or ventilation/perfusion imaging) and specific biomarkers (including N-terminal pro-B-type natriuretic peptide and troponins). This step would enable medium- to long-term action for toxicity analysis and normal tissue complication probability modeling able to include the changes caused by the pandemic.

In addition to patients with lung and esophageal cancer, those with breast cancer and mediastinal Hodgkin lymphoma treated with chemo-RT may play a pivotal role in probing the impact of COVID-19 effects on radiation-induced cardiopulmonary morbidities, due to the high rate of patients with long survival and the relatively lower average age at diagnosis. The combined treatment modality therapy, indeed, implies the risk of long-term side effects, including pulmonary function decline.[20] The sequelae from a possible case of COVID-19, even if asymptomatic, may decrease lung compliance of patients with lymphoma or breast cancer, thus reducing the patient's reserve needed to deal with future cardiopulmonary stresses.

As for the toxicity analysis, a promising ally could be a radiomic-based approach, in which quantitative features are extracted from lung images, thus facilitating higher-order characterization of complex changes in the healthy parenchyma. Furthermore, one could argue that the dose-mass histogram (DMH)−based metrics of the lungs may provide better prediction performance compared with the parameters extracted from the more common dose-volume histograms. Indeed, the DMH would intrinsically account for

patient-specific spatial patterns of baseline density variations and therefore could be proficiently used to provide more robust dose-limiting constraints.

In summary, the COVID-19 pandemic might have altered on a large scale the risk profile of thoracic RT treatments for a nonnegligible fraction of unaware patients. The radiation oncology community should be called on to adequately account for the potential occurrence of these new pretreatment conditions.

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