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.

Radiotherapy and Oncology 161 (2021) 115–117

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Letter to the Editor

Association of prior radiation dose to the cardiopulmonary system with COVID-19 outcomes in patients with cancer

Introduction

Patients with cancer have a unique susceptibility to coronavirus disease 2019 (COVID-19) [1,2]. Multiple reports have assessed the impact of anti-neoplastic therapies on COVID-19 outcomes in these patients [3–6], and although radiotherapy (RT) has been investigated [1,4,6], the exact impact of RT dose to the cardiopulmonary system on COVID-19 outcomes is largely unknown.

We investigated the effect of RT and underlying medical comorbidities on COVID-19 outcomes in patients treated at a tertiary cancer center located in the New York City metropolitan area, an early epicenter of the U.S. COVID-19 pandemic. We hypothesized that the RT dose to cardiopulmonary structures would be associated with COVID-19 outcomes.

Methods

This study was completed under the approved institutional review board protocol #20-146. All patients with a positive SARS-CoV2 RT-PCR test from the first U.S. case identified on March 8, 2020 to May 6, 2020 and who were previously treated with RT at the Memorial Sloan Kettering Cancer Center were assessed (*C.f. Supplemental material; Methods* for further details on data extraction, treatment, and analysis). Demographics, primary cancer histology, comorbidities, date of COVID-19 diagnosis, history of RT (up to 3 years prior to COVID-19 diagnosis) were extracted from the electronic medical records. The three outcomes studied were hospitalization, life-threatening disease (ICU-level acuity), and death.

Cardiopulmonary dose was represented by fractionation-corrected mean heart dose (MHD) and mean lung dose (MLD). Thirteen variables were explored as predictors for the three studied outcomes: history of acute renal injury (ARI; defined as azotemia prior to COVID-19 diagnosis) age, gender, asthma, body mass index (BMI), coronary artery disease (CAD), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), diabetes, hypertension (HTN), MHD, and MLD, and days between RT end and COVID-19 diagnosis (ΔTRT COVID). In the multivariate analysis, a TRIPOD type 2a model [7], which includes a training and validation subset (*cf. Supplemental material; Methods*), was developed.

Results

We identified 350 patients with prior RT who were subsequently diagnosed with COVID-19 from March 8th, 2020 to May 6th, 2020 (*Tables S1 and S2; Figs. S1A and B*). Of these, 195 patients had some extent of MHD and MLD. Among the 350 patients, 39% required hospital admission, 17% had life-threatening disease, and there were 48 deaths due to COVID-19 (*Table S1*).

History of acute renal injury (ARI), CKD, HTN and MHD were significantly associated with all three COVID-19 outcomes: p-value range: 6.8E-6 to 3.8E-3 (Fig. 1, *Table S3*). In addition, BMI and ΔTRT COVID were candidate predictors for hospitalization (p-value: 1.5E−3, 1.2E−4), and CAD was a candidate predictor for both life-threatening disease and death (p-value: 9.1E−4, 4.5E−4). For hospitalization, two candidate multivariate models were identified: (1) ARI, MHD and ΔTRT COVID or (2) HTN, MHD and ΔTRT COVID (model frequency: 19%, 13%). The model that included ARI, MHD and ΔTRT COVID was considered the final multivariate model since it was generalizable in the validation subset (AUC = 0.73; p = 3.85E−5; pHL = 0.53; *Table S3*) while the other model was not (p = 0.22). The dose–response curve in Fig. 2 indicates the agreement between the observed and predicted risk of hospitalization and suggests that a higher risk of hospitalization is likely with the presence of ARI, increased MHD and a shorter ΔTRT COVID. The scatterplot in *Fig. S2* further illustrates that a larger portion of patients that were hospitalized received a higher MHD compared to the non-hospitalized patients. For life-threatening disease and death from COVID-19, no multivariate association was established (*cf. Supplemental material; Results*).

Discussion

To date, this is the largest study evaluating the impact of RT on outcomes in COVID-19 patients by specifically assessing the role of cardiopulmonary dose. By using a rigorous modeling approach, we found that a history of acute renal injury (ARI), the time between RT and COVID-19 diagnosis (ΔTRT COVID) and mean heart dose (MHD) were associated with the risk of hospitalization due to COVID-19. A similar relationship was, however, not established with life-threatening COVID-19 disease or death. Based on data from 107 patients, an early analysis from another NYC-based hospital found MLD to be associated with COVID-19 mortality [8]. However, that study did not assess the impact of heart dose, patient comorbidities or other characteristics that have previously been established to impact COVID-19 outcomes. In summary, while the interactions between patient comorbidities, cancer therapies, and COVID-19 are complex, our results based on data from 350 patients suggest the need for close monitoring in patients with a history of recent thoracic radiation, but do not support withholding RT in patients with cancer to reduce the risk for life-threatening COVID-19 outcomes.

https://doi.org/10.1016/j.radonc.2021.06.002
0167-8140/Published by Elsevier B.V.

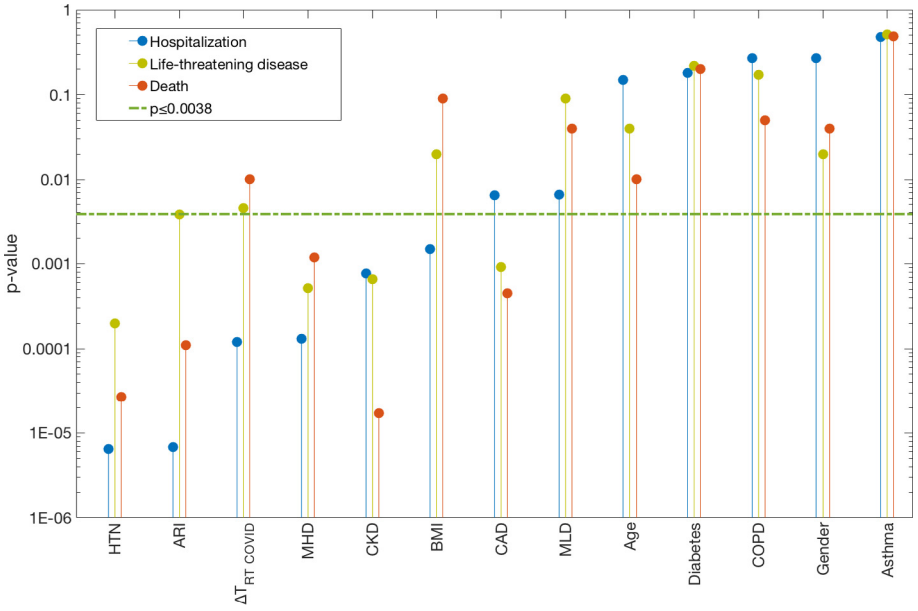

Fig. 1. Univariate analysis *p*-values (y-axis) between each of the 13 variables (x-axis) and each of the three endpoints (Hospitalization: blue; Life-threatening disease: yellow; Death: Orange). The green dash-dotted line is the significance level corrected for thirteen tests. Further details pertaining to the univariate and multivariate results are given in *Table S2*. *The Abbreviations: ARI: Acute Renal Injury; BMI: Body Mass Index; HTN: Hypertension; MHD: Mean Heart Dose; MLD: Mean Lung Dose;* $\Delta T_{RT\ COVID}$*: Time between radiotherapy and COVID-19 diagnosis.*

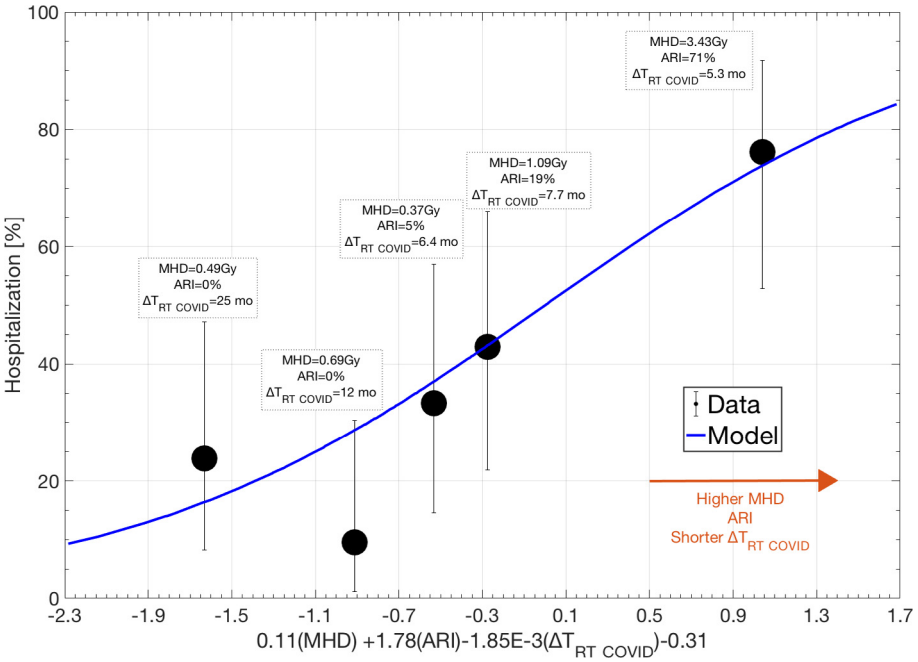

Fig. 2. The dose–response curve for the multivariate hospitalization model in the validation data. The model included ARI, MHD and $\Delta T_{RT\ COVID}$. The solid blue line is the model; black quintiles represent data (error bars: 95% exact binomial confidence intervals). Above each quintile, the population average MHD and $\Delta T_{RT\ COVID}$ are given along with the ARI rate.

Conflict of interest statement

Funding: MSKCC Cancer Center Support Grant, Principal Investigator (Thompson). Agency: NIH/NCI, 5 P30 CA008748-54. National Institutes of Health [T32-CA009207 to JL, K30-UL1TR00457 to JL]; and the Conquer Cancer Foundation [Young Investigator Award to JL].

Disclosure: JL: Reports honoraria from Targeted Oncology and Physicians' Education Resource. DRG: Reports honoraria from Merck, Bristol Myers Squibb, AstraZeneca, Reflexion, Medscape, Vindico, US Oncology, and Varian. Reports research support from Merck, Bristol Myers Squibb, AstraZeneca and Varian. Serves on advisory board for AstraZeneca. All remaining authors have declared no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2021.06.002.

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Quincey LaPlant [a,*,1]
Maria Thor [b,1]
Narek Shaverdian [a,1]
Jacob Y. Shin [a]
Philip Gilbo [a]
Jia Luo [c]
Daniel R. Gomez [a]
Daphna Y. Gelblum [a]

[a] *Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, USA*
[b] *Department of Medical Physics, Memorial Sloan Kettering Cancer Center, New York, USA*
[c] *Thoracic Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, USA*

* Corresponding author at: Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, 1275 York Ave., New York, NY 10065, USA.
E-mail address: laplantq@mskcc.org (Q. LaPlant),

Received 31 January 2021
Received in revised form 19 May 2021
Accepted 2 June 2021

Available online 06 June 2021

[1] Contributed equally to this work as joint first authors.