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Extent of prior lung irradiation and mortality in COVID-19 patients with a cancer history

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Abstract:	Purpose: There have been nearly 200,000 deaths from SARS-CoV-2 (COVID-19) worldwide so far. Cancer history appears to be a poor prognostic factor for COVID-19 patients, though the reasons for this are unclear. In this report, we assess if extent of prior lung irradiation is a risk factor for death due to COVID-19 infection. Methods: Patients who tested positive for COVID-19 between March 14th and April 15th, 2020 at our institution and previously received radiotherapy for cancer in our department were included in this analysis. Patient characteristics and metrics describing the extent of lung irradiation were tabulated. Cox regression models were used to identify predictors of death following COVID-19 diagnosis. A logistic model was used to characterize the association between mean lung radiotherapy dose and 14-day mortality risk following COVID-19 diagnosis. Results: 107 patients met inclusion criteria. With a median follow-up of 7 days from COVID-19 diagnosis for surviving patients, 24 deaths have been observed. The actuarial survival rate 14 days after COVID-19 testing is 66%. Increasing mean lung dose (HR per Gy = 1.1, p=0.002), lung cancer diagnosis (HR=3.0, p=0.034), and receiving radiotherapy between one month and one year before COVID-19 testing (HR = 3.4, p=0.013) were associated with increased risk of death. Our survival model demonstrates a near linear relationship between mortality risk following COVID-19 diagnosis and mean lung radiotherapy dose. Conclusions: COVID-19 patients with a history of radiotherapy for cancer have a poor prognosis, and mortality risk appears to be associated with extent of lung irradiation. Validation of these findings will be critical as the COVID-19 pandemic continues.

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Extent of prior lung irradiation and mortality in COVID-19 patients with a cancer history

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Cancer history appears to be a poor prognostic factor for COVID-19 patients, though the reasons for this are unclear. In this analysis of patients with COVID-19 and a history of radiotherapy, we identified extent of lung irradiation as a risk factor for death. These findings may be important for counseling cancer patients about avoiding exposure to COVID-19 and for identifying COVID-19 patients who require aggressive management.

ABSTRACT

Purpose:

There have been nearly 200,000 deaths from SARS-CoV-2 (COVID-19) worldwide so far. Cancer history appears to be a poor prognostic factor for COVID-19 patients, though the reasons for this are unclear. In this report, we assess if extent of prior lung irradiation is a risk factor for death due to COVID-19 infection.

Methods:

Patients who tested positive for COVID-19 between March 14th and April 15th, 2020 at our institution and previously received radiotherapy for cancer in our department were included in this analysis. Patient characteristics and metrics describing the extent of lung irradiation were tabulated. Cox regression models were used to identify predictors of death following COVID-19 diagnosis. A logistic model was used to characterize the association between mean lung radiotherapy dose and 14-day mortality risk following COVID-19 diagnosis.

Results:

107 patients met inclusion criteria. With a median follow-up of 7 days from COVID-19 diagnosis for surviving patients, 24 deaths have been observed. The actuarial survival rate 14 days after COVID-19 testing is 66%. Increasing mean lung dose (HR per Gy = 1.1, p=0.002), lung cancer diagnosis (HR=3.0, p=0.034), and receiving radiotherapy between one month and one year before COVID-19 testing (HR = 3.4, p=0.013) were associated with increased risk of death. Our survival model

demonstrates a near linear relationship between mortality risk following COVID-19 diagnosis and mean lung radiotherapy dose.

Conclusions:

COVID-19 patients with a history of radiotherapy for cancer have a poor prognosis, and mortality risk appears to be associated with extent of lung irradiation. Validation of these findings will be critical as the COVID-19 pandemic continues.

INTRODUCTION

As of April 23rd, 2020, over 126 million cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), COVID-19 infection have been documented worldwide, with nearly 200,000 deaths.[1] Two reports from China suggest that, among patients with COVID-19 infection, cancer history is a risk factor for severe adverse events, including death[2,3]. Larger series have demonstrated that advanced age and medical comorbidities are powerful predictors of death from COVID-19[4,5]. These factors are also associated with cancer incidence, which may explain the link between cancer history and poor outcomes with COVID infection. Alternatively, cancer or cancer treatments may directly impair patients' ability to overcome COVID infection.

Lung tissue may be exposed to therapeutic radiation when treating primary lung cancers or thoracic metastases or incidentally when treating other primary tumors, such as breast cancer or esophageal cancer. Radiation can cause lung epithelium injury and cytokine release, leading to acute/subacute inflammation (pneumonitis), which can be followed by aberrant wound healing (fibrosis)[6]. These changes can reduce pulmonary function and could conceivably impair patients' ability to withstand COVID-19 pneumonia.

In this report, we assess if extent of prior lung irradiation is a risk factor for death due to COVID-19 infection.

METHODS

In this Institutional Review Board-approved study, we utilized the electronic medical record from a single urban medical center to identify all patients who had

tested positive for COVID-19 up until April 6th, 2020 and were previously treated with therapeutic radiation in our department. Positive COVID-19 (SARS-CoV-2) status was determined based on reverse transcription qPCR assay. Patient demographics, RT dose and volume data for the lungs of all patients who received any thoracic RT, and clinical outcomes as of April 22nd, 2020 were tabulated.

The primary study outcome is overall survival (OS) duration, defined as the time from positive COVID testing until death from any cause. Patient characteristics and extent of previous lung irradiation (quantified as mean radiotherapy dose delivered to the lungs) were tested as predictors of OS using univariate Cox proportional hazards models. Multivariable modeling was not performed due to our limited sample size and strong correlation between key potential prognostic factors (eg: mean lung radiotherapy dose and lung cancer diagnosis). Kaplan-Meier curves were generated to depict survival distributions in various patient subgroups, and comparisons were performed using logrank testing.

We performed normal tissue complication probability (NTCP) modeling using a logistic function[7] to further examine the relationship between mean lung radiotherapy dose and the actuarial rate of death 14 days after COVID testing. Data were sorted into three groups based on mean lung dose, and the actuarial 14-day mortality rate for each group was calculated. These three data points were fit to the NTCP model using least-squares optimization. We utilized a bootstrap resampling method to formulate 95% confidence bounds for the NTCP curve[8]. 10,000 iterations were performed.

Statistical analyses were performed using Matlab (The Mathworks, Natick, MA, U.S.A.) and STATA (STATACORP, College Station, Tx).

RESULTS

We identified 107 patients with positive COVID-19 tests at our institution and a history of radiotherapy for cancer in our department. Patient characteristics are summarized in Table 1.

The median follow-up duration after COVID-19 testing for surviving patients is 7 days (range: 0.5 to 39 days). Twenty-four deaths have been observed, occurring a median of 3 days after COVID-19 testing (range 0.5 to 14 days). The actuarial survival rate 14 days after COVID-19 testing is 66%.

Cox proportional hazards models demonstrated a significant association between mean radiotherapy dose delivered to the lungs and risk of death (HR=1.12 per Gy, 95% CI: 1.04 to 1.20, p=0.002, Table 2). Kaplan-Meier curves depicting this association are shown in Figure 1. Lung cancer diagnosis was also associated with increased risk of death (HR=2.96, 95% CI: 1.09 to 9.27, p=0.034). Compared to patients who received radiotherapy at least five years before COVID infection, patients who received radiotherapy one month to one year before COVID infection had increased risk of death (HR=3.42, 95% CI 1.29 to 9.03, p=0.013).

NTCP modeling results are depicted in Figure 2. Though a logistic (s-shaped) model was applied, mortality risk appears to increase linearly as a function of mean lung radiotherapy dose. For cancer patients without any prior lung exposure to radiotherapy, the predicted mortality rate is approximately 30%. A mean lung

radiotherapy dose of 7 Gy yields a predicted COVID mortality rate of approximately 50%, and a mean lung radiotherapy dose of 15 Gy yields a predicted COVID mortality rate of approximately 75%.

DISCUSSION

In this analysis of emerging data from the COVID-19 pandemic, we found that prior radiotherapy for cancer is associated with a mortality risk of approximately 35%. This is consistent with prior reports that cancer history is a poor prognostic factor in the setting of COVID-19 infection[2,3,9]. We are the first to report that extent of previous lung irradiation may be a critical prognostic factor in cancer patients with COVID-19.

If validated with longer follow-up in our patients and in other datasets, our findings could have profound implications as the COVID-19 crisis evolves. Patients with a history of prior lung irradiation who acquire COVID-19 may benefit from a low threshold for hospitalization and intensive supportive care. Patients with prior lung irradiation could be alerted to be particularly attentive to measures that can reduce COVID-19 exposure risk. Vaccines or other preventative interventions to minimize infection risk or disease severity could preferentially be offered to individuals with prior lung irradiation.

We examined mean lung radiotherapy dose as a prognostic factor in this analysis. We found that other metrics, including lung $V20_{Gy}$ (percentage of lung receiving at least 20 Gy) and lung $V5_{Gy}$, showed similar predictive value as mean lung dose (data not shown). Larger studies will be needed to select the most important

dosimetric factor and examine the impact of daily fraction size. Additional work will also be required to quantify the individual contributions of lung cancer diagnosis and prior lung irradiation as risk factors in COVID patients.

Interestingly, we found that receipt of radiotherapy between one month and one year before COVID-19 diagnosis was associated with increased mortality risk. This timeframe overlaps the typical acute phase of radiation pneumonitis, which involves the induction of proinflammatory cytokines and chemokines that recruit immune cells to lung tissue, where inflammation causes damage to lung parenchyma, epithelial cells, vascular endothelial cells, and stroma.[10] Similar pathways are engaged in severe COVID-19 cases[11], supporting the hypothesis that prior lung radiotherapy may increase the severity of COVID pneumonia.

Limitations of this study include its relatively limited sample size and short follow-up duration. Validation of our findings in additional datasets is imperative. Future analyses will examine how prior lung irradiation affects the clinical presentation of patients with COVID-19, investigate outcomes other than mortality, and explore if specific interventions may be particularly effective in COVID-19 patients with a history of lung irradiation.

FIGURE LEGENDS

Figure 1. Kaplan-Meier curves showing overall survival for patients grouped by mean lung radiotherapy dose received.

Figure 2. Normal tissue complication probability model of 14-day mortality following COVID-19 testing (solid line). Data points represent subsets of patients with mean lung radiotherapy dose of 0 Gy, <4 Gy, and > 4 Gy. Dashed lines represent 95% confidence intervals.

REFERENCES

1. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis.* 2020.
2. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol.* 2020;21(3):335-337.
3. Zhang L, Zhu F, Xie L, et al. Clinical characteristics of COVID-19-infected cancer patients: A retrospective case study in three hospitals within Wuhan, China. *Ann Oncol.* 2020.
4. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet.* 2020.
5. Liang WH, Guan WJ, Li CC, et al. Clinical characteristics and outcomes of hospitalised patients with COVID-19 treated in Hubei (epicenter) and outside Hubei (non-epicenter): A Nationwide Analysis of China. *Eur Respir J.* 2020.
6. Kong F-M, Ten Haken R, Eisbruch A, Lawrence TS. Non-small cell lung cancer therapy-related pulmonary toxicity: an update on radiation pneumonitis and fibrosis. Paper presented at: Seminars in oncology2005.
7. Okunieff P, Morgan D, Niemierko A, Suit HD. Radiation dose-response of human tumors. *International Journal of Radiation Oncology* Biology* Physics.* 1995;32(4):1227-1237.

8. Deasy JO, Chao KS, Markman J. Uncertainties in model-based outcome predictions for treatment planning. *Int J Radiat Oncol Biol Phys.* 2001;51(5):1389-1399.

9. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395(10223):497-506.

10. Lierova A, Jelicova M, Nemcova M, et al. Cytokines and radiation-induced pulmonary injuries. *Journal of radiation research.* 2018;59(6):709-753.

11. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *The Lancet.* 2020.

Table

Gender, n (%)	
Male	53 (50%)
Female	54 (50%)
Age, median (range)	70 (30 to 95)
Ethnicity, n (%)	
Non-Hispanic	61 (57%)
Hispanic	38 (36%)
Other/Unknown	8 (7%)
Primary Cancer Site*, n (%)	
Breast	28 (26%)
Prostate	27 (25%)
Lung	14 (13%)
Gynecological	7 (7%)
Head and neck	6 (6%)
Hematologic	4 (4%)
Other	23 (21%)
Interval from last RT to COVID testing, n (%)	
< 1 month	10 (9%)
1 month to 1 year	18 (17%)
1 to 5 years	35 (33%)
> 5 years	44 (41%)
Mean lung radiotherapy dose, median (range)	0.2 Gy (0 to 16.6 Gy)
Mean lung radiotherapy dose, n (%)	
0 Gy	52 (49%)
0-4 Gy	30 (28%)
> 4 Gy	25 (24%)

Table 1. Patient and treatment characteristics

RT – radiotherapy

*Two patients had head and neck cancer and a second primary cancer diagnosis (lung, prostate)

Characteristic	Hazard Ratio (95% CI)	p-value
Gender		
Male	[reference]	
Female	2.48 (1.06 to 5.81)	0.037
Age, per year	1.01 (0.98 to 1.05)	0.370
Ethnicity		
Non-Hispanic/Other/Unknown	[reference]	-
Hispanic	0.66 (0.26 to 1.66)	0.374
Primary Cancer Site		
Breast	[reference]	-
Prostate	0.13 (0.02 to 1.10)	0.061
Lung	**3.18 (1.09 to 9.27)**	**0.034**
Other	1.07 (0.38 to 3.01)	0.900
Interval from last RT to COVID-19 testing		
< 1 month	0.40 (0.05 to 3.22)	0.386
1 month to 1 year	**2.96 (1.03 to 8.51)**	**0.044**
1 to 5 years	1.52 (0.57 to 4.09)	0.405
> 5 years	[reference]	-
Mean lung radiotherapy dose, per Gy	**1.12 (1.04 to 1.20)**	**0.002**
Mean lung radiotherapy dose		
0 Gy	[reference]	-
0-4 Gy	2.02 (0. 17 to 5.75)	0.856
> 4 Gy	**3.42 (1.29 to 9.03)**	**0.013**

Table 2. Cox proportional hazards models describing predictors of overall survival duration after COVID-19 testing. Bold font denotes statistical significance at the 5% level.
RT - radiotherapy

Figure1

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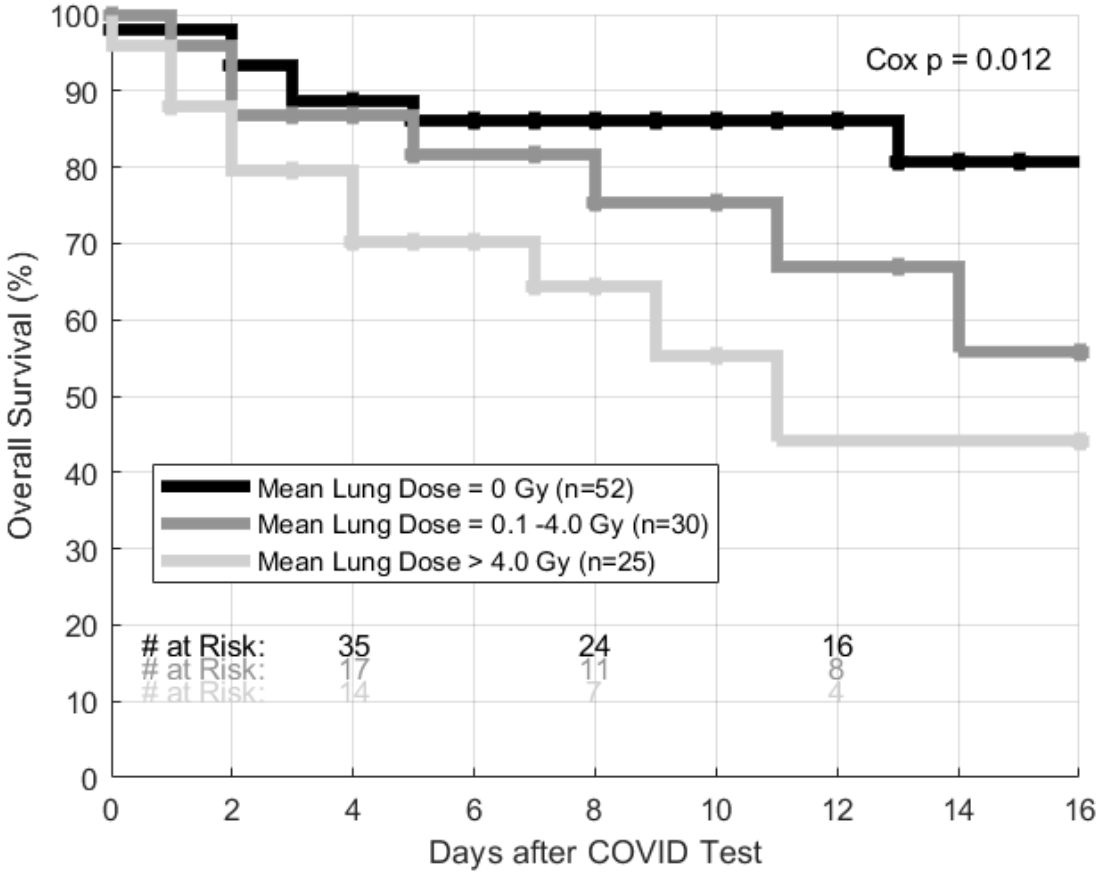

Figure2

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