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Coronavirus disease 2019 (COVID-19) in patients before, during, or after lung irradiation, and serum SP-A and SP-D levels

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Abstract

Background: The correlation between COVID-19 and RT has not been determined to date and remains a clinical question. The aim of this study was to evaluate coronavirus disease 2019 (COVID-19) pneumonia before, during, and after radiation therapy (RT) regarding the radiation doses, radiation pneumonitis, and surfactant protein levels.

Methods: We evaluated patients diagnosed with COVID-19 before, during, or after RT for the lung between August 2020 and April 2022. In patients with breast cancer, the RT dose to the ipsilateral lung was determined. In all other patients, bilateral lung RT doses were determined. Patients diagnosed with COVID-19 after RT were evaluated to determine whether radiation pneumonitis had worsened compared with before RT. The serum levels of the surfactant proteins SP-A and SP-D were measured before, during, and after RT.

Results: The patients included in the study comprised three men (27.3%) and eight women (72.7%). The primary cancer sites were the breast ($n = 7$; 63.7%), lung ($n = 2$; 18.1%), esophagus ($n = 1$; 9.1%), and tongue (9.1%). COVID-19 was diagnosed before RT in four patients, during RT in two patients, and after RT in five patients. Six (54.5%) patients developed COVID-19 pneumonia. Radiation pneumonitis grade ≥2 was not identified in any patient, and radiation pneumonitis did not worsen after RT in any patient. No rapid increases or decreases in SP-A and SP-D levels occurred after the diagnosis of COVID-19 in all patients regardless of RT timing.

Conclusions: COVID-19 did not appear to result in lung toxicity and surfactant protein levels did not change dramatically.

KEYWORDS
COVID-19, lung irradiation, radiation pneumonitis, serum SP-A, serum SP-D

INTRODUCTION

Two and a half years have passed since coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a novel coronavirus, first emerged in Wuhan, China, in December 2019.[1,2] During these years, the COVID-19 pandemic, caused by SARS-CoV-2, has spread worldwide. In Japan, 8 972 654 people have been infected with SARS-CoV-2 as of June 18, 2022.[3]

Radiation therapy (RT) is one of three major cancer treatment modalities, with surgery and chemotherapy. The number of patients receiving RT is increasing annually, with the current annual number of approximately 300 000 in Japan.[4] RT has been incorporated into the standard care for many types of cancer, including breast cancer and locally advanced lung cancer.[5,6] Regarding COVID-19, RT is associated with various risks of infection with SARS-CoV-2, namely the following: (1) Patients visit the outpatient clinic on consecutive days for treatment. (2) RT treatment rooms are poorly ventilated. (3) Multiple patients are treated in the same treatment room. (4) Patients with head and neck tumors is likely to generate aerosols, are immobilized with a

thermoplastic mask.[7] (5) Before treatment of pelvic tumors, patients drink water in the hospital to fill the bladder.[8–10] (6) Cancer patients are reportedly at a high risk of progressing to severe COVID-19.[11,12] In addition, overactivation of immunogenic pathways has been noted as a common mechanism for irradiated lung toxicity and COVID-19 pneumonia.[13,14] However, there have been only a few reports describing COVID-19 in patients receiving lung irradiation in clinical practice.[15–18] Moreover, based on our literature search, there are no published reports of patients who received lung irradiation after the onset of COVID-19. The correlation between COVID-19 and RT has not been determined to date and remains a clinical question. Thus, we herein evaluated COVID-19 pneumonia, RT doses to the lung, and radiation pneumonitis (RP) in patients who received lung irradiation and were diagnosed as having COVID-19 before, during, or after RT.

Recently, the serum levels of the surfactant (SP) proteins, SP-A and SP-D, produced by alveolar type II cells in the lung, have attracted attention as biomarkers for detecting RP.[19–21] Studies of autopsied patients with COVID-19 have shown that SARS-CoV-2 was detected from alveolar type II cells in the lung and that changes in alveolar type II cells were observed in COVID-19 pneumonia.[22,23] Thus, we also evaluated serum SP-A and SP-D levels in patients with COVID-19 for the first time.

METHODS

Patients

The first state of emergency in the COVID-19 pandemic in our country was declared on April 7, 2020, and lasted until May 25, 2020. Since then, three additional states of emergency were declared in Tokyo, where our hospital is located. During the states of emergency, no apparent decrease was noted in the number of new patients receiving RT at our hospital, compared with the number in the same months of 2019 before the first report of COVID-19. Additionally, no apparent changes were observed in the annual number of patients from 2019 to 2021 (Figure 1). We performed reverse transcription polymerase chain reaction (RT-PCR) testing of saliva samples for screening of COVID-19 in 457 asymptomatic patients who were scheduled to receive RT at our outpatient clinic between August 2020 and April 2022. All patients tested negative and received RT. Among the patients who received RT for the lung between January 2019 and May 2022, we examined 11 patients who were diagnosed as having COVID-19 before, during, or after RT. There were no asymptomatic COVID-19 patients in these 11 patients. This study was retrospectively approved by the institutional review board, and patient informed consent was obtained. Written informed consent for publication was obtained from the patients before RT.

Diagnosis of COVID-19

All patients developed a fever and were tested for COVID-19, which was confirmed by RT-PCR in seven patients and by antigen testing in four patients. To evaluate the comorbidities associated with the risk of progressing to severe COVID-19, the Charlson comorbidity index (CCI) combined with age was calculated.[24] After the diagnosis of COVID-19, all patients underwent computed tomography (CT) to determine whether they had COVID-19 pneumonia.

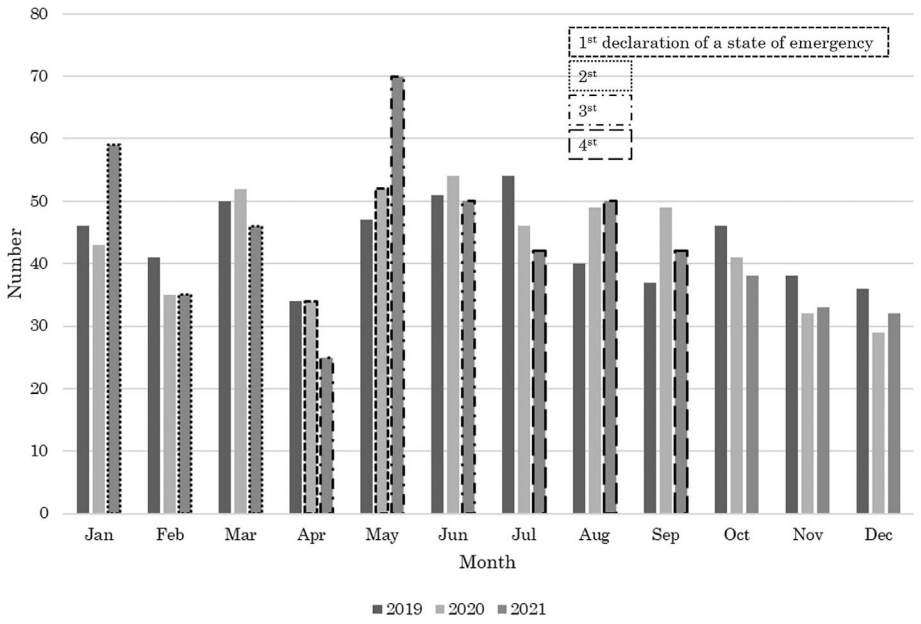

FIGURE 1 Changes in the number of new patients receiving radiation therapy at our hospital from 2019 to 2021. The four periods when a state of emergency was declared are circled. During these periods, no apparent decrease was noted in the number of new patients receiving radiation therapy compared with the number in the same months of 2019 before reports of coronavirus disease 2019. Additionally, no apparent changes were observed in the annual number of patients from 2019 to 2021

Radiation therapy and radiation pneumonitis

All except one patient were treated with three-dimensional conformal RT, and one patient was treated with volumetric-modulated arc therapy in stereotactic body radiation therapy.

In patients who were diagnosed as having COVID-19 before RT and found to have COVID-19 pneumonia by cone-beam CT (CBCT), which was used to check the setup, pneumonia was monitored by CBCT during irradiation. RT was continued after the absence of exacerbation was confirmed. CBCT during RT is useful for detecting COVID-19 pneumonia.[25,26] The RT dose to the ipsilateral lung was evaluated in patients with breast cancer, and the dose to bilateral lungs was evaluated in patients with other cancers. V5, −10, −15, −20, −25, and − 30 (Vx = the percentage of the relative lung volume that received x Gy) and the mean lung dose were calculated. The RT dose was not calculated in one patient who was treated before the RT treatment planning system was updated. RP was evaluated by CT, and a grading system was used in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.[27] Among patients who were diagnosed as having COVID-19 after RT, patients who had undergone CT before the diagnosis of COVID-19 were also evaluated to determine whether RP was exacerbated before and after the diagnosis. In one patient who completed RT but who had not undergone CT after RT, RP was evaluated by CT performed after irradiation at a dose of 38 Gy during RT.

Measurement of serum surfactant levels

The serum SP-A and SP-D levels were measured after the diagnosis of COVID-19. The serum SP-A level was measured by a chemiluminescent enzyme immunoassay with the HISCL SP-A kit (Sysmex), and serum SP-D level was measured by a chemiluminescent enzyme immunoassay using the CL SP-D YAMASA NX kit (Yamasa). The upper limits of the normal levels were as follows: 43.8 ng/ml for SP-A and 110 ng/ml for SP-D. Patients who were diagnosed as having COVID-19 before RT were also evaluated to determine whether serum surfactant levels increased or decreased before, during, and after RT.

RESULTS

Table 1 lists the patient characteristics. Eleven patients comprising three males (27.3%) and eight females (72.7%) were analyzed in this study. The age at initiation of RT ranged from 38 to 74 years (median, 51 years). The primary cancer sites were the breast in seven patients (63.7%), lung in two patients (18.1%), esophagus in one patient (9.1%), and tongue in one patient (9.1%). A smoking history was present in six patients (54.5%). Eight patients (72.7%) received postoperative irradiation after resection of cancer and another

TABLE 1 Characteristics of patients diagnosed with coronavirus disease 2019 (COVID-19) before, during, or after lung irradiation

Patient no.	Sex	Age at RT	Primary cancer site	Comorbidity score[a]	Smoking history	Chemotherapy before COVID-19	Vaccination before COVID-19	Time of positive COVID-19 test	Symptoms	CT findings of COVID-19	Antiviral drug
1	Male	56	Tongue	4	Yes	No	Yes	Before RT	Fever	Yes	Molnupiravir
2	Male	68	Lung	4	Yes	Yes	No	Before RT	Fever	Yes	None
3	Female	49	Breast	1	No	No	Yes	Before RT	Fever	Yes	None
4	Female	74	Breast	2	No	Yes	No	Before RT	Fever	Yes	Remdesivir
5	Female	48	Breast	1	Yes	No	No	During RT	Fever	None	None
6	Female	51	Breast	2	Yes	No	Yes	During RT	Fever	None	None
7	Female	38	Breast	1	No	No	No	After RT	Fever	None	None
8	Female	44	Breast	1	No	No	Yes	After RT	Fever	None	Molnupiravir
9	Female	48	Breast	2	No	No	Yes	After RT	Fever	Yes	None
10	Male	72	Esophagus	9	Yes	Yes	Yes	After RT	Fever	Yes	Nirmatrelvir/ Ritonavir
11	Female	61	Lung	4	Yes	No	Yes	After RT	Fever	None	None

Abbreviation: RT, radiation therapy.
[a]Charlson comorbidity score combined with age.

TABLE 2 Radiation therapy doses to the ipsilateral lung in patients with breast cancer and the doses to bilateral lungs in patients with other cancers, and details of radiation pneumonitis

Patient no.	RT field	RT regimen (dose/fractions)	RT technique	RT dose (%)							RP before COVID-19	RP after COVID-19
				V5[a]	V10	V15	V20	V25	V30	Mean (Gy)	Grade	Grade
1	Neck	66 Gy/33 fr	3D-CRT	9.9	6.4	2.8	1.7	1.1	0.5	2.1	N/A	0
2	Lung	66 Gy/33 fr	3D-CRT	35.2	26.8	22.4	19.2	16.7	14.2	10.9	N/A	1
3	Breast	50 Gy/25 fr	3D-CRT	27.9	20.5	17.0	14.4	12.3	10.2	7.4	N/A	1
4	Breast	50 Gy/25 fr	3D-CRT	19.4	13.2	10.6	8.8	7.3	5.9	5.2	N/A	0
5	Breast	54 Gy/27 fr	3D-CRT	22.4	15.6	12.7	10.7	9.2	7.8	6.3	N/A	1
6	Breast	50 Gy/25 fr	3D-CRT	22.0	14.3	11.3	9.2	7.4	5.7	5.5	N/A	0
7	Breast	50 Gy/25 fr	3D-CRT	27.6	19.1	15.2	12.7	10.6	8.6	6.9	N/A	0
8	Breast	50 Gy/25 fr	3D-CRT	30.1	21.9	18.3	15.8	13.7	11.7	8.3	N/A	0
9	Chest wall	60 Gy/30 fr	3D-CRT	N/A[b]	N/A	N/A	N/A	N/A	N/A	N/A	0	0
10	Esophagus	56 Gy/28fr	3D-CRT	44.5	32.7	27.7	23.5	19.5	14.2	12.1	1	1
11	Lung	48 Gy/4 fr	VMAT	16.7	12.7	9.4	6.7	4.7	3.5	4.2	1	1

Abbreviations: COVID-19 coronavirus disease 2019; RP, radiation pneumonitis; 3D-CRT, three-dimensional conformal radiotherapy; VMAT, volumetric-modulated arc therapy; N/A, not available; fr, fraction.

[a]Vx = percentage of the relative lung volume that received x Gy.

[b]The RT dose was not calculated in one patient who was treated before the RT treatment planning system was updated.

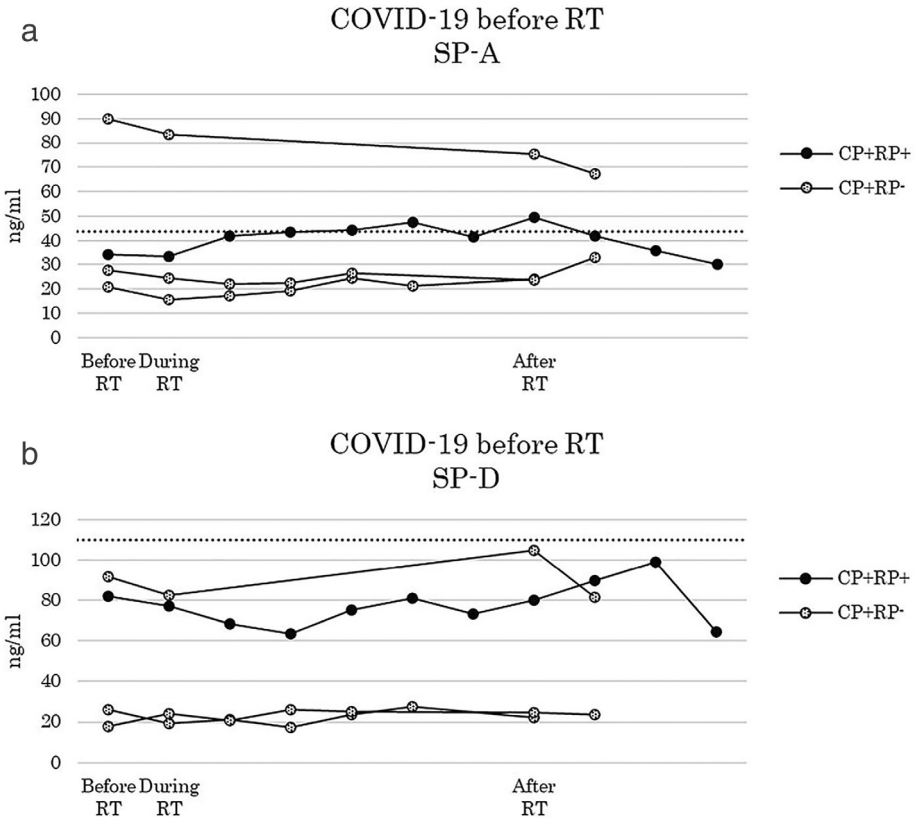

FIGURE 2 To evaluate the serum levels of surfactant proteins (SP-A and SP-D), patients who were diagnosed as having coronavirus disease 2019 (COVID-19) before starting radiation therapy were divided into groups based on their COVID-19 pneumonia (CP+/−) and radiation pneumonitis (RP+/−) statuses (a) serum SP-A level. The dashed line indicates the threshold value. (b) Serum SP-D level. The dashed line indicates the threshold value

three patients have cancer as comorbidity (27.3%). Their scores for CCI combined with age ranged from 0 to 9 points (median, 1 point). Three patients (27.3%) had received chemotherapy before the diagnosis of COVID-19. Before the diagnosis of COVID-19, seven patients were vaccinated against SARS-CoV-2. Positive results for the COVID-19 tests were obtained before RT in four patients, during RT in two patients, and after RT in five patients. In patients who tested positive before RT, the time from the COVID-19 test to the initiation of RT ranged from 43 to 84 days (median, 74 days). In those who tested positive after RT, the time from the completion of RT to the positive COVID-19 test ranged from 119 to 1064 days (median, 510 days). CT revealed COVID-19 pneumonia in six patients (54.5%); four

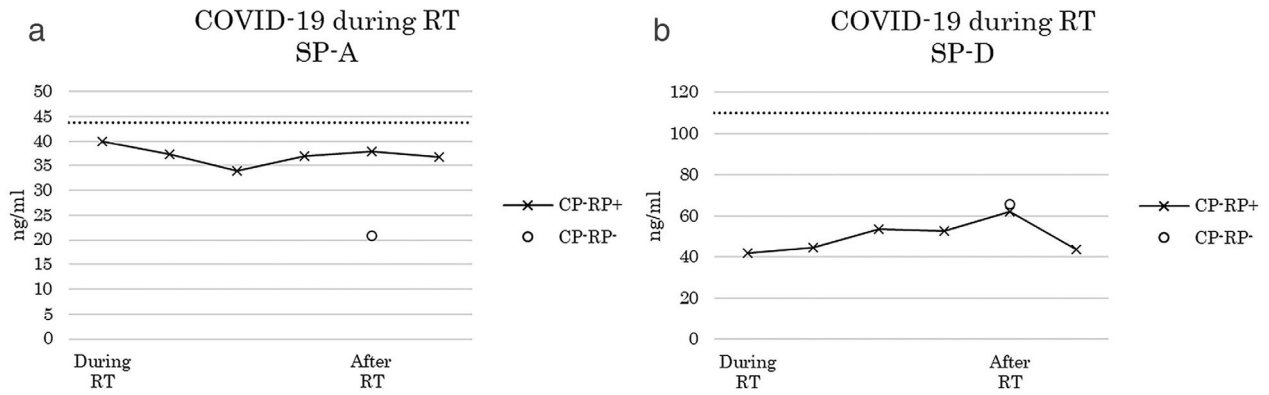

FIGURE 3 To evaluate the serum levels of surfactant proteins (SP-A and SP-D), patients who were diagnosed as having coronavirus disease 2019 (COVID-19) during radiation therapy were divided into groups based on their COVID-19 pneumonia (CP+/−) and radiation pneumonitis (RP+/−) statuses (a) serum SP-A level. The dashed line indicates the threshold value. (b) Serum SP-D level. The dashed line indicates the threshold value

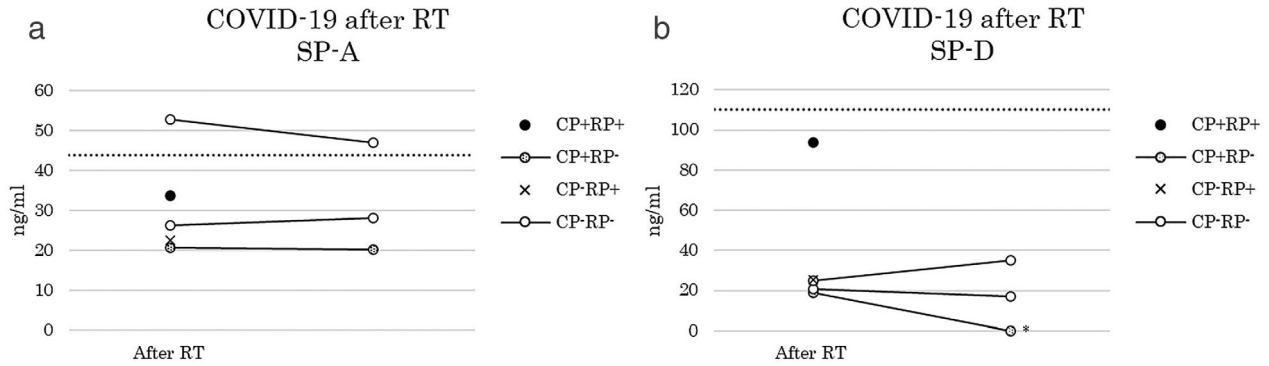

FIGURE 4 To evaluate the serum levels of surfactant proteins (SP-A and SP-D), patients who were diagnosed as having coronavirus disease 2019 (COVID-19) after the completion of radiation therapy were divided into groups based on their COVID-19 pneumonia (CP+/−) and radiation pneumonitis (RP+/−) statuses (a) serum SP-A level. The dashed line indicates the threshold value. (b) Serum SP-D level. The dashed line indicates the threshold value. *less than 15 ng/ml (lower limit of detection)

patients (36.4%) received antiviral drug treatment, and one patient required oxygen therapy. Table 2 lists the RT details. The radiation fields were the breast or chest wall in seven patients (63.6%), lung in two patients (18.1%), esophagus in one patient (9.1%), and neck in one patient (9.1%). The RT doses to the lungs were higher for the three-dimensional conformal RT regimen of 66 Gy/33 fractions for the postoperative lung cancer and the regimen of 56 Gy/28 fractions for the esophagus cancer. The V20 was 19.2 and 23.5% for the postoperative lung cancer and esophagus cancer respectively, and the mean lung doses were 10.9 and 12.1 Gy, respectively. RP of grade 2 or higher was not detected before or after the diagnosis of COVID-19. Among patients diagnosed as having COVID-19 after RT, two patients had RP before the diagnosis of COVID-19 and showed no exacerbation of RP after the diagnosis. In all four patients diagnosed as having COVID-19 before RT, COVID-19 pneumonia was detected on CT scans; however, pneumonia was not exacerbated after RT. In three out of four patients with COVID-19 pneumonia before RT, pneumonia lesions were detected on RT planning CT. The pneumonia lesions were included within the RT field in two patients. In two patients with COVID-19 pneumonia after RT, pneumonia lesions were not included within the past RT field.

The serum SP-A and SP-D levels were evaluated by dividing the patients into four groups based on the presence or absence of COVID-19 pneumonia (CP) and the presence or absence of RP (Figures 2–4). Among patients diagnosed as having COVID-19 before RT, SP-A levels were higher than the upper limit of the normal range in one patient who was CP+/RP− and one patient who was CP+/RP+. No rapid increase or decrease was noted in serum surfactant levels before, during, or after RT. Among patients diagnosed as having COVID-19 during RT, SP-A levels were at the upper limit of the normal range. Among patients diagnosed as having COVID-19 after RT, SP-A levels were higher than the upper limit of the normal range in one patient who was CP−/RP−. No patients exhibited higher SP-D levels than the upper limits of the normal range.

DISCUSSION

The results of screening for COVID-19 in patients before or during RT during the COVID-19 pandemic have been

reported in only two studies, one conducted in Germany and one in the United States.[28,29] In both studies, PCR testing was performed in asymptomatic patients (139 and 336 patients; German and US study, respectively), and the number of positive patients was one (0.7%) and 5 (1.5%), respectively. The incidence of COVID-19 in the radiation oncology departments in Japan has been investigated only in a nationwide questionnaire survey conducted in April 2020. In that survey, no patients receiving RT tested positive for COVID-19.[30] The present study is the first to show the results of screening for COVID-19 in patients receiving RT in Japan. Before the initiation of outpatient RT, none of the 457 patients tested positive for COVID-19. Based on the screening report and our findings, the risk of infection with SARS-COV-2 appeared to be low even in radiation oncology departments that treated many patients. At our hospital, patients received RT without delay, and the number of patients did not decrease even under the state of emergency. The rate of nosocomial infection with COVID-19 was estimated at 41.3% in a hospital in Wuhan, China.[31] To address this risk, we have implemented specific strategies, such as screening of patients for fever and social distancing among patients, to reduce the transmission of SARS-CoV-2 in our radiation oncology department.[32]

For lung toxicity associated with either lung irradiation or COVID-19 pneumonia, inflammation is a main pathological feature, which has been reported to cause an inflammatory cytokine storm in patients.[14,33] An analysis of 107 patients with COVID-19 who had previously received RT showed that the mortality rate was significantly higher in patients receiving a mean lung dose (MLD) of more than 4 Gy, patients with lung cancer, and patients who underwent RT 1–12 months before the onset of COVID-19, compared with patients who did not meet these criteria.[18] In patients who underwent RT 1–12 months before the onset of COVID-19, the onset of COVID-19 might have corresponded with the onset of RP. Thus, we evaluated COVID-19 pneumonia and RP in patients who received lung irradiation. In the present study, patients with breast cancer accounted for the largest proportion of the patients. Even when RT is delivered only to the residual breast after conservative surgery, the ipsilateral lung is always partially irradiated. For example, in our hospital, CT revealed RP in 50 of 133 patients (37.6%) who received irradiation only to the residual breast after conservative surgery.[34] There is a case report describing COVID-19 pneumonia occurring during RT for breast cancer in which CT revealed more severe pneumonia patterns in the radiation field than those in the contralateral lung. Attention was given to the possibility that RT might have exacerbated COVID-19 pneumonia.[17] However, another report found that none of 12 patients with COVID-19 occurring during RT for breast cancer had RP.[35] Furthermore, an analytical study reported that the RT field was not correlated with the extent of COVID-19 pneumonia in 59 patients treated with RT for breast cancer.[36] Patients included in the present study exhibited no exacerbation of RP after the diagnosis of COVID-19 or COVID-19 pneumonia after RT.

Comorbidities have been reported to be associated with progression to severe COVID-19.[12,36] However, in the present study, COVID-19 did not progress to severe disease after RT for cancer even in patients with a high CCI.

In accordance with the guidelines from the Radiation Therapy Oncology Group, RT doses to the residual breast after conservative surgery should be constrained as follows: no more than 20% of the ipsilateral lung should receive 20 Gy or higher; no more than 40% of the ipsilateral lung should receive 10 Gy or higher; and no more than 55% of the ipsilateral lung should receive 5 Gy or higher.[37] In all patients in the present study, RT doses were delivered in accordance with the guidelines. In two patients in whom irradiation was delivered to both lungs, the MLD was higher than 4 Gy, which is a poor prognostic factor for COVID-19.[18] However, the V20 and MLD were within the dose range that is associated with a low incidence of RP, in accordance with the quantitative analysis of normal tissue effects in the clinic (QUANTEC) guidelines.[38] Thus, no adverse events of grade 2 or higher occurred.

Several studies have reported that high serum SP-A and SP-D levels measured before, during, and after thoracic RT are predictors of RP.[19–21] However, the present study is the first to report serum SP-A and SP-D levels in patients with COVID-19. Although the target of both RP and COVID-19 pneumonia is alveolar type II cells, no abnormal increases in the serum SP-A or SP-D levels were observed in this study, even after the lungs affected by COVID-19 pneumonia were irradiated. Thus, this study suggests that when RT was administered using clinically standard methods, COVID-19 might not affect lung toxicity. The results of a recent clinical study involving patients with COVID-19 pneumonia have shown that the time to recovery was shorter in patients who received whole-lung RT at a low dose of 1.5 Gy than those who did not received RT.[39] In contrast to lung toxicity, RT may suppress COVID-19 pneumonia through immunomodulation. However, in the future, this effect may change depending on the emergence of new variants of SARS-COV-2.

We will continue long-term follow-up observation of patients who have just completed RT, as well as new patients who will be diagnosed with COVID-19, to monitor lung toxicity and evaluate serum SP-A and SP-D levels.

In conclusion, radiation therapy did not affect the severity of radiation pneumonititis or COVID-19 pneumonia in patients with COVID-19. No dramatic increases in surfactant protein levels were seen before, during, or after radiation therapy

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CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest

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