Original Article

Decline of circulating monocyte and neutrophil counts in COVID-19-infected patients with cancer receiving radiotherapy

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Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)/coronavirus disease 2019 (COVID-19) affects treatment outcomes in patients with cancer. This impact remains unclear in patients with cancer receiving radiotherapy (RT) who develop synchronous COVID-19 infection. The ratios of neutrophils to lymphocytes (NLR), platelets to lymphocytes (PLR), and monocytes to lymphocytes (MLR) are biomarkers of inflammation and are considered as predictors of the prognosis of systemic inflammatory diseases, which can even affect the prognosis in patients with cancer. The aim of our study was to explore the differences in absolute monocyte counts (AMC) and other cell lineages during RT between COVID-infected and COVID-naive patients.

Methods: A total of 44 cancer patients receiving RT were enrolled in the study, including 22 COVID-19-infected and 22 COVID-19-naive patients. The COVID-19 infection was confirmed by polymerase chain reaction (PCR). Complete blood count (CBC) with differential counts were evaluated weekly before and during RT.

Results: In both COVID-infected and COVID-naïve patients with cancer, the absolute counts of monocytes, neutrophils, and platelets decreased during the RT course. The degree of decline in the absolute counts of monocytes (–48% versus –31%) and neutrophils (–26% versus –13%) in the COVID-infected group was more vigorous than that in the COVID-naive group. Other blood cell counts and ratios of NLR, PLR, and MLR exhibited similar extents of alteration.

Conclusions: The decline in circulating monocytes and neutrophils in cancer patients receiving RT with synchronous COVID-19 was more pronounced than that in COVID-naive patients. It might provide an immunological reference for managing cancer patients with COVID-19 receiving RT in clinical practice.

Keywords: Monocyte; neutrophil; radiotherapy (RT); coronavirus disease 2019 (COVID-19)

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Introduction

Circulating blood monocytes are produced by hematopoiesis in the bone marrow and recruited to tissues to transform into resident macrophages. Tissue recruitment of circulating monocytes occurs in response to the increased demand following tissue inflammation, infection, and malignancy. Classically, monocytes are phagocytic innate immune cells that are divided into three subsets according to the expression of the surface antigens, CD14 and CD16 [classical ($CD14^+CD16^-$), non-classical ($CD14^{dim}CD16^+$), and intermediate ($CD14^+CD16^+$)] (1). Under pathological conditions, such as viral infection, monocytes are recruited by inflammatory mediators to infiltrate the affected tissues. Inflammatory macrophages and cell with dendritic cell-like phenotypes fulfill the effector functions, which include pro- and anti-inflammatory activities, antigen presentation, and tissue remodeling (2).

Blood monocytes provide a narrow window for the systemic immune response, from production to tissue recruitment, reflecting the impact of the infection on the host. Monocyte-derived macrophages are the main generators of inflammation in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)/coronavirus disease 2019 (COVID-19) (3). Clinical investigations have demonstrated that patients with COVID-19 have inconsistent monocyte counts (3). In a more specific monocyte subset analysis, monocytes in the blood of patients with moderate COVID-19 present an inflammatory, interferon-stimulated gene-driven phenotype. Cellular dysfunction, the dominant feature of disease severity is epitomized by the loss of HLA-DR expression and induction of S100 alarmin expression (4). Flow cytometric analyses of peripheral blood have shown a decline in the percentage of total monocytes in the blood of patients with severe COVID-19 (5,6). Notably, this reduction was observed only transiently in a longitudinal study of immune cells in severe cases, indicating a highly time-sensitive immune response (7). Another study demonstrated that the white blood cell (WBC) count and absolute neutrophil count (ANC), but not lymphocyte and monocyte counts were greater in COVID-19-infected patients in the intensive care unit (ICU) group than those in the non-ICU group (8).

Radiosensitivity of hematopoietic stem cells causes decrease in absolute monocyte count (AMC) during radiotherapy (RT) or concurrent chemoRT (9,10). However, no study has investigated the complete blood count (CBC) of COVID-infected patients during RT, especially the AMC, and as stated above, monocytes play an important role in inflammation in COVID-infected patients.

Therefore, the aim of our study was to explore the differences in AMCs and other cell lineages during RT between COVID-infected and COVID-naive patients. These results may provide an important reference for evaluating the impact of COVID-19 on CBC with differential counts in patients with cancer receiving RT. We present this article in accordance with the STROBE reporting checklist (available at https://tro.amegroups.com/article/view/10.21037/tro-23-14/rc).

Highlight box

Key findings

- The decline in circulation monocytes and neutrophils was more vigorous in cancer patients receiving radiotherapy (RT) with synchronous coronavirus 2/coronavirus disease 2019 (COVID-19) infection compared with that in COVID-naive patients.

What is known and what is new?

- Many studies have shown that monocytes play an important role in causing inflammation in COVID-infected patients. However, due to the radiosensitivity of hematopoietic stem cells, the absolute monocyte count decreases during RT or concurrent chemoRT course. In our manuscript, the absolute monocytes and neutrophils counts were significantly decreased during RT compared with the data collected before RT in COVID-infected patients.

What is the implication, and what should change now?

- The results may provide an important reference for evaluating impact of COVID-19 infection on complete blood count with differential count in cancer patients receiving RT.

Methods

Patient enrollment

This retrospective study enrolled both COVID-infected patients (n=22) and COVID-naive patients (n=22). Both groups received RT from April 2022 to August 2022. The CBC data before and during RT were available for all enrolled patients. Patients without CBC data abovementioned were excluded. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of MacKay Memorial Hospital (No. 23MMHIS154e) and individual consent for this retrospective analysis was waived.

RT technique

All patients were immobilized in the supine position using

Table 1 Patient characteristics

Characteristics	COVID-infected	COVID-naive	P
Gender, n			0.757
Male	9	8	
Female	13	14	
Age (years), median	61	58	0.553
Stage, n			0.278
In situ, I, II	9	13	
III, IV	11	8	
Not applicable	2	1	
Dose (Gy), n			0.498
<50	7	5	
≥50	15	17	
Systemic therapy			0.761
Yes	10	9	
No	12	13	
Antivirus therapy			0.002
Yes	8	0	
No	14	22	

COVID, coronavirus disease 2019.

thermoplastic facial masks or alpha-cradle molds, depending on the site of treatment. Isocenters were marked on the mask or patients' bodies using laser markers to ensure the reproducibility of daily treatment. Subsequently, the patients underwent simulated computed tomography with a thickness of 3 mm per slice. The dose and fraction of RT were planned according to cancer type, stage, and treatment intention. The patients received RT for 5 consecutive days per week. The RT was designed using an RT planning system (Eclipse version 13.0, Varian, CA, USA; Pinnacle 3 9.10, Philips, WI, USA). All RT treatments were delivered via three-dimensional RT, intensity-modulated RT, or dynamic arc using linear accelerators (Clinac iX, Varian, CA, USA; Synergy, Elekta, Stockholm, Sweden; Versa HD, Stockholm, Sweden).

Data collection and calculation

The CBC data were examined within 1 month before both COVID infection and RT treatment were selected. In contrast, blood tests for the lowest monocyte count during RT were performed. Using the above data, the ratios of neutrophils to lymphocytes (NLR), platelets to lymphocytes (PLR), and monocytes to lymphocytes (MLR) were calculated, respectively, which are biomarkers of inflammation and are considered as predictors of the prognosis of systemic inflammatory diseases, which can even affect the prognosis in patients with cancer, as evidenced in this study (11). In addition, the delta values were calculated as the blood count during RT minus the count before RT.

Polymerase chain reaction (PCR)

All COVID-infected patients in this study were diagnosed by PCR testing, which amplified and detected SARS-CoV-2 RNA in the upper respiratory tract. The PCR sequences detected at that time followed the standards provided by the National Laboratory of Taiwan Centers for Disease Control, Kwen-Yang Laboratory.

Statistics analysis

Descriptive statistical analyses were performed using SPSS software (IBM Corp., Released 2019, Version 24.0, Armonk, NY, USA). To analyze the differences in the blood cell counts of the same patients before and during RT, the paired *t*-test was used, whereas the unpaired *t*-test was performed to calculate the variation in blood cell counts between COVID-infected and COVID-naive patients.

Results

This retrospective study enrolled 44 patients between April 2022 and August 2022. The groups were well balanced, with 22 patients in each group. Detailed patient information is provided in the supplementary Information (Tables S1,S2). The median age was 60.5 years. No severe infections were observed in the COVID-infected group. Approximately 43% of the patients received chemotherapy during RT, with no significant distributional deviation in either group (P=0.761). The percentages of patients with and without COVID infection receiving RT doses ≥50 Gy were 68% and 77%, respectively (P=0.498). Detailed patient characteristics are summarized in *Table 1*.

Complete blood count profiles in COVID-infected and COVID-naive patients

In COVID-infected patients, the AMC (P<0.001), absolute

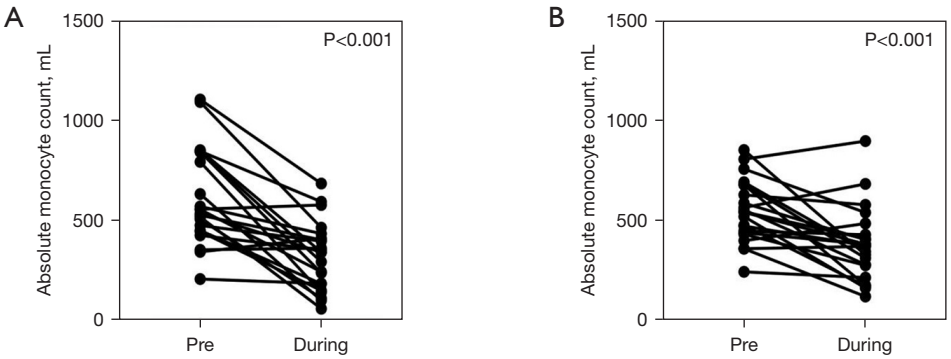

Figure 1 Difference in absolute monocyte count pre-radiotherapy and during RT between in COVID-19-infected and COVID-19-naive patients. (A) Changes in absolute monocyte count in COVID-infected patients. (B) Change in absolute monocyte count in COVID-naive patients. RT, radiotherapy; COVID-19, coronavirus disease 2019.

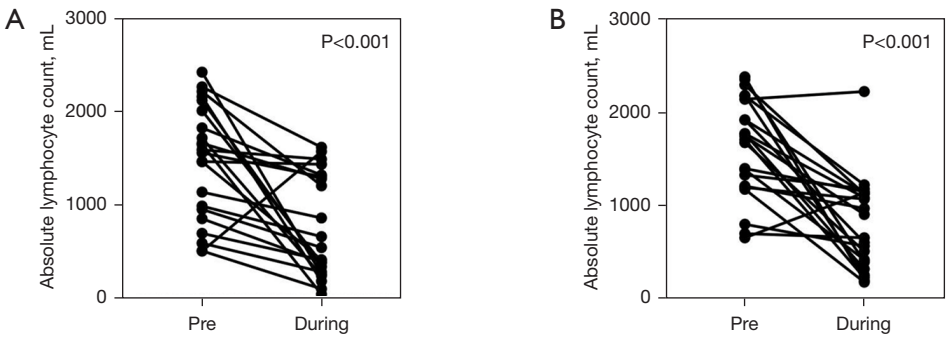

Figure 2 Difference in absolute lymphocyte count pre-radiotherapy and during RT between in COVID-19-infected and COVID-19-naive patients. (A) Change in absolute lymphocyte count in COVID-infected patients. (B) Change in absolute lymphocyte count in COVID-naive patients. RT, radiotherapy; COVID-19, coronavirus disease 2019.

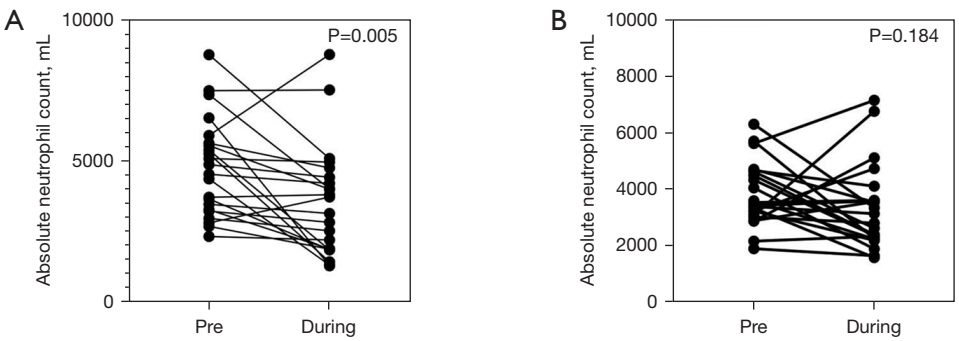

Figure 3 Difference in absolute neutrophil count pre-radiotherapy and during RT between in COVID-19-infected and COVID-19-naive patients. (A) Change in absolute neutrophil count in COVID-infected patients. (B) Change in absolute neutrophil count in COVID-naive patients. RT, radiotherapy; COVID-19, coronavirus disease 2019.

lymphocyte count (ALC) (P<0.001), ANC (P=0.005), and platelet counts (P=0.015) were significantly decreased, whereas the NLR and PLR increased during RT in comparison with the data before RT, as shown in *Figures 1-4*. Detailed data of COVID-infected patients are summarized in *Table 2*. Data from COVID-naive patients revealed a

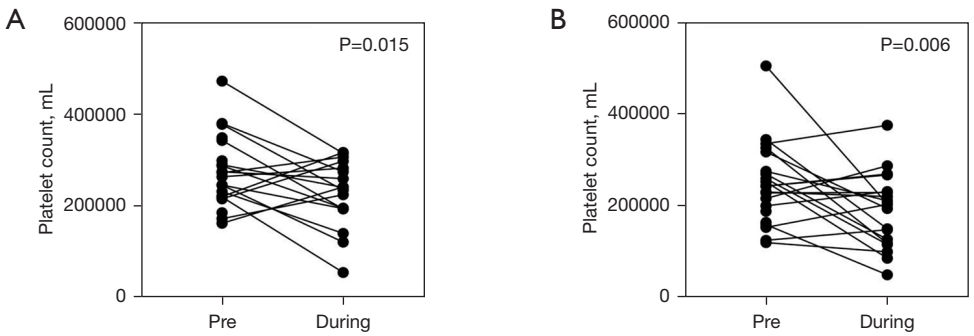

Figure 4 Difference in platelet count pre-radiotherapy and during RT between in COVID-19-infected and COVID-19-naive patients. (A) Change in platelet count in COVID-infected patients. (B) Change in platelet count in COVID-naive patients. RT, radiotherapy; COVID-19, coronavirus disease 2019.

Table 2 Complete blood count profile in COVID-infected and COVID-naive patients before and during radiotherapy

Complete blood count	COVID-infected		COVID-naive	
	Pre-radiotherapy	During radiotherapy	Pre-radiotherapy	During radiotherapy
AMC (/μL)	610.7±237.6	318.7±170 (–48%)*	544.0±154.9	374.6±182.8 (–31%)*
ALC (/μL)	1,468.8±608.6	740.2±546.3 (–50%)*	1,626.3±529.8	793.0±493.0 (–51%)*
ANC (/μL)	4,755.4±1,732.0	3,510.1±1,954.9 (–26%)*	3,812.2±1,130.7	3,301.9±1,509.7 (–13%)
PLT (1,000/μL)	273.9±82.7	228.5±72.9 (–17%)*	244.1±95.9	187.8±82.9 (–23%)*
NLR	4.0±2.5	9.8±11.6 (145%)*	2.7±1.5	6.3±5.4 (133%)*
PLR	248.6±169.3	476.0±380.9 (91%)*	187.9±122.6	343.4±229.1 (83%)*
MLR	0.5±0.4	0.7±0.6 (40%)	0.4±0.3	0.6±0.4 (50%)*

Data were presented as mean ± standard deviation. The numbers in parentheses indicate the percentage changes before and during RT in the two groups. *, differences in significance (P<0.05). COVID, coronavirus disease; AMC, absolute monocyte count; ALC, absolute lymphocyte count; ANC, absolute neutrophil count; PLT, platelet; NLR, ratio of neutrophils to lymphocytes; PLR, ratio of platelets to lymphocytes; MLR, ratio of monocytes to lymphocytes.

significant decline in AMC, ALC, and platelet count, with a significant increase in NLR, PLR, and MLR (*Table 2*).

Degree of decline of complete blood count with differential count in COVID-infected and COVID-naive patients

The percentages of change before and during RT in the two groups are shown in *Table 2*. The degree of decline in differential counts of leukocytes in COVID-infected group was more vigorous than those in COVID-naive group in terms of AMC (–48% versus –31%) and ANC (–26% versus –13%).

Discussion

The issue of COVID-19-infected patients with cancer receiving RT is an emerging concern that lacks sufficient clinical information. In the present study, a more vigorous decline in AMC and ANC was observed, which could provide an immunological reference for managing patients with cancer receiving RT in clinical practice.

The roles of monocytes and monocyte-derived macrophages in COVID-19 are important from an immunological perspective. The hyper-inflammatory response induced by COVID-19 is a major cause of severe disease and mortality. Monocyte-derived and -recruited macrophages are populations of innate immune cells that sense and respond to microbial invasion by producing inflammatory mediators that eliminate microbes and enhance tissue repair. However, a dysregulated macrophage response may damage host tissues under conditions,

such as macrophage activation syndrome (12,13). The more vigorous decline in AMC in patients with cancer and synchronous COVID-19 receiving RT indicated the potential role of RT in the management of COVID-19-induced hyper-inflammation. This association requires further investigation, involving the analysis of monocyte subsets in clinical studies and examination of causal relationships in animal experiments.

As for neutrophils, the increase in neutrophils may be related to unfavorable outcome in COVID-19-infected patients as well as patients with cancer and without COVID-19 infection. In adult COVID-19-infected patients with cancer, an elevated NLR is significantly associated with poor survival (14). However, the role of neutrophil count in the prognosis of patients with cancer and synchronous COVID-19 receiving RT remains uncertain. Our results demonstrated a more vigorous decline in ANC in COVID-19-infected patients receiving RT. These data may provide an alert in clinical practice, suggesting the consideration of risks of other infections, such as bacterial infections.

This study had several limitations, including a relatively small sample size and lack of subset analysis for AMC and ANC. Although this study provided clinical information regarding COVID-19-infected patients with cancer receiving RT, further investigations are warranted to validate and confirm these findings.

Conclusions

In conclusion, a more vigorous decline in circulating monocytes and neutrophils was noted in patients with cancer receiving RT for synchronous COVID-19 infection.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tro.amegroups.com/article/view/10.21037/tro-23-14/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tro.amegroups.com/article/view/10.21037/tro-23-14/coif). Y.J.C. serves as the Editor-in-Chief of *Therapeutic Radiology and Oncology*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of MacKay Memorial Hospital (No. 23MMHIS154e) and individual consent for this retrospective analysis was waived.

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Supplementary

Table S1 Detailed patient profile in COVID-infected group

No.	Diagnosis	Stage	RT dose	RT field	Intention	Chemotherapy
1	Breast CA	IA	50 Gy/20 fx	Breast	Adjuvant	NA
2	Esophageal CA	IVA	48 Gy/24 fx	Mediastinum	Neoadjuvant	Paclitaxel + cisplatin
3	Prostate CA	IIIC	75.6 Gy/42 fx	Pelvis	Definitive	NA
4	Endometrial CA	rIIIC1	59.4 Gy/33 fx	Pelvis	Palliation	cisplatin
5	Breast CA	IA	50 Gy/20 fx	Breast	Adjuvant	NA
6	Meningioma	NA	60 Gy/30 fx	Brain	Definitive	NA
7	Tongue CA	III	60 Gy/30 fx	Head and neck	Adjuvant	Cisplatin
8	Breast CA	IA	42.5 Gy/16 fx	Breast	Adjuvant	NA
9	Kaposi's sarcoma	NA	50 Gy/25 fx	Foot	Palliation	NA
10	Esophageal CA	IVB	48 Gy/24 fx	Mediastinum	Neoadjuvant	Fluorouracil + cisplatin
11	Breast CA	IIA	50 Gy/20 fx	Breast	Adjuvant	NA
12	Breast CA	IIB	60 Gy/30 fx	Breast	Adjuvant	NA
13	Ovarian CA	rIIIA1	59.4 Gy/33 fx	Pelvis	Palliation	Doxorubicin + carboplatin
14	Esophageal CA	III	48 Gy/24 fx	Mediastinum	Neoadjuvant	Fluorouracil + cisplatin
15	Breast CA	0is	42.5 Gy/16 fx	Breast	Adjuvant	NA
16	Breast CA	IIA	42.5 Gy/16 fx	Breast	Adjuvant	NA
17	Esophageal CA	III	48 Gy/24 fx	Mediastinum	Neoadjuvant	NA
18	Cervical CA	IIA2	60 Gy/30 fx + brachytherapy 30 Gy/6 fx	Pelvis	Definitive	Cisplatin
19	Laryngeal CA	IVA	70 Gy/35 fx	Neck	Definitive	Cisplatin
20	Breast CA	0is	50 Gy/20 fx	Breast	Adjuvant	NA
21	Colon CA	IVA	50.4 Gy/28 fx	Abdomen	Palliation	Trifluridine + tipiracil
22	Lung CA	rIIIB	50 Gy/25 fx	Neck	Palliation	Osimertinib + durvalumab

COVID, coronavirus disease; RT, radiotherapy; CA, cancer; NA, not applicable.

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Table S2 Detailed patient profile in COVID-naive group

No.	Diagnosis	Stage	RT dose	RT field	Intention	Chemotherapy
1	Breast CA	IIB	42.5 Gy/16 fx	Breast	Adjuvant	NA
2	Colon CA	IV	30 Gy/10 fx	L5–S2	Palliation	Capecitabine
3	Prostate CA	IIIC	75.6 Gy/42 fx	Pelvis	Definitive	NA
4	Nasopharyngeal CA	II	70 Gy/35 fx	Head and neck	Definitive	Cisplatin
5	Tonsil CA	I	59.4 Gy/33 fx	Head and neck	Adjuvant	NA
6	Anaplastic astrocytoma	NA	60 Gy/30 fx	Brain	Adjuvant	Temozolomide
7	Nasopharyngeal CA	III	70 Gy/35 fx	Head and neck	Definitive	Cisplatin
8	Prostate	IIIB	70.2 Gy/39 fx	Pelvis	Adjuvant	NA
9	Breast CA	IA	50 Gy/20 fx	Breast	Adjuvant	NA
10	Breast CA	IA	50 Gy/20 fx	Breast	Adjuvant	NA
11	Breast CA	IA	50 Gy/20 fx	Breast	Adjuvant	NA
12	Breast CA	IA	50 Gy/20 fx	Breast	Adjuvant	NA
13	Cervical CA	IIB	60 Gy/30 fx + brachytherapy 30 Gy/6 fx	Pelvis	Definitive	Cisplatin
14	Breast CA	IIA	42.5 Gy/16 fx	Breast	Adjuvant	NA
15	Esophageal CA	rIII	48 Gy/24 fx	Mediastinum	Palliation	Paclitaxel + carboplatin
16	Hepatoma	rIVA	50.4 Gy/28 fx	Abdomen	Palliation	Sorafenib
17	Lung CA	IVB	30 Gy/10 fx	L1–L4	Palliation	Vinorelbine
18	Cervical CA	IIB	45 Gy/25 fx + brachytherapy 20 Gy/4 fx	Pelvis	Adjuvant	Cisplatin
19	Breast CA	IIIC	60 Gy/30 fx	Breast	Adjuvant	NA
20	Breast CA	IA	50 Gy/20 fx	Breast	Adjuvant	NA
21	Breast CA	IIA	50 Gy/20 fx	Breast	Adjuvant	NA
22	Breast CA	IA	50 Gy/20 fx	Breast	Adjuvant	NA

COVID, coronavirus disease; RT, radiotherapy; CA, cancer; NA, not applicable.

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