



Impact of COVID-19 Pandemic on Carbon-Ion Radiation Therapy in Japan: A Japanese National Registry Study

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ABSTRACT

Purpose: This study aimed to investigate the impact of the COVID-19 pandemic on carbon-ion radiation therapy (CIRT) in Japan by evaluating patient numbers and treatment trends from 2019 to 2022.

Patients and Methods: Data from 5 CIRT facilities were analyzed, encompassing a total of 13 224 patients treated over the 4-year period. Patient demographics, cancer types, treatment protocols, and adherence to national health insurance coverage were examined. The study period was divided into unaffected (2019), significantly affected (2020–2021), and poststabilization (2022) phases, corresponding to progression of the pandemic. For monthly analysis, the period during which a state of emergency was declared by the Japanese government was defined as the pandemic period.

Results: Prostate cancer comprised the majority of CIRT cases (62.4%), followed by hepatocellular carcinoma, bone and soft tissue tumors, locally advanced pancreatic cancer, and nonsquamous cell carcinoma of the head and neck. Despite the pandemic, the annual reduction in CIRT patients remained < 5%, suggesting treatment continuity. Analysis of monthly treatment figures revealed a significant reduction in the number of patients with nonprostate cancers treated during the state of emergency, while a reduction in the number of prostate cancer treatments was observed approximately 6 months later. Although the number of COVID-19 patients continued to increase after 2022, the number of patients receiving CIRT increased after the state of emergency was declared. **Conclusion:** Although there was a reduction in monthly CIRT patient numbers during the COVID-19 pandemic, yearly analysis revealed that this amounted to < 5%.

Introduction

COVID-19, caused by the SARS-CoV-2, spread worldwide from 2020. In Japan, the first case of COVID-19 was reported on January 16, 2020. Between 2020 and 2021, the Japanese government declared a "state of emergency" 4 times, requiring people to refrain from non-essential activities.^{1,2} This had a serious impact on the social system, including the health care system.^{3,4}

The number of cancer screenings and surgeries fell during this period, reflecting the impact of the pandemic.^{5–7} In the field of radiation therapy, treatment for patients who could afford to wait and exploration of

hypofractionation were considered between 2020 and 2021.^{8,9} Compared with x-ray radiation therapy, carbon-ion radiation therapy (CIRT) can be completed in a shorter time.¹⁰ While the number of facilities providing CIRT has increased worldwide, Japan still has the most.¹¹ Since 2016, Japan has been conducting prospective registration trials for all cases, thereby enabling assessment of the number of patients treated with CIRT throughout the whole country.¹² The beneficial characteristics of CIRT, which include short treatment times, walk-in availability, and minimal invasiveness, were useful during the pandemic phase of COVID-19.

The aim of this study was to investigate the impact of COVID-19 on CIRT delivery. To do this, we evaluated the number of CIRT patients

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treated during the unaffected year of 2019, the significantly affected years of 2020-2021, and the poststabilization period of 2022. Additionally, we assessed the cancer types and related CIRT protocols in Japan.

Materials and methods

Data source for carbon-ion radiation therapy patients

Multicenter, prospective observational registry data collected by the Japan Carbon-Ion Radiation Oncology Study Group were analyzed. Although Japan Carbon-Ion Radiation Oncology Study Group includes all 7 current CIRT facilities in Japan, only data from 5 institutions, collected during 2019-2022, were used. These were SAGA-HIMAT Foundation (HIMAT, Saga), the National Institutes for Quantum and Radiological Science and Technology (Chiba), the Ion Beam Therapy Center, Hyogo Ion Beam Medical Center (HIBMC, Hyogo), Gunma University Heavy Ion Medical Center (GHMC, Gunma), and the ion beam Radiation Oncology Center in Kanagawa (i-ROCK, Kanagawa). The other 2 facilities were excluded because their operational start dates (in 2018 and 2021) coincided with the COVID-19 pandemic. Tumors were treated using 23 protocols for which the Japanese Society for Radiation Oncology defines dose fractionations for various cancer types. Furthermore, clinical trials, treatment of patients from abroad, and other cases not covered by the 23 protocols were categorized as "extra protocol." The protocol names and corresponding diseases in Japan are summarized in Table 1, which also includes information about whether CIRT is covered by national health insurance. The study was approved by the Institutional Review Board of Gunma University Hospital as an Opt-Out consent model (number: HS2023-133).

Data source for COVID-19 patients

The number of newly confirmed COVID-19 cases in Japan was assessed.¹³ The Japanese government declared a state of emergency to control the spread of COVID-19; this encouraged, rather than mandated, individuals and businesses to practice social distancing and

avoid nonessential activities.¹ In total, a state of emergency was declared 4 times in Tokyo, the first from April 7 to May 25, 2020, the second from January 8 to March 21, 2021, the third from April 25 to June 20, 2021, and the fourth from July 12 to September 30, 2021.

Statistical analysis

The number of treatments delivered monthly and annually was counted based on the start date of irradiation. Additionally, a 3-month moving average curve was used to represent the average value for the target month and the months before and after it. Differences in numerical variables were examined using the Wilcoxon rank sum test. A *P*-value < .05 was considered statistically significant. All statistical analyses were conducted using R version 4.3.3.¹⁴

Results

Number of carbon-ion radiation therapy patients

Over the 4-year period from 2019 to 2022, a total of 13 224 patients underwent CIRT across the 5 facilities (Table 2). The 5 most common cancers treated with CIRT were prostate cancer (8217 cases, 62.4%), hepatocellular carcinoma (862 cases, 6.5%), bone and soft tissue tumors (747 cases, 5.6%), locally advanced pancreatic cancer (686 cases, 5.2%), and nonsquamous cell carcinoma of head and neck (439 cases, 3.3%). Of the patients analyzed, 11 318 were male, 1906 were female, and the median age was 69.8 years. The highest median age was observed in patients with localized lung cancer (C-LU-1) (75.4 years, range: 45-93), while the youngest was seen in patients with locally advanced cervical cancer (C-GY-1) (53.2 years, range: 20-83). The facility with the highest treatment volume treated 4440 cases over 4 years, while the facility with the lowest treated 429 cases.

COVID-19 patients and Japan's state of emergency

Figure 1 shows the number of COVID-19 patients in Japan, alongside the periods during which a state of emergency was declared in the

Table 1
Protocols and national insurance coverage for carbon-ion radiation therapy.

Protocol	Type of cancer	Japan's NHI coverage date ^a
C-BS-1	Skull base tumor	2018/04
C-BS-2	Bone and soft tissue tumors	2016/04
C-BS-3	Bone and soft tissue tumors (head and neck)	2018/04
C-HN-1	Nonsquamous cell carcinoma of the head and neck and lacrimal gland cancer	2018/04
C-HN-2	Head and neck melanoma	2018/04
C-HN-3	Head and neck squamous cell carcinoma	2018/04
C-LU-1	Localized lung cancer	Not covered
C-LU-2	Locally advanced non-small cell lung cancer	Not covered
C-GE-1	Locally advanced esophageal cancer	Not covered
C-GE-2	Locally recurrent rectal cancer	2022/04
C-GE-3	Postoperative pelvic recurrence of colorectal cancer	2022/04
C-LI-1	Hepatocellular carcinoma	2022/04
C-LI-2	Intrahepatic cholangiocarcinoma	2022/04
C-LI-3	Resectable pancreatic cancer	Not covered
C-LI-4	Locally advanced pancreatic cancer	2022/04
C-GY-1	Locally advanced cervical cancer	2022/04
C-GY-2	Locally advanced endometrial cancer	Not covered
C-GY-3	Gynecologic melanoma	Not covered
C-UR-1	Prostate cancer	2018/04
C-UR-2	Renal cancer	Not covered
C-ME-1	Metastatic lung tumor	Not covered
C-ME-2	Metastatic liver tumor	Not covered
C-ME-3	Metastatic lymph nodes	Not covered
Extra protocol ^b	Others	Not covered

Abbreviation: NHI, national health insurance system.

^a Japan's NHI coverage date: information obtained in March 2024.

^b Extra protocol: clinical trials, treatment of patients from abroad, and other cases not covered by the 23 protocols.

Table 2

Number of patients treated with carbon-ion radiation therapy (2019–2022).

Protocol	Male	Female	Median age	Number of patients				Total
			(Min-max)	2019	2020	2021	2022	
C-BS-1	19	16	61 (31–80)	10	10	9	6	35
C-BS-2	453	294	63.4 (11–93)	198	213	160	176	747
C-BS-3	28	25	55.5 (18–93)	17	16	12	8	53
C-HN-1	233	206	61.7 (6–91)	119	105	93	122	439
C-HN-2	117	131	68.3 (15–92)	56	63	57	72	248
C-HN-3	52	25	70.1 (32–94)	26	15	18	18	77
C-LU-1	308	110	75.4 (45–93)	115	94	115	94	418
C-LU-2	49	12	73.4 (42–90)	8	12	14	27	61
C-GE-1	25	7	71.1 (57–89)	10	7	7	8	32
C-GE-2	75	32	61.9 (29–82)	25	14	23	45	107
C-GE-3	112	55	60.7 (33–87)	36	37	44	50	167
C-LI-1	664	198	73.4 (31–96)	186	193	177	306	862
C-LI-2	93	56	72.7 (41–92)	38	26	28	57	149
C-LI-3	8	5	74.4 (57–85)	2	8	3	0	13
C-LI-4	384	302	70.7 (37–93)	162	156	135	233	686
C-GY-1	0	86	53.2 (20–83)	13	23	14	36	86
C-GY-2	0	0	N/A	0	0	0	0	0
C-GY-3	0	11	69.1 (54–83)	1	2	3	5	11
C-UR-1	8217	0	71.1 (42–98)	1892	2149	1922	2254	8217
C-UR-2	14	2	65.8 (44–84)	3	0	6	7	16
C-ME-1	54	35	70.5 (50–89)	25	23	20	21	89
C-ME-2	111	50	66.4 (34–92)	34	30	47	50	161
C-ME-3	79	99	64.2 (33–90)	39	55	36	48	178
Extra protocol ^a	223	149	64.8 (5–95)	132	105	70	65	372
Total	11 318	1906	69.8 (5–98)	3147	3356	3013	3708	13 224

Abbreviation: N/A, not applicable.^a Extra protocol: clinical trials, treatment of patients from abroad, and other cases not covered by the 23 protocols.

capital city. The first patient was confirmed in January 2020, after which cases increased rapidly. The first state of emergency was declared from April 7, 2020 to May 25, 2020. Although the state of emergency did not enforce restrictions on outings, the government requested, rather than mandated, individuals and businesses to practice social distancing and refrain from nonessential activities. The increase in vaccination rates for COVID-19 since 2021 meant that the state of emergency concluded with the fourth declaration (from July 12, 2021 to September 30, 2021).

Impact of COVID-19 on carbon-ion radiation therapy

Analysis of yearly data (with 2019, when COVID-19 cases had not yet emerged in Japan, as the baseline) revealed a 7% increase in treatments in 2020, followed by a 4% decrease in 2021 and an 18% increase in 2022 (Figure 2). Even during the year with the lowest case count (ie, 2021), the reduction was < 5%. Prostate cancer accounted for approximately 60% of all cases treated; therefore, it was analyzed separately from other cancers. With respect to prostate cancer, there

was a 14% increase in treatments in 2020, a 2% increase in 2021, and a 19% increase in 2022. There was a reduction in 2021 relative to both 2020 and 2022; however, this was not evident when data were compared with the prepandemic year of 2019. By contrast, there was a 4% decrease in nonprostate cancer treatments in 2020, a 13% decrease in 2021, and a 16% increase in 2022. Figure 2 shows the changes in the number of people treated per year at each facility. The trends in most facilities were similar, with the greatest decline observed in 2021 and the greatest improvement in 2022. At HIBMC, patient numbers declined earlier than at other facilities because prostate cancer patients were not treated at this center. At Quantum and Radiological Science and Technology, which treats large numbers of patients from outside the region where it is located, patient numbers notably declined due to the significant impact of travel restrictions imposed by the state of emergency.

Figure 3 shows the monthly treatment numbers from 2019 to 2022, along with a 3-month moving average. Movement restrictions and other anti-COVID-19 measures were implemented in Japan following the declaration of a state of emergency. From May 2020 to September

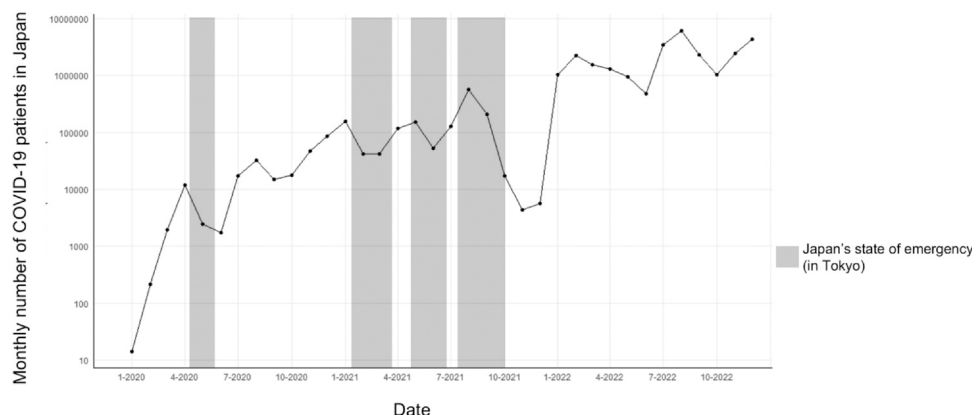
**Figure 1.** The trend in COVID-19 cases in Japan. The gray periods denote the states of emergency declared in Tokyo.



Figure 2. Number of patients treated per year with carbon-ion radiation therapy (CIRT) relative to the number in 2019. The figure shows both the total number of patients treated across all institutions as well as the number of patients treated at each individual institution. The blue bars represent the number of prostate cancer patients treated with CIRT, while the red bars indicate the number of nonprostate cancer patients treated with CIRT. The values are presented as relative to those of 2019, with the number of patients at each institution in 2019 normalized to 1.

2021, 4 separate declarations were made. Figure 4 compares the monthly treatment figures for the period before the state of emergency (January 2019–April 2020) with those during the state of emergency (May 2020–September 2021). For all cancers, the average number of CIRT patients before the state of emergency was 269.3, decreasing to 259.3 during the state of emergency ($P = .368$). For prostate cancer, the numbers of patients were 161.5 and 168.4, respectively ($P = .438$), while those for nonprostate cancers were 107.8 and 90.9, respectively ($P = .003$). Only nonprostate cancers showed a significant reduction in treatment numbers during the state of emergency. Although there was no significant reduction in prostate cancer treatments during the state of emergency, the monthly treatment numbers increased until October 2020, followed by a 45% decrease in December 2020 (compared with October 2020).

Discussion

To the best of our knowledge, this is the first report to examine the impact of the COVID-19 pandemic on CIRT treatments delivered by multiple facilities. In terms of annual treatment numbers, even in 2021 (which was the most affected year), the decrease was $< 5\%$. Examination of monthly treatment numbers revealed that the number of treatments for diseases other than prostate cancer fell quickly in response to the declaration of a state of emergency, although the number of prostate cancer treatments decreased approximately 6 months after the declaration. One reason for this could be the requirement for intermediate-risk and high-risk prostate cancer patients to undergo androgen deprivation therapy for approximately 5 to 8 months prior to CIRT.¹⁵ Since nonprostate cancers did not require any

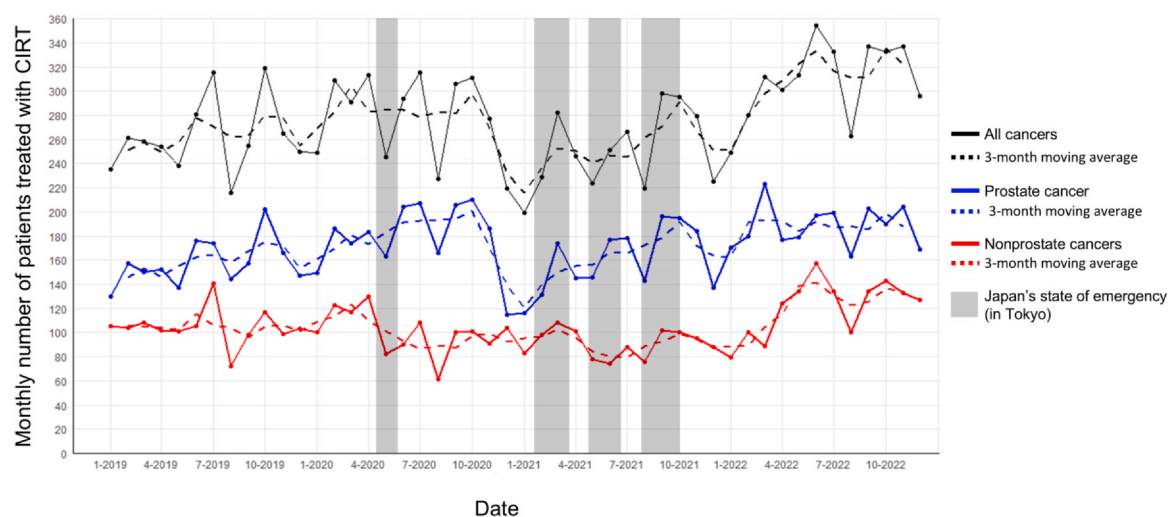


Figure 3. Trend in the number of patients treated with carbon-ion radiation therapy from 2019 to 2022 in Japan. The solid line shows the monthly trend, and the dashed line shows the 3-month average. Black represents all cancers, blue represents prostate cancer, and red represents nonprostate cancers. The gray periods denote the states of emergency in Tokyo.

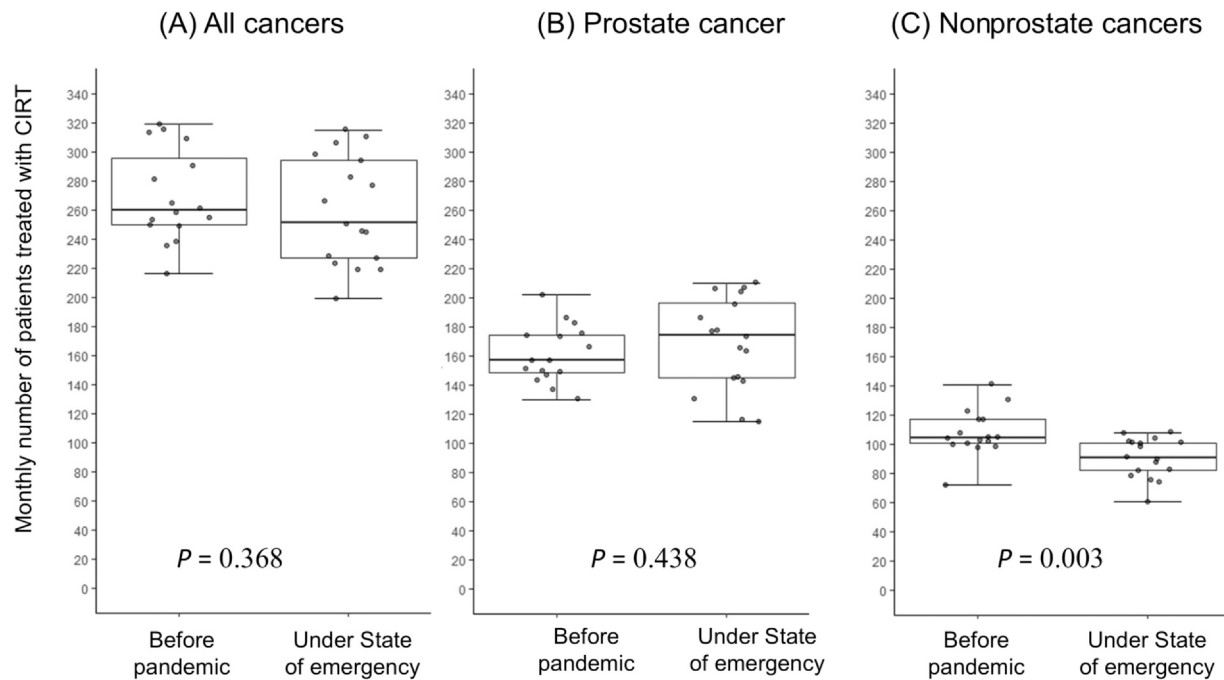


Figure 4. The monthly number of patients treated with carbon-ion radiation therapy in Japan. The number of treatments is split into the period before the pandemic (January 2019–April 2020) and during the state of emergency (May 2020–September 2021). (A) All cancers, (B) prostate cancer, and (C) nonprostate cancers.

such treatment prior to CIRT, the number of patients might have been affected earlier in the pandemic period. Additionally, while the number of COVID-19 cases continued to increase even after 2022, the number of CIRT patients also increased. This suggests that the state of emergency has a greater effect on treatments than the actual number of patients who contracted COVID-19.

A systematic review reported the recommendations for radiation therapy during the COVID-19 pandemic. These were (1) use hypofractionated regimens for therapeutic/palliative indications, (2) delay radiation therapy for several weeks or until the pandemic is over, (3) omit radiation therapy and replace it with alternative therapies or active surveillance, (4) apply safer patient setups and preparation protocols, (5) develop a telemedicine/telehealth service.¹⁶ For CIRT, hypofractionated regimens ranging from 1 day to 4 weeks were already in use and continued to be used throughout the pandemic. Concomitant chemotherapy was administered in the same manner as before the COVID-19 pandemic. Delaying or omitting radiation therapy was an option, but few patients were eligible due to the limited availability of other modalities, such as surgery, during the pandemic. For setup, patients were asked to wear surgical masks. The spacing between the chairs in the waiting room for CIRT was widened to maintain social distancing. During the treatment period, fever was checked every day. In principle, in accordance with government measures, CIRT was suspended not only for COVID-19-positive patients but also for those in close contact with COVID-19 patients during the isolation period and was resumed after the end of this period. Telemedicine is not an option for patients who need radiation therapy. The decrease in the number of patients treated was due to a decrease in the number of referred patients since CIRT facilities did not refuse patients who were indicated for CIRT. All CIRT facilities had almost the same measures for the prevention of COVID-19 infection as described above. The trends in patient numbers in most facilities were similar, with the greatest decline observed in 2021 and an improvement in patient numbers in 2022. However, a relatively earlier decline in patient numbers was observed at facilities with small numbers of prostate cancer patients, and facilities that treated a relatively large proportion of patients from outside the facility's region were more affected by travel restrictions due to the state of emergency.

Several studies have examined the impact of COVID-19 on health care in Japan. Data from hospital-based cancer registries covering > 70% of newly diagnosed cases suggest that there was only a 1.9% reduction in the number of cancer treatments in 2020 when compared with the previous 4 years; however, when viewed monthly, the data suggest a 22% reduction in May 2020.⁵ These data appear to agree with our own data, suggesting that the number of CIRT patients treated for nonprostate cancers decreased in May 2020. The registry data also suggested an 8.1% to 24.3% reduction in the number of cancers detected by cancer screening in 2020. Although prostate cancer screening was not mentioned specifically in the report, it is highly likely that the number of prostate cancers detected by cancer screening also decreased. Another report using the national clinical database illustrated a 5% reduction in thoracic surgeries in 2020. The monthly number of surgeries for primary lung cancer decreased from May of that year.⁶ Similarly, another study reported a 19.0% reduction in the number of distal gastrectomies performed for gastric cancer and an 8.6% reduction in anterior resections for rectal cancer, during the pandemic period; the number of these surgeries also showed a sharp decline from May 2020.¹⁷ However, while our study defines the period of emergency declarations as “the pandemic period,” previous studies did not have consistent criteria for defining the pandemic period. Moreover, most previous reports only included data collected up until 2020 or 2021, with few including data from 2022.

Several reports have examined the impact of COVID-19 on the delivery of x-ray radiation therapy in Japan. According to a survey conducted at 184 facilities during the first emergency declaration, 39.8% answered “Yes” to the question “Have you postponed the start of RT when possible?”¹⁸ Multiple surveys conducted at different time points showed that 98.7% answered “None” to the question “Postponed treatment to patients?” in June 2021. Furthermore, in May 2020, 41.2% of facilities answered “decrease” and 4.0% answered “increase,” to a question related to “The number of patients receiving radiotherapy,” whereas in June 2021 these percentages improved to 30.7% and 16.8%, respectively.¹⁹ It may be that the use of hypofractionated regimens gave CIRT an advantage over x-ray radiation therapy during the COVID-19 pandemic; however, a quantitative comparison with the number of x-ray therapy patients is needed to confirm this.

Our data also revealed the cancer types and number of patients treated with CIRT at multiple facilities in Japan. Approximately 60% of patients had prostate cancer. Among the top 5 diseases, prostate cancer, bone and soft

tissue tumors, and head and neck nonsquamous cell carcinomas were covered by national health insurance as of January 2019. From April 2022, hepatocellular carcinoma and locally advanced pancreatic cancer were also covered. The monthly average number of patients treated for hepatocellular carcinoma and locally advanced pancreatic cancer increased by 1.8 to 1.9-fold after the introduction of national health insurance coverage. In Japan, patients are required to pay a prefixed ceiling amount to cover medical expenses; this ceiling is dependent on the patient's income and age²⁰; therefore, the number of patients treated is dependent on whether their cancer type is covered by national health insurance.

Other countries have reported the effects of the COVID-19 pandemic on the number of patients undergoing particle therapy. Similar to our study, policies such as lockdowns and travel restrictions had significant effects on patient numbers.²¹ A survey comparing the number of treatments at 9 European institutions up until February 2021 showed that the number of patients undergoing proton therapy and CIRT did not significantly decrease during the pandemic.²² In our study, patient numbers just started to decline in 2021, indicating a slight difference in the study periods, making the subsequent changes in treatment numbers interesting to observe. However, careful consideration is required when interpreting the overall evaluation because several institutions appeared to be in the early stages after establishing the facility, with fewer than 100 cases in the year of comparison and more than a 2-fold increase in cases during the pandemic period. Additionally, differences in health care systems across countries also make direct comparisons difficult.

This study has several limitations. First, it was difficult to exclude factors other than COVID-19 that may have influenced the number of treated patients; however, the decrease since May 2020 was consistent with observations for other modalities, suggesting that the first state of emergency had a significant impact. Additionally, the inclusion of data from multiple facilities may have masked facility-specific impacts. Second, there is no strict definition of the COVID-19 pandemic period. While the number of COVID-19 cases continued to increase after 2022, the state of emergency ended in 2021, after which restrictions on social activities were tapered. In this study, we defined the pandemic period as that covered by the state of emergency.

In summary, while there were periods during which the number of monthly CIRT treatments fell during the COVID-19 pandemic, yearly analysis suggests that the overall total amounted to < 5%.

Ethical approval

All patient data were collected under an internal review board-approved protocol.

Author Contributions

Nobuteru Kubo: Methodology, Visualization, Formal analysis, Data curation, Writing the original draft. Toshiki Ozawa: Visualization, Formal analysis, Data curation, Writing the original draft. Yoshiyuki Shioyama, Shigeru Yamada, Hiroyuki Katoh, Tomoaki Okimoto: Investigation, Resources. Tatsuya Ohno: Conceptualization, Project administration.

Declaration of Conflicts of Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Hiroyuki Katoh reports financial support was provided by Toshiba Energy Systems & Solutions Corporation. If there are other authors, they declare that they have no known competing financial interests or

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