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Cost-effectiveness of carbon-ion radiotherapy versus stereotactic body radiotherapy for non-small-cell lung cancer

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Abstract

Carbon-ion radiotherapy (CIRT) for clinical stage I non-small-cell lung cancer (NSCLC) is used as an advanced medical treatment regimen in Japan. Carbon-ion radiotherapy reportedly aids in achieving excellent treatment outcomes, despite its high medical cost. We aimed to compare CIRT with stereotactic body radiotherapy (SBRT) in terms of cost-effectiveness for treating clinical stage I NSCLC. Data of patients with clinical stage I NSCLC treated with CIRT or SBRT at Gunma University between 2010 and 2015 were analyzed. The CIRT and SBRT groups included 62 and 27 patients, respectively. After propensity-score matching, both groups comprised 15 patients. Life year (LY) was used as an indicator of outcome. The CIRT technical fee was 3 140 000 JPY. There was no technical fee for the second CIRT carried out on the same organ within 2 years. The incremental cost-effectiveness ratio (ICER) was calculated by dividing the incremental cost by the incremental LY for 5 years after treatment. Sensitivity analysis was applied to evaluate the impact of LY or costs of each group on ICER. The ICERs were 7 491 017 JPY/LY and 3 708 330 JPY/LY for all patients and matched patients, respectively. Hospitalization and examination costs were significantly higher in the CIRT group, and the impact of the CIRT technical costs was smaller than other costs and LY. Carbon-ion radiotherapy is a cost-effective treatment approach. However, our findings suggest that reducing excessive costs by considering the validity and necessity of examinations and hospitalizations would make CIRT a more cost-effective approach.

KEYWORDS
carbon ion radiotherapy, cost-effectiveness analysis, health-care cost, non-small-cell lung cancer, stereotactic body radiotherapy

1 | INTRODUCTION

Lung cancer is the third highest cancer morbidity and the leading cause of cancer-related death in Japan.[1] It is possible to cure early-stage lung cancer incidentally detected by imaging studies or other methods, suggesting the importance of early cancer detection.[2] Surgery is offered as a curative treatment for early-stage lung cancer.[3,4] However, many patients are not eligible for surgical treatment for various reasons, such as deterioration of pulmonary or cardiac function.[5] Furthermore, as the number of older adult patients increases in Japan,[6] less-invasive treatment strategies are becoming increasingly necessary.

Carbon-ion radiotherapy has the advantage of the Bragg peak and minimal lateral scattering, enabling a high dose to be administered to the tumor while reducing the dose to the normal lung tissue. In addition to this advantageous physical property, the biological property of CIRT, in terms of high linear energy transfer, elicits more efficient tumor cell killing.[7-9] Therefore, CIRT is a promising treatment strategy. An excellent treatment outcome of CIRT for clinical stage I NSCLC was proposed in a Japanese multicenter study with a 3-year overall survival rate of 83.6% and a 3-year local control rate of 88.6%.[10] At present (September 2021), CIRT for clinical stage I NSCLC is not covered by the national health insurance but is used as an advanced medical treatment in Japan.[11] However, CIRT is more expensive than other treatment options because it requires higher costs for the construction and operation of the accelerator system.[7,12]

Stereotactic body radiotherapy, a radiotherapy technique that enables many beams to concentrate on the tumor, has also been reported to have satisfactory treatment outcomes for patients with clinical stage I NSCLC that is not amenable to surgical treatment.[13]

A comparison between patients who received CIRT at GHMC and those who received SBRT at Gunma University Hospital showed that the CIRT group was associated with significantly better overall survival in all patients before propensity-score matching (PSM) and matched patients after PSM.[14] Their study suggested the superiority of CIRT over SBRT in terms of treatment effectiveness.

Health economic evaluation is necessary to make decisions regarding health-care resource allocation.[15] Economic evaluation is defined as "a comparative analysis of alternative courses of action in terms of both their costs and their consequences."[16]

Although CIRT is expensive, it has the excellent therapeutic effects described above. Given the economic situation in Japan and the recent escalation in medical costs,[17] cost-effectiveness analysis is necessary to determine whether it is appropriate for the costs of CIRT to be covered by health insurance in the future. Regarding the cost-effectiveness of CIRT, there are currently few reports evaluating its cost-effectiveness for clinical stage I NSCLC, despite previous rectal cancer studies.[18] Therefore, the purpose of this study was to examine the validity of CIRT for clinical stage I NSCLC from the viewpoint of medical economics. The comparative technology for health economic evaluation is defined as "a medical technology that is widely used in clinical practice, and that is expected to be the most replaceable when the concerned technology is introduced."[19] Thus, we considered that it was appropriate to use SBRT as the comparative technology in this study. For these reasons, we compared CIRT with SBRT from the viewpoint of cost-effectiveness.

2 | MATERIALS AND METHODS

2.1 | Study design and patients

This study was undertaken in compliance with the standards of the Declaration of Helsinki and was approved by the Gunma University Institutional Review Board (registration no. HS2018-171). The need for written informed consent was waived due to the study's retrospective observational nature, but all the participants or their relatives had the opportunity to opt out.

The analysis was undertaken on the same patients as those analyzed by Miyasaka et al,[14] that is, patients with clinical stage I NSCLC treated with CIRT at GHMC or treated with SBRT at Gunma University Hospital from June 2010 to December 2015. The eligibility and exclusion criteria, as well as the patient characteristics and the PSM procedures, are described in their report. The patients had clinical T1a-2aN0M0 (UICC, 7th edition) and peripheral disease. The CIRT and SBRT groups included 62 patients and 27 patients, respectively. The CIRT group had significantly more patients of younger age and with larger tumors before PSM. Propensity-score matching was carried out using the following covariates: age, sex, ECOG performance status, Charlson comorbidity index, smoking status, Brinkman index, presence of chronic obstructive pulmonary disease, presence of interstitial pneumonia, T stage, pathological diagnosis, and calendar year of treatment. After PSM, both the CIRT group and the SBRT group included 15 patients. The total dose prescribed to the isocenter was 52.8 Gy or 60.0 Gy (relative biological effectiveness) in four fractions over 1 week for CIRT and 48 Gy in four fractions over 1 week for SBRT.

2.2 | Data on outcomes

Although the guidelines for the economic evaluation of health-care technologies in Japan recommend QALY as an index of outcome,[19] we used LY as an alternative indicator because data on QOL in the SBRT group were unavailable, as SBRT is carried out in a clinical practice setting. The LY was calculated from data on the overall survival rate of each group in the aforementioned report.[14] Particularly, the area under the Kaplan-Meier curve was defined as LY. The upper and lower limits of LY were also calculated from the curve showing the 95% CI of the overall survival rate. The analysis period was set to 5 years.

2.3 | Data on costs

Data on technical fees for CIRT, health insurance medical fees, and out-of-insurance medical costs were extracted from patient records

stored at Gunma University Hospital. The cost of the diagnosis procedure, along with the hospitalization costs, was converted into fee-for-service-based medical costs. We extracted the data 2 months before the start of treatment up to October 2020.

Gunma University Heavy Ion Medical Center charges a CIRT technical fee of 3 140 000 JPY, as mentioned above. If a second CIRT is carried out on the same organ within 2 years from the first CIRT, the second technical fee is free and considered one series of treatments. The analysis in this study was undertaken with this rule applied because it might have influenced patients' decision-making. We also carried out an analysis assuming that the CIRT technical fee was charged at 1 600 000 JPY. The CIRT technical fee for common cancer, namely, prostate cancer, covered by the current health insurance in Japan, is 1 600 000 JPY.[20]

We calculated the total cost as an indicator of cost, defined as the cost from the preparatory period to 5 years after treatment initiation. The preparatory period was defined as a period of 4 weeks before the start of treatment. The mean value and the minimum and maximum values of the costs during this period were used for the analysis.

The mean cost difference for each item in each group was calculated, and the significance was evaluated using the *t* test. A *P* value of less than .05 was considered to indicate statistical significance.

2.4 | Actual measurement-based analysis

Cost-effectiveness analysis was carried out using TreeAge Pro Healthcare 2021 (TreeAge Software) according to the following principles: if either CIRT or SBRT has both better outcomes and lower total cost, then the treatment was regarded as "dominant," and no further analysis was performed. In this patient cohort, CIRT was considered "dominant" if the total cost of CIRT was less than those of SBRT because it is known that the CIRT group had a significantly better overall survival rate than the SBRT group.[14] Cost-effectiveness analysis was carried out when the total cost of CIRT was higher than that of SBRT. The ICER is provided by the following formula:

$$ICER = \frac{(C_i - C_c)}{(E_i - E_c)},$$

where C_i is the cost in the intervention group, C_c is the cost in the control group, E_i is the effect in the intervention group, and E_c is the effect in the control group. Therefore, ICER is calculated by dividing the incremental total cost by the incremental LY in this study.

2.5 | Sensitivity analysis

Considering the uncertainty, one-way and probabilistic sensitivity analyses were applied to evaluate the robustness of this analysis.

The variables of the one-way sensitivity analysis included the mean total cost of the CIRT group, mean total cost of the SBRT group, LY of the CIRT group, and LY of the SBRT group. The total cost was indicated as between the minimal and maximum values, and LY between the upper and lower limits, calculated from the 95% CI curve of the overall survival rate as described above.

In the probabilistic sensitivity analysis, random numbers were generated to calculate the ICER according to the triangular distribution, where the mean value of the total cost and the point estimate of LY were assigned as the expected values. The range of the triangular distribution was set to be the same as that used in the one-way sensitivity analysis. The reason for applying the triangular distribution was that the total cost and LY were not normally distributed, causing difficulty in applying other distributions. The number of trials was set to 10 000.

Another sensitivity analysis was carried out to evaluate the impact of the CIRT technical fee on ICER. The CIRT technical fee was moved between 1 600 000 JPY and 3 140 000 JPY. In this analysis, the CIRT technical fee and the other costs were separated. The other costs were moved in the same way as those in the above-described sensitivity analysis. The CIRT technical fee and the other costs were then added to calculate the total cost.

3 | RESULTS

3.1 | Follow-up information of the entire cohort

Fifty-one patients in the CIRT group and 11 patients in the SBRT group were followed up at our institution for at least 5 years or until death and were not treated for lung cancer at other institutions, except for terminal care. Seven patients in the CIRT group and four in the SBRT group received at least a part of the treatment (including surgery, chemotherapy, and radiotherapy) for lung cancer recurrence at other institutions within 5 years. The remaining four patients in the CIRT group and 12 in the SBRT group had no recurrence and could not be followed up at our institution for 5 years due to refusal or difficulty visiting a hospital. None of the patients were treated for treatment-induced adverse events at other institutions, as far as we know.

Twelve of 62 patients in the CIRT group received a second CIRT, and one of them received a third CIRT within 5 years after initial treatment. In addition, two patients in the CIRT group received SBRT. Five of the 15 matched patients in the CIRT group received a second CIRT, and one received a third CIRT. In addition, one patient in the CIRT group received SBRT. One of 27 patients in the SBRT group received CIRT within 5 years after initial treatment. This patient was included in the 15 matched patients. No patients in the SBRT group received a second SBRT. Except for three with local recurrence, all patients received a second or third treatment for out-of-field recurrence or metachronous double cancer.

3.2 | Life year in each group

The LY in all patients before PSM (89 patients) as determined from the Kaplan-Meier curve was 4.330 (95% CI, 3.986-4.706) in the CIRT group and 3.812 (95% CI, 3.234-4.582) in the SBRT group, with an LY difference of 0.518. The LY in matched patients after PSM (30 patients) was 4.515 (95% CI, 3.954-4.999) in the CIRT group and 3.358 (95% CI, 2.590-4.670) in the SBRT group, with an LY difference of 1.157.

3.3 | Medical costs

The mean total cost was 5 597 585 JPY (range, 3 686 840-10 762 790 JPY) in the CIRT group and 1 717 238 JPY (range, 702 040-6 525 640 JPY) in the SBRT group for all patients. The mean preparatory cost was 378 855 JPY (6.7%) in the CIRT group and 93 235 JPY (5.4%) in the SBRT group. The mean cost for the first year from the start of treatment was 3 940 972 JPY (70.4%) in the CIRT group and 981 479 JPY (57.2%) in the SBRT group, accounting for the large proportion of the total cost, especially in the CIRT group (Figure 1A and Table 1). In the 30 matched patients, the mean total cost was 5 719 532 JPY (range, 3 801 030-8 954 750 JPY) in the CIRT group and 1 428 994 JPY (range, 702 040-4 922 820 JPY) in the SBRT group (Figure 1B and Table 1). There was a significant and large difference of more than 100 000 JPY between each group in terms of hospitalization fee, image examination fee, and laboratory test fee for all patients and matched patients (Table 2).

The total cost tended to be higher in patients who received treatment at other institutions and lower in patients who were lost to follow-up (Figure S1) after collating the follow-up status and the total cost. Although the patient who incurred the most cost in the CIRT group received palliative radiotherapy for bone metastases at another institution, he received almost all other treatments at our hospital.

Assuming that the CIRT technical fee was 1 600 000 JPY, the mean total cost was 3 983 069 JPY (range, 2 146 840-9 222 790 JPY) in the CIRT group and 1 660 201 JPY (range, 702 040-6 525 640 JPY) in the SBRT group for all patients (Figure S2A and Table S1). For matched patients, the mean total cost was 3 974 199 JPY (range, 2 261 030-7 414 750 JPY) in the CIRT group and 1 326 328 JPY (range, 702 040-3 382 820 JPY) in the SBRT group (Figure S2B and Table S1).

3.4 | Incremental cost-effectiveness ratio

The ICER was 7 491 017 JPY/LY for all patients and 3 708 330 JPY/LY for matched patients. Conversely, assuming a CIRT technical fee of 1 600 000 JPY, the ICER was 4 484 303 JPY/LY for all patients and 2 288 566 JPY/LY for matched patients.

3.5 | Sensitivity analysis

The results of the one-way sensitivity analysis are shown in Figure 2. The ICERs tended to be more influenced by the effectiveness (LY) of the CIRT group in all patients. The impact of LY of the CIRT group was relatively small in matched patients, and it became even smaller, assuming a CIRT technical fee of 1 600 000 JPY (Figure S3). The SBRT was considered "dominant" for CIRT when the LY in the SBRT group moved to the upper limit.

Figure 3 shows the acceptability curves obtained from the probabilistic sensitivity analysis. When willingness to pay (WTP, the threshold of ICER) was 4 000 000 JPY and 8 000 000 JPY, the acceptability for CIRT at WTP was 22.1% and 50.3% in all patients and 49.7% and 81.6% in matched patients, respectively. However, these values were 45.9% and 68.6% in all patients and 67.9% and 87.6% in matched patients, respectively, assuming a CIRT technical fee of 1 600 000 JPY (Figure S4).

Figure 4 shows the tornado diagrams and acceptability curves of the result of another sensitivity analysis where the CIRT technical fee ranged between 1 600 000 JPY and 3 140 000 JPY. According to the tornado diagram, the ICER fluctuated between 4 663 658 and 8 015 478 JPY/LY in all patients and between 3 028 660 and 4 754 755 JPY/LY in matched patients. The intersections of the acceptability curve were located at almost the same range as the results of the tornado diagram. Thus, the impact of the CIRT technical fees on ICER was smaller than that of the LY in the CIRT group and other costs in each group.

4 | DISCUSSION

Both CIRT and SBRT are minimally invasive treatments for clinical stage I NSCLC. Favorable outcomes from SBRT have been shown to date, and SBRT has been widely used as a treatment covered by insurance in Japan.[13,21-24] In addition, several reports have shown better cost-effectiveness for SBRT than for other treatments, including surgery.[25-27] Currently, CIRT is performed as an advanced medical treatment, requiring a more expensive technical fee than that for SBRT. However, a retrospective analysis by Miyasaka et al[14] showed superior treatment outcomes following CIRT than those following SBRT. Furthermore, CIRT reduced the dose to normal in lung tissues compared to SBRT, suggesting that CIRT was a less invasive treatment.[28] It is expected that the demand for CIRT will increase in the future, especially for patients with impaired respiratory function or for the elderly. Carbon-ion radiotherapy must be covered by health insurance in Japan for more Japanese patients to benefit from CIRT. However, there is insufficient evidence to consider the validity and optimal price for health insurance coverage of CIRT for clinical stage I NSCLC. Grutters et al[29] developed a Markov model to compare CIRT and SBRT based on existing published reports. However, this comparison might provide insufficient evidence for health insurance coverage because they analyzed data only based on published
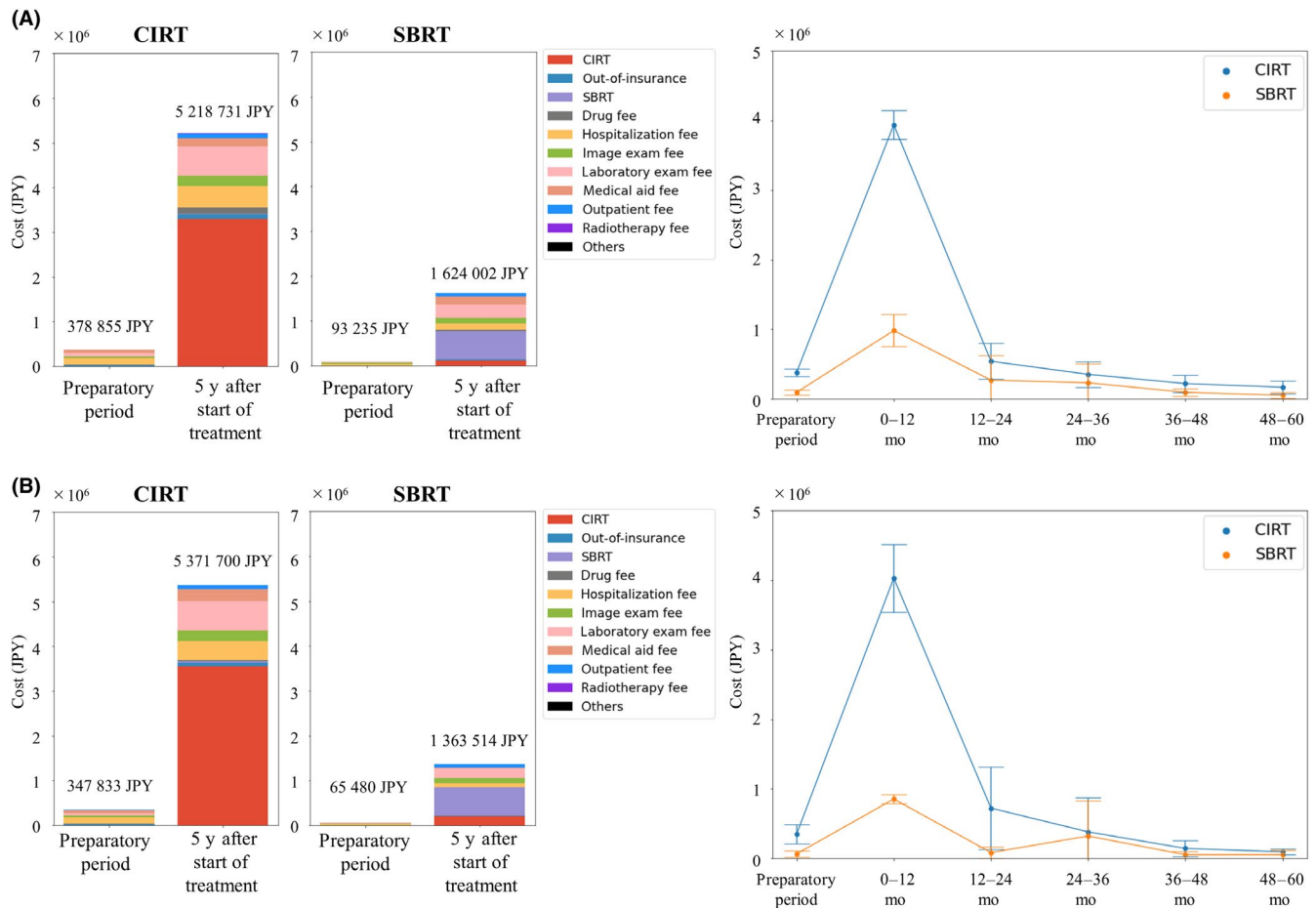
FIGURE 1 Left panels, mean cost and breakdown for the preparatory period and 5 years after treatment initiation in patients with non-small-cell lung cancer treated with carbon-ion radiotherapy (CIRT) or stereotactic body radiotherapy (SBRT). The preparatory period was defined as a period of 4 weeks before treatment. Right panels, time-series graphs showing the mean annual cost in each group. Error bars indicate 95% confidence intervals. A, All patients. B, Matched patients

TABLE 1 Mean medical costs in patients with non-small-cell lung cancer treated with carbon-ion radiotherapy (CIRT) or stereotactic body radiotherapy (SBRT)

		Preparatory period[a]	5 y after treatment initiation	1 y after treatment initiation	Total period[b]
Mean medical costs for all patients	CIRT	378 855 JPY	5 218 731 JPY	3 940 972 JPY	5 597 585 JPY
	SBRT	93 235 JPY	1 624 002 JPY	981 479 JPY	1 717 238 JPY
Mean medical costs for matched patients	CIRT	347 833 JPY	5 371 700 JPY	4 031 526 JPY	5 719 532 JPY
	SBRT	65 480 JPY	1 363 514 JPY	852 695 JPY	1 428 994 JPY

[a]Defined as a period of 4 weeks before treatment.
[b]Defined as the sum of the preparatory period and the first 5 years after treatment initiation.

reports, which caused many uncertainties. By contrast, our study can provide more substantial evidence because patients treated in the same institution were analyzed using the actual measurement data.

In this study, the actual measurement based on ICER was 7 491 017 JPY/LY for all patients and 3 708 330 JPY/LY for matched patients. Life year was used as an index of outcome in this study. Although LY has the advantage that it does not require QOL data, it has the disadvantage that it is difficult to interpret the results of

ICER, unlike QALY, which allows for absolute evaluation of ICER.[30] A questionnaire survey revealed that 41.0% of Japanese oncologists felt that the maximum allowable medical expenses for cancer treatment to prolong the life expectancy of patients by 1 year should be 4 000 000 JPY/LY or less, and another 39.8% answered that the fees should range from 4 000 000 to 8 000 000 JPY/LY.[31] In our analysis, ICER was less than 8 000 000 JPY/LY for all patients and less than 4 000 000 JPY/LY for matched patients, meeting the maximum allowable medical expenses for 39.8% and 80.8% of Japanese

TABLE 2 Mean itemized costs and differences between all patients and matched patients with non-small-cell lung cancer treated with carbon-ion radiotherapy (CIRT) or stereotactic body radiotherapy (SBRT)

	All patients				Matched patients			
	CIRT group (JPY)	SBRT group (JPY)	Cost difference (JPY)	P value	CIRT group (JPY)	SBRT group (JPY)	Cost difference (JPY)	P value
CIRT technical fee	3 291 935	116 296	3 175 639	<.001	3 558 667	209 333	3 349 334	<.001
Out-of-insurance fee	133 539	28 166	105 373	<.001	96 104	9592	86 512	.034
SBRT fee	20 323	630 000	609 677	<.001	42 000	630 000	588 000	<.001
Drug fee	134 549	30 574	103 975	.028	28 867	9485	19 382	.300
Hospitalization fee	636 236	177 927	458 309	<.001	585 933	111 135	474 798	.006
Image examination fee	267 335	149 301	118 033	.004	264 441	129 985	134 457	.016
Laboratory test fee	730 468	320 590	409 878	<.001	707 109	231 111	475 998	<.001
Medical aid fee	255 037	181 223	73 813	.543	336 535	20 107	316 429	.081
Outpatient fee	109 836	83 160	26 676	.163	98 875	78 247	20 629	.487
Radiotherapy fee	17 618	0	17 618	.083	0	0	0	–
Others	711	0	711	.042	1001	0	1001	.314

Note: Difference in the mean cost was assessed using the *t* test.
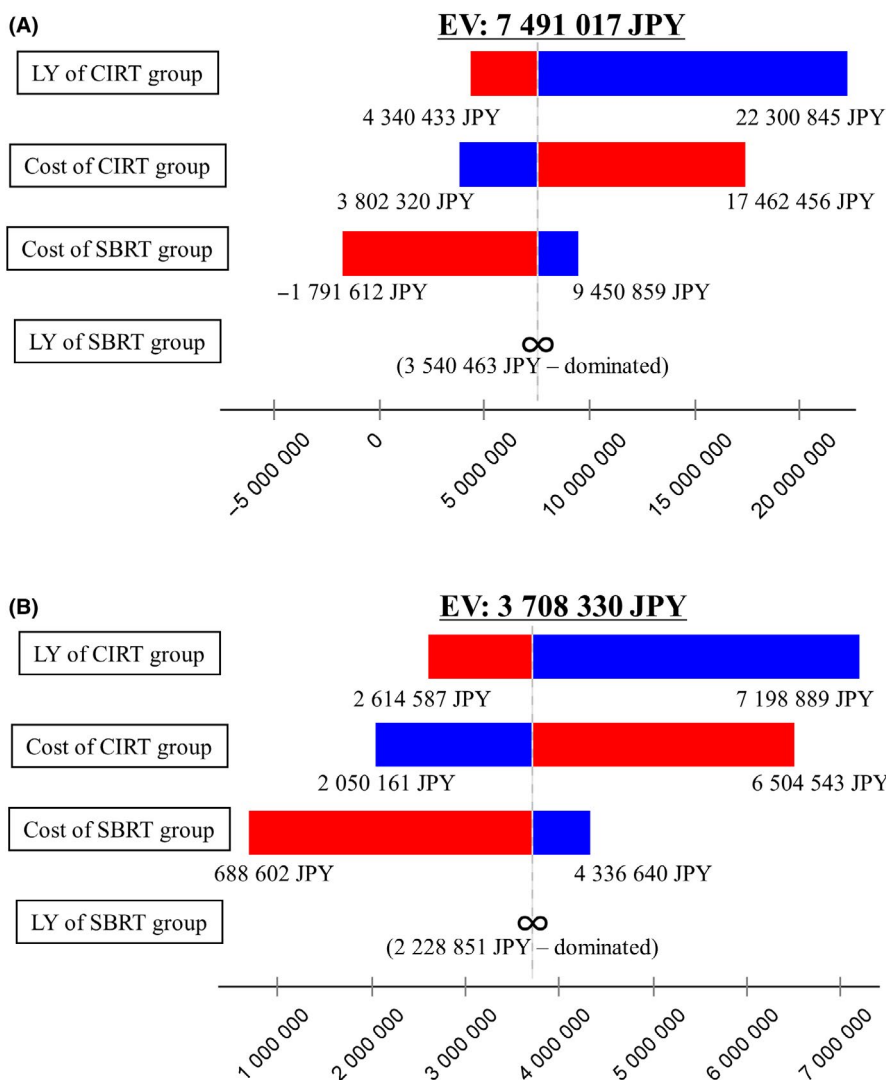

FIGURE 2 Tornado diagram showing the results of one-way sensitivity analysis in patients with non-small-cell lung cancer treated with carbon-ion radiotherapy (CIRT) or stereotactic body radiotherapy (SBRT). The items are arranged from the top in descending order of impact on incremental cost-effectiveness ratio (ICER). Bars show the range of the ICER for each value higher (red) and lower (blue) than the point estimate. The bar for life year (LY) of SBRT is not displayed because the CIRT is regarded as "dominated" against SBRT at the upper limit. A, All patients. B, Matched patients. EV, expected value
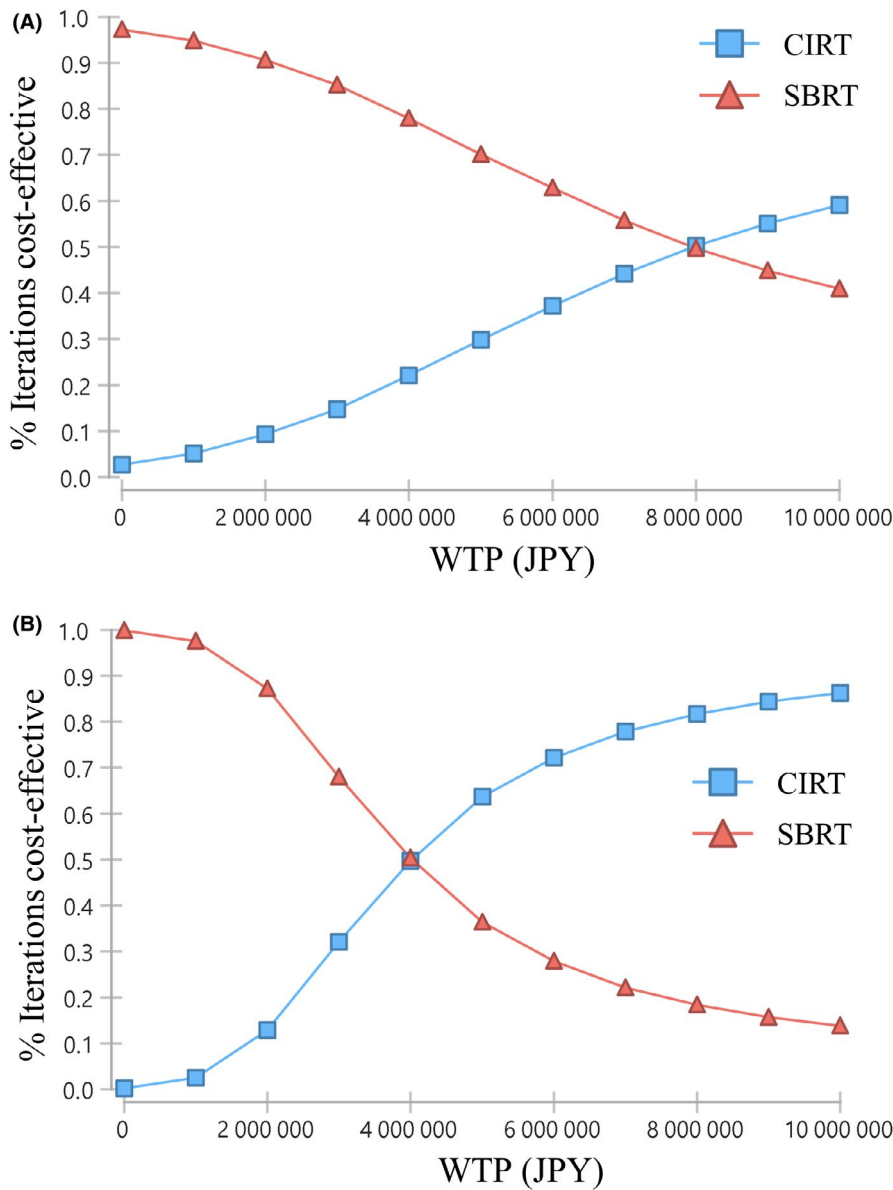
FIGURE 3 Acceptability curve showing the change in acceptability for willingness-to-pay (WTP) in the probabilistic sensitivity analysis of patients with non-small-cell lung cancer treated with carbon-ion radiotherapy (CIRT) or stereotactic body radiotherapy (SBRT). Plots were constructed for every WTP of 1 000 000 JPY in each graph. A, All patients. B, Matched patients

oncologists, respectively. Although this is a relatively subjective evaluation with a questionnaire survey, these results suggested that CIRT is cost-effective, especially for matched patients. Considering that the total cost was slightly higher in matched patients, the increase in the LY difference after PSM might have strongly influenced ICER. Furthermore, the CIRT group included more patients with larger tumors than the SBRT group in all patients before PSM, which might have decreased the LY in the CIRT group. Therefore, it was indicated that the PSM enabled a fair comparison in the cost-effectiveness analysis and lowered ICER.

The sensitivity analyses supported the results based on the actual measurement. The impact of LY and costs on ICER fluctuated depending on PSM or the CIRT technical fee (1 600 000 JPY or 3 140 000 JPY) in the one-way sensitivity analysis, probably because of the difference in LY before and after PSM and the relative change in the degree of influence of costs other than the CIRT technical

fee. In any case, the impact of the CIRT technical fee on ICER was smaller than the LY and the other costs, although there was a slight error from the actual measurement-based analysis because the CIRT technical fee and the other costs were calculated separately. The acceptability curve indicated that matching patient characteristics by PSM seemed to improve the acceptability for WTP over lowering the CIRT technical fee. Moreover, CIRT was carried out as a clinical study, whereas SBRT was undertaken in a clinical practice setting. Clinical trials require many examinations and frequent follow-ups according to protocols. In addition, a larger proportion of patients who are hospitalized for preparation or those that are treated for accidentally discovered diseases is estimated. Therefore, CIRT required more frequent pre- and posttreatment examinations, hospitalizations, and follow-up visits than SBRT, which led to higher total costs for the CIRT group. The ICER could be decreased with a similar frequency of examinations, hospitalizations, and follow-up in
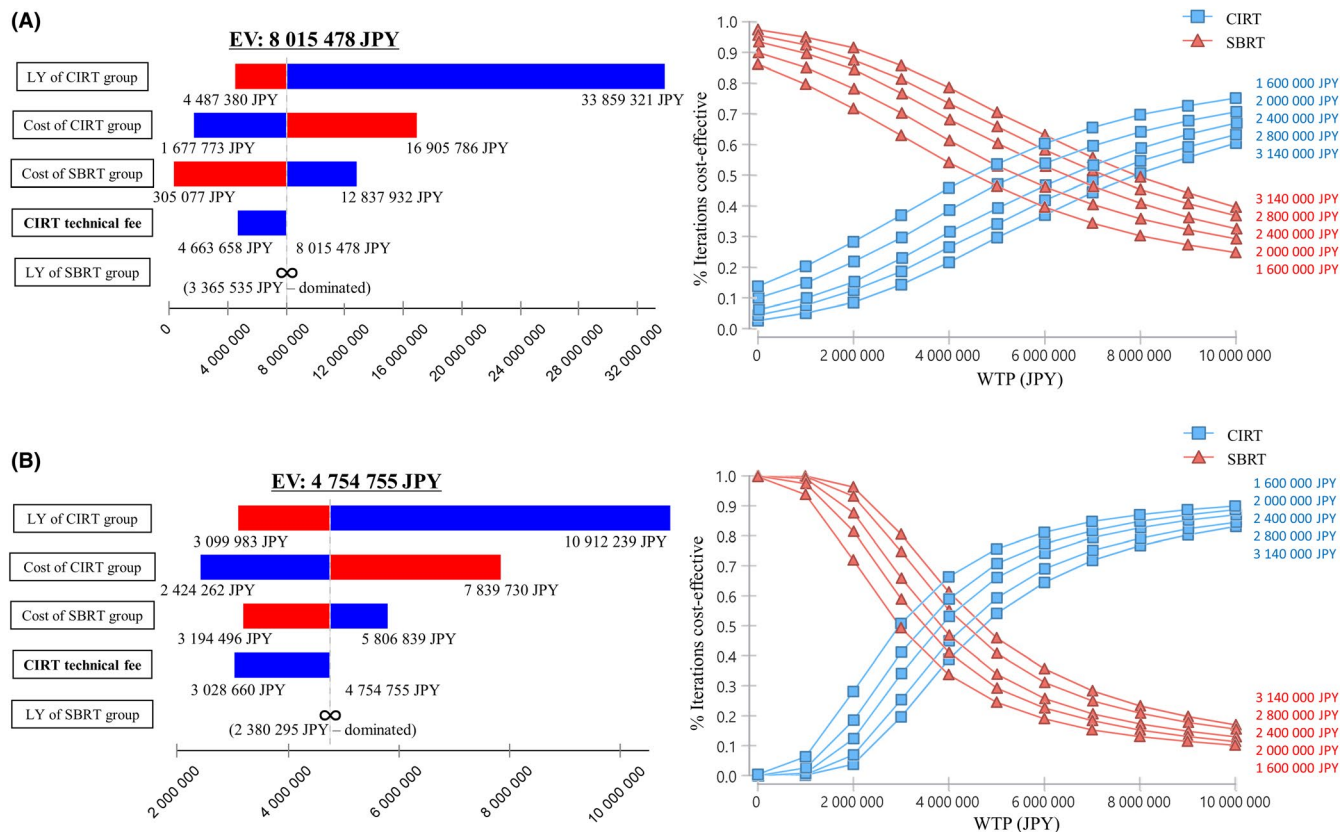
FIGURE 4 Left panels, tornado diagrams showing the results of one-way sensitivity analysis of carbon-ion radiotherapy (CIRT) and stereotactic body radiotherapy (SBRT) treatment for patients with non-small-cell lung cancer. The total cost was separated into the CIRT technical fee and other costs. The CIRT technical fee ranged between 1 600 000 JPY and 3 140 000 JPY. Right panels, the acceptability curves focusing on fluctuations in the CIRT technical fee. These figures are superpositions of the acceptability curves, assuming that the CIRT technical fees are 1 600 000 JPY, 2 000 000 JPY, 2 400 000 JPY, 2 800 000 JPY, and 3 140 000 JPY. A, All patients. B, Matched patients. EV, expected value

each group. Although CIRT was an expensive treatment in the short term, ICER was strongly influenced by factors such as the characteristics of the case group and costs other than the CIRT technical fees, including examination and hospitalization costs. Our findings suggested that CIRT was a cost-effective treatment. However, it can be more cost-effective by considering the validity and necessity of examinations and hospitalizations and reducing high costs as much as possible.

The largest limitation of this study is that the cost data used in this analysis do not include cost data in medical institutions other than Gunma University, because it was calculated from the accounting data preserved in Gunma University Hospital. Considerable costs might have been incurred in other medical institutions for some patients. It is desirable but difficult to collect the cost data from all medical institutions. In this study, follow-up and treatment at our institution were incompletely carried out in 11 patients in the CIRT group and 16 patients in the SBRT group. More patients in the SBRT group were lost to follow-up because SBRT was carried out in a clinical practice setting. Therefore, it is suggested that the total cost in the SBRT group might have been underestimated. Patients who received treatment at other institutions tend to have higher total costs because they had a recurrence. Their total cost will be even

higher if costs at other institutions are included. However, this cohort included a small proportion of patients, with seven in the CIRT group and four in the SBRT group. Most of the total cost of patients included in this study is expected to be within the range set in the sensitivity analysis. Therefore, it was indicated that the uncertainty caused by this limitation had at least no favorable effect on the CIRT group and could be evaluated by the sensitivity analysis.

Another limitation is that this is a single institutional retrospective study, which could have caused various uncertainties and biases. For example, the follow-up policies, regular examinations, treatment for recurrence, and the convenience of hospital visits can affect cost-effectiveness. In facilities with a higher frequency of follow-up or where more examinations and treatments are actively carried out for recurrence, the impact of the CIRT technical fee will be relatively small, and the ICER will be improved. These uncertainties and biases might not be appraised by the sensitivity analysis. Multi-institutional prospective studies are required to resolve these problems. Notwithstanding, no cost-effectiveness analysis dealing with CIRT and SBRT for clinical stage I NSCLC using actual measurement data has been reported. It is therefore inferred that this report is valuable in describing CIRT from the viewpoint of medical economics.

In addition, a randomized phase III trial that evaluates the dose escalation of SBRT has now been undertaken in Japan.[32] If an increased dose results in an improvement in local control, it could replace the standard doses of SBRT. In this case, the LY difference between the CIRT and the SBRT groups will become smaller, and the ICER will worsen. If the LY of the SBRT group exceeds that of the CIRT group, the SBRT group will be "dominant," as shown in our one-way sensitivity analysis. A novel dose-fractionation schedule has been devised for CIRT,[33] and the LY of the CIRT group could be improved in the future. Therefore, it is expected that the ICER will constantly change, and continuing the cost-effectiveness analysis will be necessary.

In conclusion, CIRT is a cost-effective treatment strategy for clinical stage I NSCLC. Reducing excessive costs by considering the validity and necessity of examinations and hospitalizations can make CIRT more cost-effective. Although the CIRT technical fee is high, the impact of the CIRT technical fee on ICER was small from a long-term perspective of 5 years. This study was based on the analysis of actual, measured data, and our data could be meaningful for assessing CIRT from the standpoint of medical economics in the future.

CONFLICT OF INTEREST

Tatsuya Ohno received a scholarship endowment from Hitachi, Ltd.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.