

## Scientific Article

# Cost-Effectiveness Comparison of Carbon-Ion Radiation Therapy and Transarterial Chemoembolization for Hepatocellular Carcinoma

Shohei Okazaki, MD, PhD,<sup>a,b</sup> Kei Shibuya, MD, PhD,<sup>a,\*</sup>  
Shintaro Shiba, MD, PhD,<sup>a,c</sup> Tomoyuki Takura, MD, PhD,<sup>d,e</sup> and  
Tatsuya Ohno, MD, PhD<sup>a,f</sup>

<sup>a</sup>Department of Radiation Oncology, Gunma University Graduate School of Medicine, Maebashi, Japan; <sup>b</sup>Department of Radiology, Gunma Prefectural Cancer Center, Ota, Japan; <sup>c</sup>Department of Radiation Oncology, Shonan Kamakura General Hospital, Kamakura, Japan; <sup>d</sup>Department of Health Care Services Management, Nihon University School of Medicine, Tokyo, Japan; <sup>e</sup>Department of Healthcare Economics and Health Policy, University of Tokyo, Tokyo, Japan; and <sup>f</sup>Gunma University Heavy Ion Medical Center, Showa-machi, Maebashi, Japan

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**Purpose:** Carbon-ion radiation therapy (CIRT) is a treatment option for patients with hepatocellular carcinoma (HCC) that results in better outcomes with fewer side effects despite its high cost. This study aimed to evaluate the cost-effectiveness of CIRT for HCC from medical and economic perspectives by comparing CIRT and transarterial chemoembolization (TACE) in patients with localized HCC who were ineligible for surgery or radiofrequency ablation.

**Methods and Materials:** This study included 34 patients with HCC who underwent either CIRT or TACE at Gunma University between 2007 and 2016. Patient characteristics were employed to select each treatment group using the propensity score matching method. Life years were used as the outcome indicator. The CIRT technical fee was ¥3,140,000; however, a second CIRT treatment on the same organ within 2 years was performed for free.

**Results:** Our study showed that CIRT was dominant over TACE, as the CIRT group had a higher life year (point estimate, 2.75 vs 2.41) and lower total cost (mean, ¥4,974,278 vs ¥5,284,524). We conducted a sensitivity analysis to validate the results because of the higher variance in medical costs in the TACE group, which demonstrated that CIRT maintained its cost effectiveness with a high acceptability rate.

**Conclusions:** CIRT is a cost-effective treatment option for localized HCC cases unsuitable for surgical resection.

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## Introduction

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death worldwide.<sup>1,2</sup> The treatment strategy is mainly determined based on the disease stage and hepatic function.<sup>3</sup> Although several treatment options, such as immunotherapy and molecular targeted therapy, are emerging,<sup>4,5</sup>

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\*Corresponding author: Kei Shibuya, MD, PhD;  
Email: [shibukei@gunma-u.ac.jp](mailto:shibukei@gunma-u.ac.jp)

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local therapies, including surgical resection and radiofrequency ablation (RFA), remain essential for localized HCC due to their curative potential.<sup>3,6,7</sup> However, many patients with HCC are ineligible for surgery and RFA owing to poor hepatic function or tumor size.<sup>3,8,9</sup> They frequently undergo transarterial chemoembolization (TACE), which leads to a higher incidence of local and intrahepatic recurrence, necessitating frequent retreatments.<sup>10</sup>

Carbon-ion radiation therapy (CIRT) is an emerging treatment option for HCC, offering enhanced tumoricidal effects due to its high linear energy transfer compared with x-rays. Its unique properties, such as the Bragg peak and reduced lateral scattering, result in a superior dose distribution over conventional x-ray treatments.<sup>11-14</sup> Thus, CIRT can be safely applied to various patients with localized HCC.<sup>15-19</sup> A single-institution retrospective study using propensity score matching (PSM) demonstrated that CIRT resulted in better outcomes than TACE (3-year overall survival rate, 88% in the CIRT group vs 58% in the TACE group).<sup>20</sup> Therefore, CIRT may be a promising treatment option for patients with localized HCC who are ineligible for surgery or RFA. However, the higher costs of constructing and operating an accelerator system make CIRT an expensive treatment option,<sup>21,22</sup> which may hinder its widespread use. Nevertheless, the superior local control and minimal adverse effects of CIRT may reduce long-term medical costs.

Health economic evaluations are essential for the optimal allocation of health care resources.<sup>23</sup> This evaluation should be conducted as “a comparative analysis of alternative courses of action, regarding both costs and consequences.”<sup>24p4</sup> Previous studies have shown that CIRT for clinical stage I non-small cell lung cancer and locally recurrent rectal cancer is cost effective in the long term compared with stereotactic body radiation therapy (SBRT) and conventional multimodality therapy, respectively.<sup>25,26</sup> If CIRT for HCC is also cost effective, concerns regarding medical costs can be alleviated. However, to the best of our knowledge, no current, robust, and conclusive data exist regarding the cost-effectiveness of CIRT for HCC. Therefore, this study aimed to evaluate the cost-effectiveness of CIRT for HCC from medical and economic perspectives. Furthermore, we compared CIRT with TACE, as TACE is a medical technology that is extensively used in clinical settings and is considered the most likely to be replaced by the introduction of new technologies, such as CIRT.<sup>27</sup>

## Methods and Materials

### Study design and patients

This study was conducted in compliance with the standards outlined in the Declaration of Helsinki and was

approved by the Gunma University institutional review board before the commencement of the study (registration number: HS2018-271). Informed consent was obtained from all participants or their guardians.

We analyzed the cost and outcome data of 34 Japanese patients with localized HCC treated with either CIRT or TACE at Gunma University between 2007 and 2016. Patients were selected using the PSM method as described in a previous study by Shiba et al.<sup>20</sup> Each treatment group comprised of 17 patients. The patient characteristics in each group were matched according to age, sex, performance status, tumor size, Child-Pugh class, Barcelona Clinic Liver Cancer stage, and alpha-fetoprotein level. The eligibility and exclusion criteria are described in this report.

### Data on outcome

We used the Kaplan-Meier curve from a previous report<sup>20</sup> on overall survival to calculate the number of life years (LYs) as an indicator of the outcome. LY was defined as the area under the curve. Although quality-adjusted LYs (QALYs) were recommended as an outcome indicator,<sup>27</sup> we did not calculate them because of the difficulty in retrospectively obtaining quality of life data, especially in the TACE group. The upper and lower limits of LY were calculated using 95% CIs. We analyzed the outcome data for 3 years from the start of treatment.

### Data on cost

We conducted an analysis from the perspective of public health care payers, following the recommendations of the guideline for the economic evaluation of health care technologies.<sup>27</sup> However, as will be mentioned subsequently, because the technical fees for CIRT are excluded from public health care expenses, we considered the cost scope to encompass both public expenditure and patient out-of-pocket expenses.

Cost data were electronically extracted from the accounting records maintained by Gunma University. Each medical fee was classified into corresponding categories (including CIRT technical fees, TACE fees, outpatient medical fees, hospitalization medical fees, image examination fees, laboratory examination fees, medication fees, treatment fees, radiation therapy fees, out-of-insurance fees, and other costs) based on the medical diagnosis identification in Japan (Table 1). Diagnostic procedure combination costs were converted into fee-for-service-based medical costs. We analyzed the cost data from 1 month before treatment initiation to 3 years thereafter.

Although CIRT for HCC with a tumor size of 4 cm or more has been covered by health insurance in Japan since April 2022, all 17 patients in this study received CIRT as

**Table 1 Expense categories**

Major Expense Categories	Medical Diagnosis Identification
Outpatient medical fee	Initial visit Follow-up visit Medical management Home care
Hospitalization medical fee	Basic hospitalization fee Specific hospitalization fee
Image examination fee	Imaging diagnosis
Laboratory examination fee	Examinations and pathology
Medication fee	Internal medication Topical medication External medication Dispensing Narcotics Adjustments
Treatment fee	Treatments Surgery Anesthesia
Radiation therapy fee	Radiation therapy
Out-of-insurance fee	Dietary therapy and standard patient share
Each medical fee has been categorized into relevant groups based on the medical diagnosis identification in Japan.	

advanced medical technology. The advanced medical technology system in Japan permits the use of innovative medical technologies that are not yet covered by health insurance in conjunction with standard treatments. The technical fees for these advanced technologies are entirely self-funded, while other medical expenses, such as consultations and hospitalization, are covered by insurance. These technical fees vary depending on the type of technology and the institution. If CIRT was performed as an advanced medical technology, a technical fee of ¥3,140,000 was charged at Gunma University. As per a specific rule of our institution, a second CIRT for tumors in the same organ (the liver) within 2 years from the beginning of CIRT was performed for free. We conducted the primary analysis with this rule applied, as it may have influenced patients' decision making. Additionally, considering the potential cost-effective advantages of CIRT resulting from this rule, further analysis was conducted by setting all CIRT technical fees at ¥3,140,000.

**Cost-effective analysis**

Cost-effectiveness analysis (CEA) was conducted based on the LY and total costs of each group, calculated from the outcome and cost data, respectively. If 1 of the CIRT and TACE groups had both a higher LY and a lower total cost, the treatment of the group was regarded as

dominant. Otherwise, the incremental cost-effectiveness ratio (ICER) was calculated using the following formula:

$$ICER = \frac{Ci - Cc}{Ei - Ec}$$

where *Ci* represents the cost in the intervention group, *Cc* signifies the cost in the control group, *Ei* represents the effect in the intervention group, and *Ec* denotes the effect in the control group. Therefore, ICER in this study was calculated by dividing the incremental total cost by the incremental LY.

Deterministic sensitivity analyses (DSA) and probabilistic sensitivity analyses (PSA) were performed to ensure the robustness of the analysis. In DSA, 1 variable was varied between its lower and upper limits to calculate the ICER range. In PSA, random numbers were generated for all variables using a triangular distribution that includes the lower limit, mode, and upper limit to calculate the ICERs. The number of PSA iterations was set to 10,000. The variables analyzed included total cost and LY in the CIRT and TACE groups. The lower limit, upper limit, and mode of the total cost were set as the minimum, maximum, and median values, respectively, in each group. For LY, lower limit, upper limit, and point estimates were used for each group.

The costs were aggregated and analyzed using the NumPy and Pandas libraries in Python version 3.9.16. All figures were generated using the Matplotlib library.

To enable a comparison of costs standardized internationally, from this point onwards, amounts stated in ¥ are accompanied by their converted USD values using the average exchange rate of ¥102 per USD from 2007 to 2019.

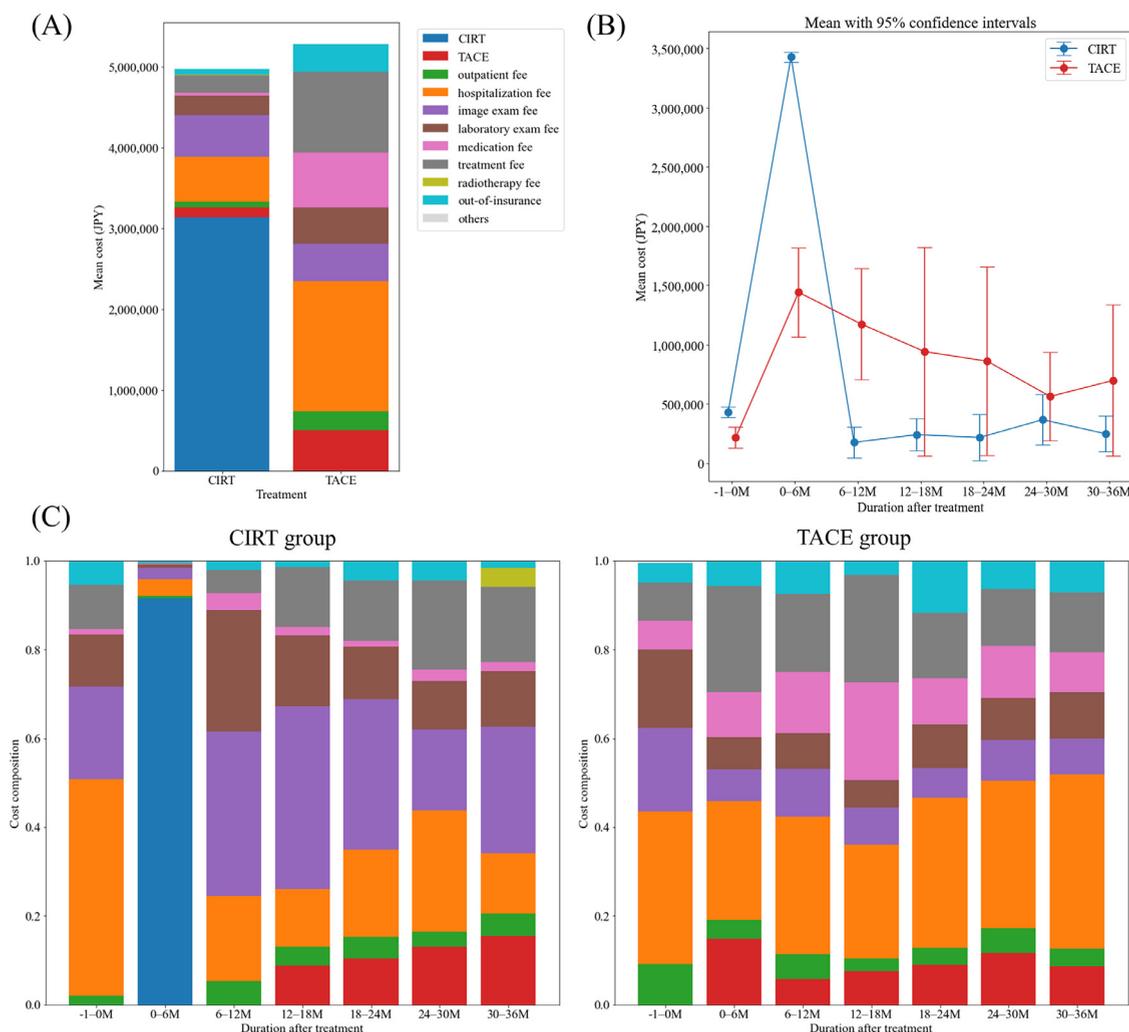
**Results**

**Follow-up information**

Fourteen and 15 patients in the CIRT and TACE groups, respectively, were followed up at Gunma University for more than 3 years or until their death. The remaining patients in both groups were followed up for at least 2 years. In the CIRT group, 2 patients required both additional CIRT and TACE, while 5 required TACE during the follow-up period. The second CIRTs were performed free of charge. In contrast, 11 patients in the TACE group underwent repeated TACE, 2 received RFA, and none were treated with CIRT during the follow-up period. No patients received systemic treatments, such as chemotherapy, molecular targeted therapy, or immunotherapy.

**LY**

The calculated LY was 2.747 (95% CI, 2.381-3.000) and 2.413 (95% CI, 1.974-2.836) in the CIRT and TACE groups, respectively, with an incremental LY of 0.334.



**Figure 1** (A) The mean total cost and its breakdown from 1 month before the treatment initiation to 3 years thereafter. (B) The time-series graph shows the mean cost in each group with error bars of 95% CIs. The mean costs were calculated by dividing the total cost in each interval by the number of patients who followed up during the interval. (C) The proportion of the costs during each interval. The colors showing the breakdown are the same as those of panel A. *Abbreviations:* CIRT, carbon-ion radiation therapy; TACE, transarterial chemoembolization.

**Medical costs**

The mean total cost was ¥4,974,278 (approximately 48,767 USD; range, ¥3,790,320-6,808,619 or 37,160-66,751 USD) in the CIRT group and ¥5,284,524 (approximately 51,809 USD; range, ¥1,074,270-9,722,276 or 10,532-95,316 USD) in the TACE group. The CIRT technical fee accounted for most of the medical costs in the CIRT group, whereas higher hospitalization medical, medication, and treatment fees were observed in the TACE group (Fig. 1A, Table 2). The medical costs for both groups were the highest during the first 6 months following treatment initiation. Subsequently, the TACE group had consistently higher costs, whereas the CIRT group had lower costs (Fig. 1B). During the follow-up period, the CIRT group

incurred a higher proportion of medical costs from image examination fees, while the TACE group incurred a higher proportion from hospitalization fees (Fig. 1C).

CIRT was considered dominant over TACE because the CIRT group results revealed a higher LY and a lower total cost. Nevertheless, a sensitivity analysis was conducted to validate the results because the medical costs in the TACE group had a higher variance according to each patient, especially the hospitalization medical and treatment fees (Fig. 2, Table 2).

**Sensitivity analysis**

In DSA, varying the LY of each group within their interval led to divergence to positive and negative infinity,

**Table 2** Descriptive statistics of medical costs in each treatment group

Fee	CIRT mean	TACE mean	CIRT SD	TACE SD	CIRT min	TACE min	CIRT median	TACE median	CIRT max	TACE max
Cirt	¥3,140,000	¥0	¥0	¥0	¥3,140,000	¥0	¥3,140,000	¥0	¥3140,000	¥0
Tace	¥114,724	¥499,641	¥161,819	¥309,100	¥0	¥127,000	¥0	¥533,700	¥507,900	¥999,000
Outpatient	¥71,806	¥239,823	¥32,999	¥294,012	¥19,190	¥35,990	¥66,620	¥109,840	¥136,190	¥967,610
Hospitalization	¥555,664	¥1,602,969	¥317,279	¥905,442	¥137,300	¥248,370	¥397,290	¥1473,760	¥1,212,460	¥3,173,120
Image examination	¥516,046	¥467,088	¥215,405	¥207,002	¥145,690	¥132,410	¥567,020	¥501,880	¥919,300	¥725,960
Laboratory examination	¥240,884	¥448,284	¥104,202	¥208,482	¥35,310	¥190,270	¥233,760	¥436,080	¥428,660	¥912,940
Medication	¥39,458	¥676,987	¥45,787	¥843,632	¥1,120	¥58,740	¥21,470	¥304,820	¥147,220	¥2,851,200
Treatment	¥214,392	¥999,244	¥250,947	¥102,8330	¥20,100	¥155,410	¥100,100	¥1006,290	¥859,400	¥4,275,700
Radiation therapy	¥9,035	¥971	¥36,971	¥1,734	¥0	¥0	¥0	¥0	¥152,500	¥6,600
Out-of-insurance	¥72,270	¥343,204	¥53,338	¥331,453	¥8,766	¥28,420	¥46,810	¥239,330	¥194,995	¥1,316,661
Others	¥0	¥6,315	¥0	¥15,782	¥0	¥0	¥0	¥0	¥0	¥48,700

Abbreviations: CIRT = carbon ion radiation therapy; max = maximum; min = minimum; TACE = transarterial chemoembolization. These descriptive statistics encompass the medical costs incurred from 1 month before treatment initiation to 3 years thereafter.

making it difficult to evaluate the impact of the LY on ICERs (Fig. E1A). When the total cost of TACE was minimized, the ICER of CIRT was ¥11,684,403/LY, approximately 114,652 USD/LY. In contrast, when maximizing the total cost of CIRT, the ICER of CIRT compared with TACE was ¥4,566,179/LY, approximately 44,774 USD/LY.

In the PSA, the acceptability of CIRT surpassed that of TACE, even when the willingness to pay (WTP), which represents the maximum threshold of ICER that individuals are willing to spend to receive treatment, was close to ¥0/LY (Fig. E1B). When WTP increased to ¥4,000,000/LY, approximately 39,216 USD/LY, the acceptability rate increased to >70%.

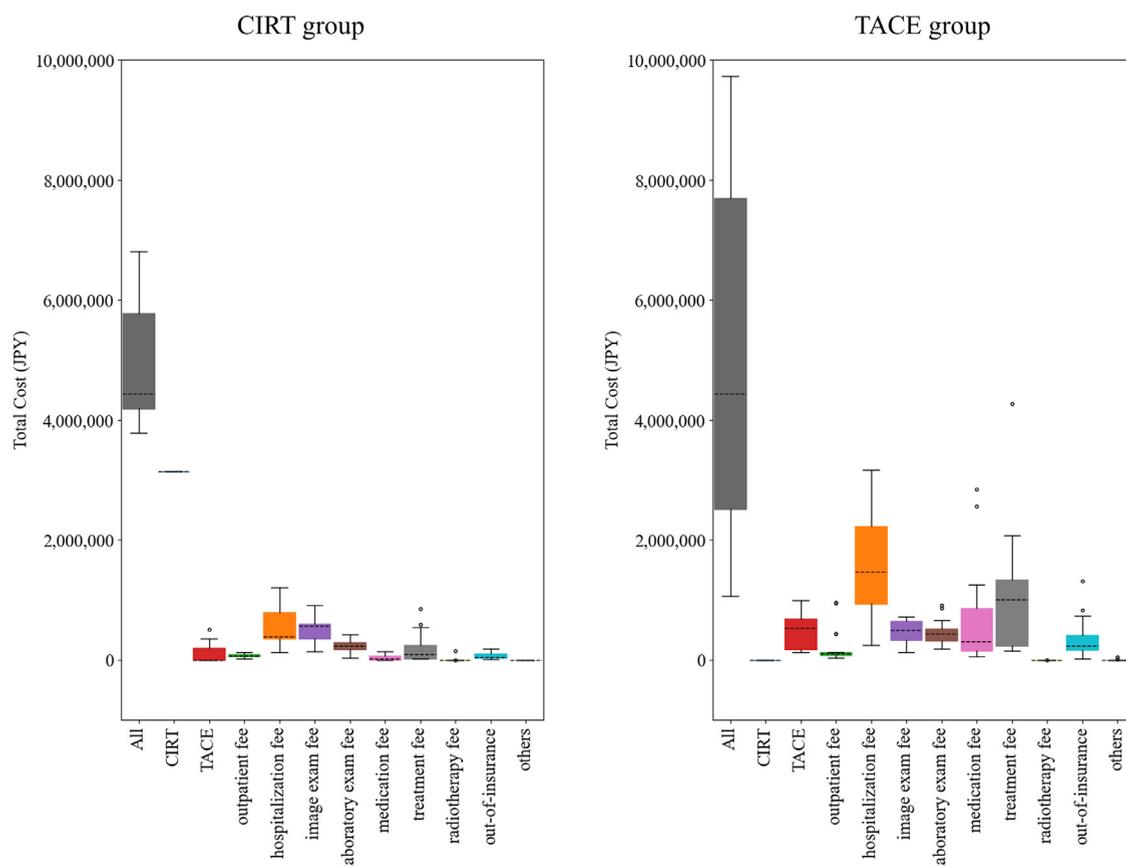
**Additional analysis**

Summing up the costs, assuming all CIRT technical fees to be ¥3,140,000, the mean total cost of the CIRT group was ¥5,343,690 (approximately 52,389 USD; range, ¥3,790,320-9,310,796 or 37,160-91,282 USD), slightly exceeding that of the TACE group (Fig. E2A). The calculated ICER stood at ¥177,259/LY, approximately 1738 USD/LY. In DSA, when maximizing the total cost of CIRT, the ICER of CIRT compared with TACE increased to ¥12,062,688/LY, approximately 118,262 USD/LY (Fig. E2B). Nevertheless, the impact of CIRT’s total cost on ICER remained smaller than that of TACE. Within PSA, the acceptability of CIRT surpassed that of TACE, even when WTP was below ¥4,000,000/LY (Fig. E2C).

**Discussion**

We demonstrated that CIRT is a dominant treatment for localized HCC compared with TACE based on the CEA. This study provides evidence from a health economics perspective that CIRT is a high-performance treatment option for patients with HCC ineligible for surgical resection.

CIRT is a minimally invasive treatment option for HCC.<sup>28-30</sup> Although surgical resection is the standard treatment for localized HCC, it inherently has a high propensity to coexist with liver disease, and many patients have insufficient liver function to tolerate the surgery.<sup>31</sup> Additionally, RFA is subject to drawbacks based on the size, location, and extent of the lesions, thereby restricting its suitability to a limited number of patients.<sup>3</sup> Therefore, CIRT is in high demand as a treatment option for HCC. However, despite its clinical benefits, the high cost associated with CIRT limits its accessibility. HCC is a common cancer in Asia, including Japan,<sup>31</sup> and the cost of medical care for HCC can significantly impact Japan’s health care economy. Hence, evaluating the cost effectiveness of HCC treatment is important to ensuring the soundness of Japan’s health care economy in the future.



**Figure 2** The boxplots depict the distribution of total costs for each patient categorized based on breakdowns. *Abbreviations:* CIRT, carbon-ion radiation therapy; TACE, transarterial chemoembolization.

The total cost in the TACE group exhibited significant variability, which could have potentially affected the CEA results. Therefore, sensitivity analysis is necessary to address the uncertainties involved.<sup>27</sup> The large variability in the TACE group may be due to the inclusion of patients who died early after treatment and those who required repeated hospitalization and/or retreatment. Generally, the total cost tends to be lower when early deaths are more frequent. However, in the TACE group, which has a high recurrence rate, repeated treatments became necessary as the survival duration increased. This could affect the variability in total costs. In contrast, CIRT showed little variability, probably because it was performed as an advanced medical technology during treatment, and follow-up was conducted in a standardized manner according to the protocol and because of fewer recurrences.

Our analysis followed the methods recommended by the guidelines for economic evaluation of health care technologies;<sup>27</sup> however, several noteworthy considerations exist, particularly regarding outcome data. First, due to the unavailability of quality-of-life data for the TACE group, we used LY as an outcome indicator. Using QALY as an outcome indicator can make it easier to assess cost

effectiveness. In Japan, although there are no formally authorized criteria for WTP in health care policy decisions, the generally referenced WTP per QALY ranges between ¥5 and 6 million.<sup>32,33</sup> However, interpreting the results becomes more challenging when the treatment outcome is measured in LY. A questionnaire survey revealed that 41.0% of Japanese oncologists believed that the maximum allowable medical expenses for cancer treatment to prolong the life expectancy of patients by 1 year should be  $\leq$ ¥4,000,000, while another 39.8% suggested that the fees should range from ¥4,000,000 to 8,000,000.<sup>34</sup> This serves as a valuable reference for our study in interpreting the results of CEA, as both studies use LY in cancer treatment as the outcome indicator. The median value identified in this study, ¥4,000,000, can be adopted as WTP threshold for our analysis. In the sensitivity analysis, DSA indicated ICERs of ¥11,684,403/LY, approximately 114,553 USD/LY, when the total cost of the TACE group was at its lowest and ¥4,566,179/LY, approximately 44,766 USD/LY, when the cost of the CIRT group was at its highest. Meanwhile, PSA demonstrated that the acceptability of CIRT exceeded 70% at the WTP threshold of ¥4,000,000/LY. As discussed earlier, considering that shorter survival tends to result in lower

**Table 3 Comparative study overview**

Study	Focus	Analysis method	Expected costs	ICER	Cost-effectiveness
Ikeda et al (2005) <sup>38</sup>	RFA vs surgical therapy for small HCC	Comparison based on patient data	Single RFA: ¥849,900; Repeated RFA: ¥1,086,000; Surgery: ¥1,745,100	Not specified	RFA superior to surgery
Cucchetti et al (2013) <sup>39</sup>	Hepatic resection vs RFA for early HCC	Meta-analysis and Markov model	Varies with HCC stage	Not specified	Depends on HCC stage
Cammà et al (2013) <sup>40</sup>	Sorafenib vs BSC for BCLC B or C HCC not eligible for local therapy	Markov decision model	Dose-adjusted sorafenib for BCLC B and C: €19,944; BSC: €4,142	€34,534/QALY for BCLC B and C patients together	Dose-adjusted sorafenib favorable
Parikh et al (2017) <sup>41</sup>	Sorafenib vs untreated in advanced HCC	SEER-Medicare database analysis	Sorafenib: \$31,364; Control: \$10,950 in overall cohort	\$84,250/LY in overall cohort	Sorafenib was not cost-effective among patients with hepatic decompensation
Pollom et al (2017) <sup>42</sup>	SBRT vs RFA for HCC	Decision-analytical Markov model	SBRT-SBRT: \$197,557; RFA-SBRT: \$193,288	\$558,679/QALY for SBRT-SBRT relative to RFA-SBRT	RFA-SBRT preferred strategy
Marqueen et al (2021) <sup>43</sup>	SIRT vs sorafenib in locally advanced HCC	State-transition microsimulation model	Sorafenib: \$78,859; SIRT: \$58,397	\$1,280,224/QALY for sorafenib	Sorafenib was not cost-effective compared with SIRT
Current study	CIRT vs TACE for localized HCC not eligible for local therapy	Comparison based on actual measurement data	CIRT: ¥4,974,278; TACE: ¥5,284,524	CIRT was “dominant” over TACE	CIRT superior to TACE

*Abbreviations:* BCLC = Barcelona clinic liver cancer; BSC = best supportive care; CIRT = carbon ion radiation therapy; HCC = hepatocellular carcinoma; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; RFA = radiofrequency ablation; SBRT = stereotactic body radiation therapy; SEER = surveillance, epidemiology, and end results; SIRT = selective internal radiation therapy; TACE = transarterial chemoembolization.

total costs in the TACE group, these results suggest that CIRT is likely to be cost effective, even with various uncertainties. This supports the primary analysis based on actual measurement data.

Second, although the guidelines recommend using high-level evidence data that reflect real-world clinical outcomes,<sup>27</sup> this study used retrospective data from a single facility, which may have introduced various uncertainties and biases. Factors such as follow-up policies, regular checkups, treatment policies for recurrence, and ease of hospital visits can influence cost-effectiveness outcomes. Additionally, PSM was used to ensure a fair comparison by aligning patient backgrounds, which resulted in a reduced sample size of only 17 patients in each group. Consequently, the total costs and LY of each patient had a more pronounced impact on the analysis results, potentially reducing the robustness of our analysis. Furthermore, the large CIs in the survival curves of each group made it difficult to assess the impact of LY variations on ICERs in DSA. Despite these challenges, it is notable that the treatment outcomes for both CIRT and TACE were consistent with previous literature,<sup>12,20,35-37</sup> and the calculated LYs in this study are credible. Sensitivity analyses were conducted to address the uncertainties and biases arising from these limitations.

Several studies have assessed the cost effectiveness of various HCC treatment options (Table 3). For example, 2 studies specifically compared the cost effectiveness of RFA versus surgery for early stage HCC and found that RFA was cost effective in selected patients.<sup>38,39</sup> These studies focused on resectable HCC, which differed from the target population of this study. Similarly, 2 other studies demonstrated the cost effectiveness of sorafenib in selected patients;<sup>40,41</sup> however, they included patients with advanced HCC for which local therapy is unsuitable, which is different from the target population of this study. Pollom et al<sup>42</sup> and Marqueen et al<sup>43</sup> developed a Markov model to compare the cost effectiveness of inoperable, locally advanced HCC treatment options, including RFA versus SBRT and selective internal radiation therapy (SIRT) with Yttrium-90 versus sorafenib. A former study concluded that RFA, followed by SBRT as salvage therapy, is preferred regarding cost effectiveness. The latter study could not demonstrate the superiority of SIRT over sorafenib. In these studies, the expected costs were high (RFA + SBRT: 193,288 USD, approximately ¥19,715,376; SIRT: 58,397 USD, approximately ¥5,956,494). CIRT may be a more cost-effective option; however, it is unclear whether simulated patients are suitable for CIRT. Furthermore, these studies have significant uncertainties because they are based on the literature and rely on some assumptions. In contrast, our study used actual measurement data obtained from the same facility, reducing uncertainties based on assumptions and providing reliable, valuable data.

Gunma University has implemented a policy that exempts the CIRT technical fee under specific conditions.

This aspect could complicate the interpretation of the findings in this study. Our focus was to ensure the reliability and accuracy of the results through an analysis based on real-world data. Consequently, the primary analysis was conducted with this policy considered. However, recognizing the potential advantage that this policy might confer to CIRT, we performed an additional analysis where all CIRT technical fees were standardized at ¥3,140,000. The 2 sessions of CIRT technical fees, initially considered free, were adjusted to ¥3,140,000 in the additional analysis, leading to the average total cost for the CIRT group slightly exceeding that of the TACE group. Although CIRT was not dominant over TACE, it still exhibited favorable cost effectiveness. Importantly, the additional analysis produced no changes to the conclusions drawn from the primary analysis.

In addition to what has been discussed, this study had some other limitations. First, this study only included analyzed cost databased on the costs incurred at Gunma University. Thus, some patients may have incurred considerable costs at other medical institutions. Although we desired to collect cost data from all medical institutions, this is difficult to achieve. As almost all patients were followed up for 3 years from the start of treatment or until death (with only a few exceptions who were lost to follow-up), this limitation may have a relatively small impact. Any uncertainty caused by this limitation was also addressed in sensitivity analyses. Second, the chances of survival have recently increased owing to advancements in the treatment techniques for HCC, including CIRT and TACE, and the development of systemic therapies.<sup>44,45</sup> Our study analyzed patients treated between 2007 and 2016, which may differ from the current patient population in real-world settings. Additionally, medical expenses may have changed owing to revisions in the medical payment system. With CIRT for HCC now covered by health insurance from 2022 onward, the total cost for patients currently receiving CIRT may be lower than that in our study. Although we have provided reliable databased on actual measurements, it is important to continue conducting health economic evaluations in the future.

## Conclusion

In conclusion, CIRT is a cost-effective treatment option for localized HCC cases unsuitable for surgical resection or RFA. This conclusion is based on an actual measurement-based analysis, which provides more reliable and accurate results than a simulation-based analysis, which is prone to greater uncertainty. Although CIRT incurs high technical fees, its long-term cost effectiveness remains favorable over a 3-year perspective due to reduced posttreatment expenses. Data and findings from

this study are valuable for CIRT medical economic evaluation.

## Disclosures

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## Supplementary materials

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.adro.2024.101441](https://doi.org/10.1016/j.adro.2024.101441).

## References

- Chen Z, Xie H, Hu M, et al. Recent progress in treatment of hepatocellular carcinoma. *Am J Cancer Res*. 2020;10:2993-3036.
- Piñero F, Dirchwolf M, Pessôa MG. Biomarkers in hepatocellular carcinoma: Diagnosis, prognosis and treatment response assessment. *Cells*. 2020;9:1370.
- Kudo M, Kawamura Y, Hasegawa K, et al. Management of hepatocellular carcinoma in Japan: JSH consensus statements and recommendations 2021 update. *Liver Cancer*. 2021;10:181-223.
- Llovet JM, Castet F, Heikenwalder M, et al. Immunotherapies for hepatocellular carcinoma. *Nat Rev Clin Oncol*. 2022;19:151-172.
- Alqahtani A, Khan Z, Alloghbi A, Ahmed TSS, Ashraf M, Hamouda DM. Hepatocellular carcinoma: Molecular mechanisms and targeted therapies. *Medicina*. 2019;55:526.
- Erstad DJ, Tanabe KK. Hepatocellular carcinoma: Early-stage management challenges. *J Hepatocell Carcinoma*. 2017;4:81-92.
- Arita J, Ichida A, Nagata R, et al. Conversion surgery after preoperative therapy for advanced hepatocellular carcinoma in the era of molecular targeted therapy and immune checkpoint inhibitors. *J Hepatobiliary Pancreat Sci*. 2022;29:732-740.
- Pang TC, Lam VW. Surgical management of hepatocellular carcinoma. *World J Hepatol*. 2015;7:245-252.
- Jiang YQ, Wang ZX, Deng YN, Yang Y, Wang GY, Chen GH. Efficacy of hepatic resection vs. radiofrequency ablation for patients with very-early-stage or early-stage hepatocellular carcinoma: A population-based study with stratification by age and tumor size. *Front Oncol*. 2019;9:113.
- Kinugasa H, Nouseo K, Takeuchi Y, et al. Risk factors for recurrence after transarterial chemoembolization for early-stage hepatocellular carcinoma. *J Gastroenterol*. 2012;47:421-426.
- Kato H, Tsujii H, Miyamoto T, et al. Results of the first prospective study of carbon ion radiotherapy for hepatocellular carcinoma with liver cirrhosis. *Int J Radiat Oncol Biol Phys*. 2004;59:1468-1476.
- Shibuya K, Ohno T, Terashima K, et al. Short-course carbon-ion radiotherapy for hepatocellular carcinoma: A multi-institutional retrospective study. *Liver Int*. 2018;38:2239-2247.
- Shibuya K, Ohno T, Katoh H, et al. A feasibility study of high-dose hypofractionated carbon ion radiation therapy using four fractions for localized hepatocellular carcinoma measuring 3 cm or larger. *Radiother Oncol*. 2019;132:230-235.
- Shibuya K, Katoh H, Koyama Y, et al. Efficacy and safety of 4 fractions of carbon-ion radiation therapy for hepatocellular carcinoma: A prospective study. *Liver Cancer*. 2022;11:61-74.
- Shiba S, Abe T, Shibuya K, et al. Carbon ion radiotherapy for 80 years or older patients with hepatocellular carcinoma. *BMC Cancer*. 2017;17:721.
- Imada H, Kato H, Yasuda S, et al. Comparison of efficacy and toxicity of short-course carbon ion radiotherapy for hepatocellular carcinoma depending on their proximity to the porta hepatis. *Radiother Oncol*. 2010;96:231-235.
- Shiba S, Shibuya K, Katoh H, et al. No deterioration in clinical outcomes of carbon ion radiotherapy for sarcopenia patients with hepatocellular carcinoma. *Anticancer Res*. 2018;38:3579-3586.
- Shiba S, Shibuya K, Okamoto M, et al. Clinical impact of hypofractionated carbon ion radiotherapy on locally advanced hepatocellular carcinoma. *Radiat Oncol*. 2020;15:195.
- Okazaki S, Shibuya K, Shiba S, et al. Carbon ion radiotherapy for patients with hepatocellular carcinoma in the caudate lobe carbon ion radiotherapy for hepatocellular carcinoma in caudate lobe. *Hep- atol Res*. 2021;51:303-312.
- Shiba S, Shibuya K, Katoh H, et al. A comparison of carbon ion radiotherapy and transarterial chemoembolization treatment outcomes for single hepatocellular carcinoma: A propensity score matching study. *Radiat Oncol*. 2019;14:137.
- Ohno T. Particle radiotherapy with carbon ion beams. *EPMA J*. 2013;4:9.
- Ohno T, Kanai T, Yamada S, et al. Carbon ion radiotherapy at the Gunma University heavy ion medical center: New facility set-up. *Cancers*. 2011;3:4046-4060.
- Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluation publication guidelines good reporting practices task force. *Value Health*. 2013;16:231-250.
- Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes*. 4th ed. Oxford University Press; 2015.
- Okazaki S, Shibuya K, Takura T, Miyasaka Y, Kawamura H, Ohno T. Cost-effectiveness of carbon-ion radiotherapy versus stereotactic body radiotherapy for non-small-cell lung cancer. *Cancer Sci*. 2022;113:674-683.
- Mobaraki A, Ohno T, Yamada S, Sakurai H, Nakano T. Cost-effectiveness of carbon ion radiation therapy for locally recurrent rectal cancer. *Cancer Sci*. 2010;101:1834-1839.
- Fukuda T, Shiroya T, Ikeda S, et al. Guideline for economic evaluation of healthcare technologies in Japan. *J Natl Inst Public Health*. 2013;62:590-598.
- Shiba S, Shibuya K, Kawashima M, et al. Comparison of dose distributions when using carbon ion radiotherapy versus intensity-modulated radiotherapy for hepatocellular carcinoma with macroscopic vascular invasion: A retrospective analysis. *Anticancer Res*. 2020;40:459-464.
- Tomizawa K, Shibuya K, Shiba S, et al. Repeated carbon-ion radiation therapy for intrahepatic recurrent hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys*. 2023;116:1100-1109.

30. Abe T, Saitoh J, Kobayashi D, et al. Dosimetric comparison of carbon ion radiotherapy and stereotactic body radiotherapy with photon beams for the treatment of hepatocellular carcinoma. *Radiat Oncol.* 2015;10:187.
31. Gomaa AI, Khan SA, Toledano MB, Waked I, Taylor-Robinson SD. Hepatocellular carcinoma: Epidemiology, risk factors and pathogenesis. *World J Gastroenterol.* 2008;14:4300-4308.
32. Shiroywa T, Sung YK, Fukuda T, Lang HC, Bae SC, Tsutani K. International survey on willingness-to-pay (WTP) for one additional QALY gained: What is the threshold of cost effectiveness? *Health Econ.* 2010;19:422-437.
33. Shiroywa T, Igarashi A, Fukuda T, Ikeda S. WTP for a QALY and health states: More money for severer health states? *Cost Eff Resour Alloc.* 2013;11:22.
34. Takura T, Fujiya M, Shimada Y, Kohgo Y. Perspectives of Japanese oncologists on the health economics of innovative cancer treatments. *Int J Clin Oncol.* 2016;21:633-641.
35. Kasuya G, Kato H, Yasuda S, et al. Progressive hypofractionated carbon-ion radiotherapy for hepatocellular carcinoma: Combined analyses of 2 prospective trials. *Cancer.* 2017;123:3955-3965.
36. Kudo M, Izumi N, Ichida T, et al. Report of the 19th follow-up survey of primary liver cancer in Japan. *Hepatol Res.* 2016;46:372-390.
37. Terzi E, Piscaglia F, Forlani L, et al. TACE performed in patients with a single nodule of Hepatocellular Carcinoma. *BMC Cancer.* 2014;14:601.
38. Ikeda K, Kobayashi M, Saitoh S, et al. Cost-effectiveness of radiofrequency ablation and surgical therapy for small hepatocellular carcinoma of 3cm or less in diameter. *Hepatol Res.* 2005;33:241-249.
39. Cucchetti A, Piscaglia F, Cescon M, et al. Cost-effectiveness of hepatic resection versus percutaneous radiofrequency ablation for early hepatocellular carcinoma. *J Hepatol.* 2013;59:300-307.
40. Cammà C, Cabibbo G, Petta S, et al. Cost-effectiveness of sorafenib treatment in field practice for patients with hepatocellular carcinoma. *Hepatology.* 2013;57:1046-1054.
41. Parikh ND, Marshall VD, Singal AG, et al. Survival and cost-effectiveness of sorafenib therapy in advanced hepatocellular carcinoma: An analysis of the SEER-Medicare database. *Hepatology.* 2017;65:122-133.
42. Pollom EL, Lee K, Durkee BY, et al. Cost-effectiveness of stereotactic body radiation therapy versus radiofrequency ablation for hepatocellular carcinoma: A Markov modeling study. *Radiology.* 2017;283:460-468.
43. Marqueen KE, Kim E, Ang C, Mazumdar M, Buckstein M, Ferket BS. Cost-effectiveness analysis of selective internal radiotherapy with yttrium-90 versus sorafenib in locally advanced hepatocellular carcinoma. *JCO Oncol Pract.* 2021;17:e266-e277.
44. Torimura T, Iwamoto H. Treatment and the prognosis of hepatocellular carcinoma in Asia. *Liver Int.* 2022;42:2042-2054.
45. Su TH, Hsu SJ, Kao JH. Paradigm shift in the treatment options of hepatocellular carcinoma. *Liver Int.* 2022;42:2067-2079.