

Efficacy and safety of carbon-ion radiotherapy for large hepatocellular carcinoma (diameter ≥ 10 cm)

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Abstract

Background

Large, unresectable hepatocellular carcinoma (HCC) remains incurable, and the risk of radiation-induced liver damage makes definitive radiotherapy challenging. We aimed to evaluate the efficacy and safety of carbon-ion radiotherapy (CIRT).

Methods

We retrospectively analyzed records of 33 CIRT-treated patients with HCC (diameter ≥ 10 cm) at Osaka Heavy Ion Therapy Center. Rates of local control (LC), progression-free survival (PFS), and overall survival (OS) were calculated using the Kaplan–Meier method. Toxicities were evaluated according to the Common Terminology Criteria for Adverse Events v5.0.

Results

The median tumor diameter was 11 (range: 10–18) cm. Stage IB was the most common disease stage, and alcoholic liver disease was the most common underlying condition. The relative biological effectiveness-weighted dose was 60 Gy/4 fractions, 67.2 Gy/12 fractions, and 60 Gy/12 fractions in 19, 8, and 12 patients, respectively. Based on pretreatment liver function, 27 and 6 patients were categorized as Child–Pugh classes A and B, respectively. The median follow-up period was 15.1 (range: 2.8–54.0) months. The 1-year LC, PFS, and OS rates were 85.9%, 30.0%, and 74.8%, respectively. Grade ≥ 3 toxicities included pleural effusion in 2 patients (6%) and hepatic failure, heart failure, bile duct stricture, and biliary tract infection in 1 patient (3%) each. No grade ≥ 4 toxicities occurred. Radiation-induced liver damage, defined as a Child–Pugh score increase ≥ 2 points from the pretreatment baseline, occurred in 5 patients (15%).

Conclusions

CIRT for large HCC (≥ 10 cm) was effective in the short term, with acceptable toxicities.

Trial registration: Not applicable.

Background

Hepatocellular carcinoma (HCC) is the fifth most common cause of cancer-related deaths worldwide [1]. When HCC is confined to the liver and liver function is good, surgery or radiofrequency ablation (RFA) is the first choice for local therapy [2, 3]. Alternative treatment includes stereotactic body radiotherapy (SBRT) [4]. RFA is generally well-suited for HCCs measuring < 3 cm in diameter, whereas SBRT is generally well-suited for HCCs measuring < 5 cm in diameter. However, for liver-confined HCCs measuring ≥ 10 cm, RFA and SBRT are difficult to apply. Surgery remains the first choice if the tumor is resectable; however, the 3-year overall survival (OS) rate is 52%, indicating a poor prognosis [5]. In

addition, factors such as tumor number, vascular invasion, residual liver volume after resection, liver dysfunction, medical history, age, and patient refusal may render patients ineligible for surgery. In such cases, transcatheter arterial chemoembolization (TACE) serves as an alternative local therapy for large HCCs; however, the 1-year OS rate is 33%, indicating a very poor prognosis [3, 6].

Carbon-ion radiotherapy (CIRT) is characterized by its high antitumor efficacy and dose concentration compared with X-ray radiotherapy [7]. Previous reports on CIRT for HCC have shown 3-year local control (LC) and OS rates of 76.5–100% and 50–76.7%, respectively, indicating favorable treatment outcomes [8–11]. Moreover, CIRT delivers higher dose concentrations than SBRT, with fewer toxicities [12, 13]. The number of CIRT centers is gradually increasing in Japan, Asia, and Europe. In Japan, CIRT for HCCs measuring ≥ 4 cm has been covered under the Japanese national health insurance system since April 2022.

To date, no studies have evaluated CIRT for large HCCs (≥ 10 cm), and its efficacy and safety remain unknown. Therefore, in this study, we aimed to retrospectively evaluate the treatment outcomes of CIRT for large HCC.

Methods

Study design and population

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Review Committee (Identification Number 210901). All patients provided informed consent for the use of their personal information for research purposes.

A CIRT protocol for HCC was established when the Osaka Heavy Ion Therapy Center opened in 2018, and CIRT was performed accordingly. The eligibility criteria were as follows: HCC diagnosis by imaging (contrast-enhanced computed tomography [CT] or contrast-enhanced magnetic resonance imaging [MRI]) or biopsy; a performance status of 0–2; T1-4N0-1M0 according to the International Union Against Cancer Tumor-Node-Metastasis Classification (seventh edition) [14]; liver function between Child–Pugh classes A and B; and indication review by our institutional Cancer Board.

We conducted a retrospective survey of all patients treated with CIRT for HCCs measuring ≥ 10 cm in diameter at our center between December 2018 and December 2024. Of the 34 eligible patients, 1 was excluded because of a lack of follow-up examinations (including imaging or blood tests) after CIRT; consequently, 33 patients were included in the final analysis.

CIRT

The methodological details have been described previously [15, 16]; however, they are briefly summarized here. Marker implantation was performed percutaneously. The patients were immobilized

using an individually tailored fixation shell (Esform; Engineering System Co., Ltd., Matsumoto, Japan), and four-dimensional CT images were obtained in the supine or/and prone position. The tumor was contoured on CT images as the gross tumor volume (GTV) based on contrast-enhanced CT or MRI. The clinical target volume (CTV) was defined as the GTV with a margin of 0–5 mm. The internal target volume (ITV) was defined as the CTV plus a margin accounting for the respiratory motion based on four-dimensional CT. A beam-specific planning target volume (PTV) was created in each direction of irradiation, featuring a 3–5 mm margin on the ITV on the lateral side of the irradiation direction and a margin of 2.0–3.5% plus 1 mm of the beam range on the distal and proximal sides of the ITV [17]. The dose distribution for each beam was generated using a beam-specific PTV. Finally, to evaluate the combined dose distribution for each beam, the PTV was defined as the region encompassing the ITV with a 2–5-mm safety margin.

Regarding the dose prescription, a dose of 60 Gy in 4 fractions is generally used. However, when normal organs such as the gastrointestinal tract are in close proximity, a dose of 67 Gy in 12 fractions or 60 Gy in 12 fractions is employed. The relative biological effectiveness-weighted dose was 60 Gy/4 fractions in 19 patients, 67.2 Gy/12 fractions in 8 patients, and 60 Gy/12 fractions in 6 patients. The prescribed dose was delivered to the isocenter, and the PTV was conformally surrounded by at least a 95.0% isodose line of the prescribed dose. The basic dose constraints were as follows: the minimum dose delivered to 0.1 cc of the most irradiated gastrointestinal tract volumes ($D_{0.1cc}$) was < 15 Gy in 4 fractions; the $D_{0.1cc}$ of gastrointestinal tract volumes < 50 Gy in 12 fractions and D_{2cc} < 46 Gy in 12 fractions; the skin dose was < 30 Gy in 4 fractions or < 50 Gy in 12 fractions; the normal liver volume was defined as the liver volume excluding the GTV, and the volume of normal liver receiving < 20 Gy was > 600 cm³; and, for cases treated in 2024 and later, the normal liver volume was additionally spared from < 30 Gy (VS_{30} > 739 cm³) [16]. All doses were administered four times per week. Treatment planning was performed using RayStation (RaySearch Laboratories, Stockholm, Sweden) and the VQA Plan (Hitachi Ltd., Tokyo, Japan) [18]. Carbon ions were generated using a heavy ion therapy system (HyBEAT; Hitachi, Ltd.).

After 1 month of treatment, the patients were examined. If no abnormalities were observed, enhanced CT or MRI, blood tests, or medical examinations were conducted every 3–6 months at our center or the referring hospital.

Statistical analysis

The LC, progression-free survival (PFS), and OS rates were calculated using the Kaplan–Meier method. LC was defined as the period from the start of irradiation until tumor regrowth was observed within the PTV or until final follow-up. PFS was defined as the period from the start of irradiation until detection of disease progression at any site, death from any cause, or until final follow-up. OS was defined as the period from the start of irradiation until death or final follow-up. To identify the prognostic factors for LC, PFS, and OS, univariate analysis was performed using the log-rank test. A two-tailed p -value < 0.05 was considered statistically significant. All statistical analyses were conducted using the JMP statistical software (version 18.0; SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

The patient and tumor characteristics are summarized in Table 1. The median age was 83 (range: 54–94) years, and the median tumor diameter was 11.0 (range, 10.0–18.0) cm. Stage IB was the most common disease stage (16 patients), and alcoholic liver disease was the most common underlying condition (8 patients). Based on pretreatment liver function, 27 and 6 patients were categorized as Child–Pugh classes A and B, respectively. The median follow-up period was 15.1 (range, 2.8–54.0) months overall and 19.1 months for surviving patients.

[insert Table 1 here]

LC and survival

By the end of the follow-up period, 13 (39.4%) of the 33 patients had died of the disease, and 1 (3.0%) had died of unrelated causes; the remaining 4 patients survived. A typical CIRT dose distribution for a large HCC is illustrated in Fig. 1a and b; the MRI images acquired before CIRT and 20 months after treatment are illustrated in Fig. 1c and d. Tumors were considered locally controlled if their size decreased or remained unchanged. Regarding the site of initial recurrence, local recurrence within the PTV occurred in 3 (9.1%) of the 33 patients, whereas intrahepatic recurrence outside the PTV occurred in 18 (54.5%) patients. Two patients developed regional lymph node recurrence, and four developed distant metastases. The 1-year LC, PFS, and OS rates were 85.9% (95% confidence interval [CI], 63.8–95.5%), 30.0% (95% CI, 16.8–47.6%), and 74.8% (95% CI, 57.0–86.9%), respectively (Fig. 2a–c). The median OS was 25.4 months.

Toxicities

Grade ≥ 3 toxicities included grade 3 pleural effusion in 2 patients (6%) and hepatic failure, bile duct stenosis, bile tract infection, and heart failure in 1 patient each (3%) (Table 2). No grade ≥ 4 toxicities were observed. Radiation-induced liver damage, defined as a Child–Pugh score increase ≥ 2 points from the pretreatment baseline, was observed in 5 patients (15%). As grade 3 pleural effusion and heart failure occurred in the same patient, the percentage of patients with grade ≥ 3 toxicities was 15%.

[insert Table 2 here]

Discussion

CIRT is a promising treatment option for patients with unresectable HCC [8–10, 19]; however, no studies have focused on CIRT for large HCCs measuring ≥ 10 cm. Therefore, achieving definitive CIRT for large HCC while minimizing radiation-induced liver damage and serious toxicities is challenging. To the best of our knowledge, this is the first study to evaluate the efficacy and safety of CIRT for large HCC. In our

study, the 1-year LC, PFS, and OS rates were 85.9%, 30.0%, and 74.8%, respectively. Grade 3 toxicities were observed in 15% of the patients; however, no grade ≥ 4 toxicities occurred. Therefore, our findings indicate that CIRT for unresectable large HCC may be an effective treatment option with acceptable short-term toxicities.

For liver-confined HCCs measuring ≥ 10 cm, surgery and TACE are generally considered definitive local therapies. Regarding surgery, Wang et al. conducted a meta-analysis and systematic review of 1,770 patients who underwent surgery for large HCCs measuring ≥ 10 cm [5]. The outcomes revealed that the 1-year OS and recurrence-free survival rates were 75% and 46%, respectively. Xue et al. retrospectively analyzed data from 511 patients who underwent TACE for large HCCs measuring ≥ 10 cm, reporting a 1-year OS rate of 33% and no data on PFS [6]. As a multidisciplinary treatment, Chierici et al. conducted a meta-analysis comparing patients who underwent surgery plus TACE with those who underwent surgery alone for large HCCs measuring ≥ 10 cm. Although the specific survival rates were not reported, the results showed that the combination of surgery and TACE yielded a significantly better prognosis than surgery alone [20]. As an additional multidisciplinary treatment, Huang et al. retrospectively compared surgery plus TACE (control group) with surgery plus TACE plus programmed cell death ligand 1 (PD-L1) inhibitor (the PD-L1 inhibitor group) for large HCCs measuring ≥ 10 cm using propensity score matching. Their outcomes revealed that the PD-L1 inhibitor group demonstrated significantly better survival than the control group, with 1-year recurrence-free survival rates of 49.9% vs. 24.7% and 1-year OS rates of 83.6% vs. 50.6% [21]. However, reports on the use of radiotherapy for large HCC are scarce. Wong et al. retrospectively analyzed data from 156 patients with large HCC (median size, 12.9 [range, 5.1–12.7] cm) who underwent radiotherapy and, in approximately half, TACE. The median 2 Gy-equivalent radiation dose was 32.7 (range, 28–46.7) Gy. The results showed a 1-year OS rate of 45.4%, with an unspecified PFS [22]. The present study revealed a 1-year OS rate of 74.8% and a 1-year PFS rate of 30.0%. These results are comparable to those achieved with surgery, surgery plus TACE, or surgery plus TACE plus PD-L1 inhibitors as local therapies. The results also indicate better outcomes than TACE alone or radiotherapy. Furthermore, considering that most patients included in our study were deemed inoperable, this can be considered a relatively favorable outcome.

According to previous reports on CIRT for HCC, regardless of size, grade ≥ 3 toxicities according to the Common Terminology Criteria for Adverse Events have been reported at rates of 5.7–14.3% [10, 23]. Moreover, radiation-induced liver injury worsening by two or more points on the Child–Pugh classification compared with pretreatment has been reported in 8–15.7% of patients [8, 9, 23]. In the current study, grade ≥ 3 toxicities occurred in 15% of all patients, and radiation-induced liver injury, assessed using the Child–Pugh classification, was observed in 15% of the patients. The incidence of these toxicities was slightly higher than that reported in previous CIRT studies. However, considering that the HCCs in the current study were very large (≥ 10 cm) and no grade ≥ 4 adverse events were observed, these toxicities may be considered within an acceptable range.

Our study has some limitations. First, this was a single-center retrospective study with a small sample size. Second, selection bias may be present because CIRT eligibility was determined on a case-by-case

basis by our institutional Cancer Board. Third, the median follow-up period was 15.1 months, which may have led to underestimation of late toxicities associated with CIRT.

Conclusions

Our findings indicate that CIRT may be an effective treatment option for unresectable HCCs measuring ≥ 10 cm, with acceptable toxicities in the short term, warranting further large-scale prospective trials.

Abbreviations

CI, confidence interval

CIRT, carbon-ion radiotherapy

CT, computed tomography

CTV, clinical target volume

GTV, gross tumor volume

HCC, hepatocellular carcinoma

ITV, internal target volume

LC, local control

OS, overall survival

PD-L1, programmed cell death ligand 1

PFS, progression-free survival

PTV, planned target volume

RFA, radiofrequency ablation

SBRT, stereotactic body radiotherapy

TACE, transcatheter arterial chemoembolization

Declarations

Ethical approval and consent to participate: This study was approved by the Osaka Heavy Ion Beam Center Ethics Committee (identification number: 210901) and conducted in accordance with the Declaration of Helsinki. All patients provided informed consent for the use of their personal information for research purposes.

Consent for publication: Not applicable.

Availability of data and materials:

Competing interests: The authors declare that they have no competing interests.

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Tables

Table 1 to 2 are available in the Supplementary Files section.

Figures

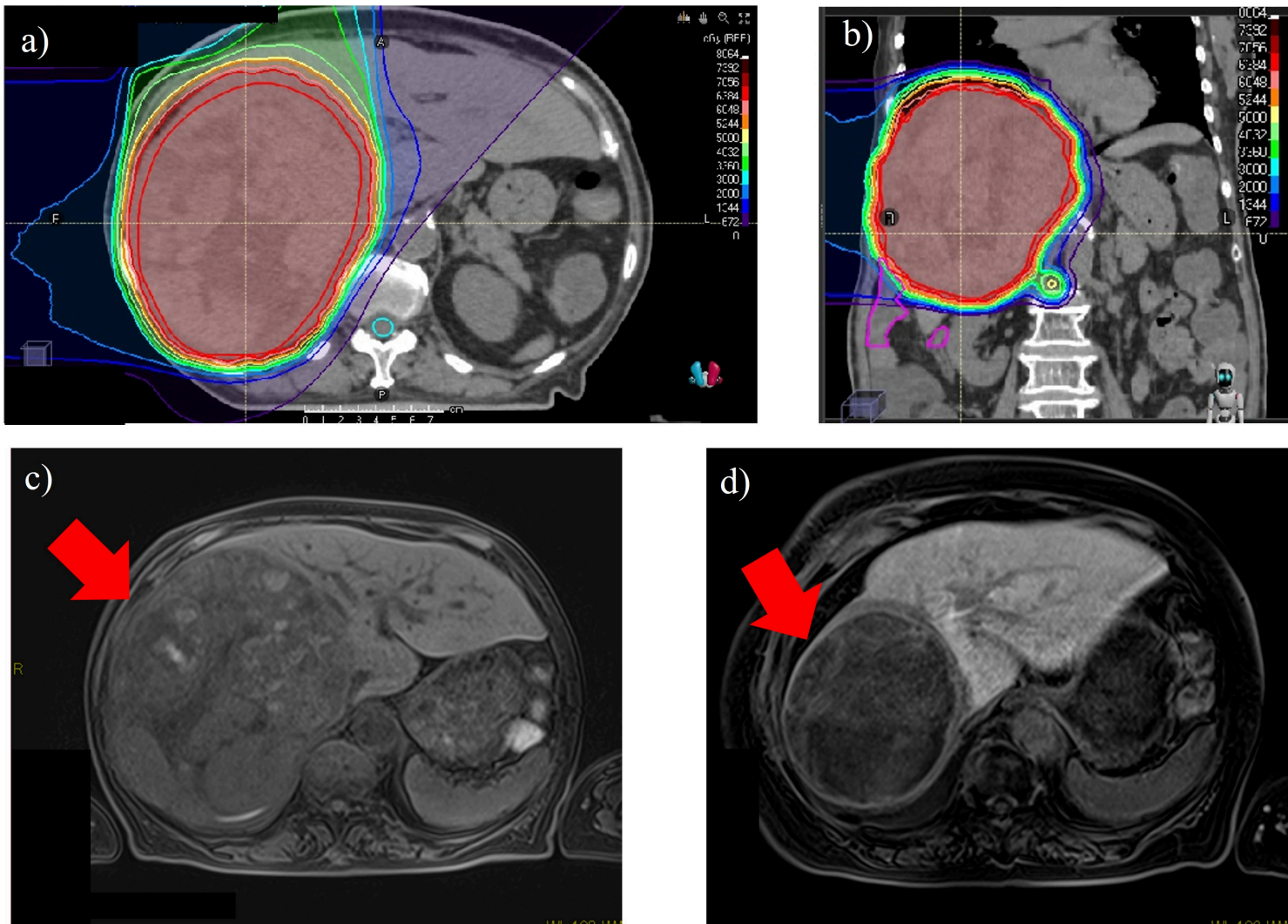


Figure 1

Typical dose distribution

Axial and coronal (a and b, respectively) images show the dose distribution in the supine position. Carbon-ion radiotherapy was delivered at 67.2 Gy in 12 fractions. Pretreatment T1-weighted magnetic resonance images with fat suppression are shown in (c), and follow-up T1-weighted magnetic resonance images with fat suppression acquired 20 months after treatment in the supine position are shown in (d); the hepatocellular carcinoma had not recurred 24 months after treatment. Red arrows indicate primary tumor sites

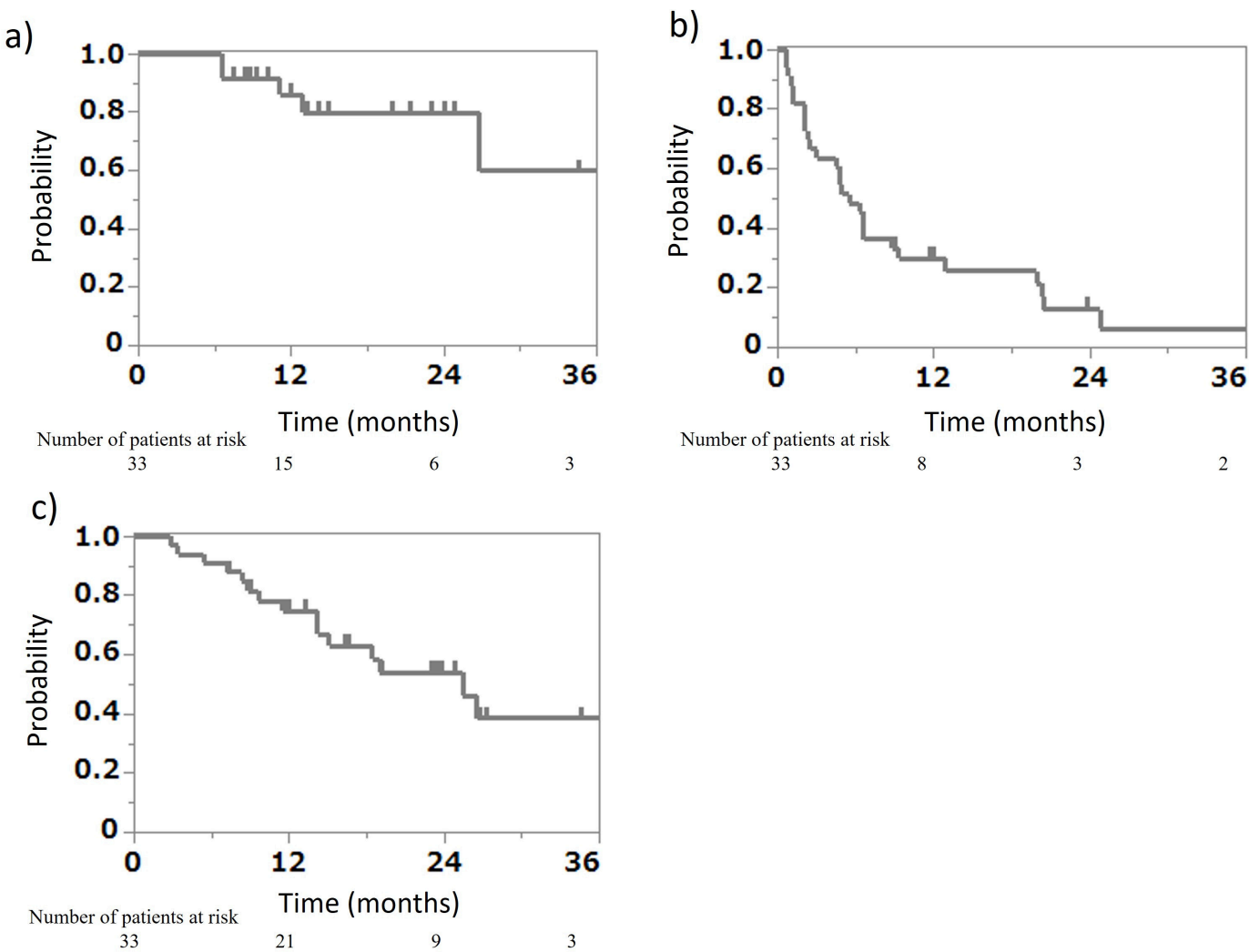


Figure 2

Kaplan–Meier survival curves

Assessment of the local control (a), progression-free survival (b), and overall survival (c) rates after carbon-ion radiotherapy for hepatocellular carcinoma using the Kaplan–Meier method

Supplementary Files

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