Laparoscopic liver resection for local recurrence after carbon-ion radiotherapy for hepatocellular carcinoma: A case report

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Abstract. Numerous potentially curative treatments have become available for patients with hepatocellular carcinoma (HCC) on the basis of the individual patient and tumor characteristics. Carbon-ion radiotherapy (C-ion RT) is a novel treatment option to reduce the physical burden in patients with HCC. However, the long-term outcomes and the clinical and pathological features of locoregional recurrence after initial C-ion RT are unclear. The present study reports the case of a patient who underwent a curative laparoscopic liver resection for the local recurrence of HCC after C-ion RT. A 73-year-old man was diagnosed with chronic hepatitis C and achieved a sustained virological response. During subsequent surveillance, a solitary HCC of 2.3 cm in diameter appeared in liver segment 7 (S7). While surgical resection was considered the best option, the patient chose C-ion RT as the initial HCC treatment. Although C-ion RT appeared to be successful for the primary lesion, enhanced computed tomography revealed that a hypervascular tumor had reappeared in the same area 16 months later. As HCC recurrence was suspected, several different examinations were performed. Computed tomography and magnetic resonance imaging showed that the recurrent tumor had irregular margins, and communication was suspected with the intrahepatic portal vein. A laparoscopic partial liver resection of S7 was planned. Histopathological examination of the excised specimen revealed proliferation of viable moderately to poorly differentiated HCC, with marked invasive growth and numerous portal vein infiltrations. To the best of our knowledge, this is the first report of surgery for locally recurrent HCC after C-ion RT. Oncological outcomes following C-ion RT for HCC remain unclear. Notably, there are cases of unusual recurrence with massive vascular invasion after C-ion RT. In the present case, the histological features were confirmed after C-ion RT for HCC. This case may raise concerns about the true efficacy of C-ion RT and warns against the easy choice of C-ion RT in spite of a resectable HCC.

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Abbreviations: HCC, hepatocellular carcinoma; RT, radiotherapy; C-ion, carbon-ion; RFA, radiofrequency ablation; S7, segment 7; CT, computed tomography; EOB-MRI, gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging; PIVKAII, protein induced by vitamin K absence; ICG, indocyanine green

Key words: HCC, C-ion RT, local recurrence, laparoscopic liver resection

Introduction

The treatments for hepatocellular carcinoma (HCC) are diverse and multidisciplinary. While multi-modal therapies are available for HCC, therapy is determined on the basis of tumor- and patient-related factors, including liver function (1,2). Recently, owing to advances in radiotherapy (RT), there have been numerous reports of the efficacy of particle beam treatment, such as carbon-ion RT (C-ion RT) and proton beam RT for HCC (3-7). However, to the best of our knowledge, there are no prospective studies regarding the treatment outcomes of particle beam therapy for solitary and small HCCs for which resection or radiofrequency ablation (RFA) is recommended. Additionally, C-ion RT and proton beam RT are performed mainly for recurrent cases and for patients with poor liver function who cannot tolerate surgery. To the best of our knowledge, there are no reports of surgical resection for local recurrence after these RTs. Therefore, the long-term outcomes and clinical and pathological features of locoregional recurrence after initial treatment by particle beam therapy are still unclear.

The present study reports the case of a patient who underwent a curative laparoscopic liver resection for a local recurrence of HCC after C-ion RT. The study presents the intraoperative features and histopathological findings of this locoregional recurrent tumor and the surrounding liver parenchyma after initial C-ion RT.

Case report

A 73-year-old man was referred to Department of Surgery in Saga University Hospital (Saga, Japan) in September 2022 for recurrence of HCC in segment 7 (S7) after C-ion RT, which was performed 16 months earlier in May 2021 as an initial treatment. Approximately 15 years earlier, the patient was diagnosed as hepatitis C virus-positive, and

antiviral therapy with pegylated interferon-α2b and oral ribavirin (pegylated interferon-α2b, 80 μg/week, oral ribavirin: 600 mg/day) for 24 weeks was administered 5 years after the diagnosis. A sustained virological response was achieved with this treatment, and the patient underwent regular examinations including physical examination, blood test and abdominal ultrasonography, at the Department of Hepatology in Saga University Hospital, thereafter. A total of 8 years after first achieving a sustained virological response, the initial HCC was detected by imaging examinations in March 2021. Contrast-enhanced computed tomography (CT) showed an 18-mm lesion on the surface of liver S7 that was heterogeneously enhanced in the arterial phase and washed out in the delayed phase (Fig. 1A and B). Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging (EOB-MRI) showed no EOB uptake in the tumor (Fig. 1C). At that point, the HCC was diagnosed as T1aN0M0, stage IA, in accordance with the Union for International Cancer Control 8th edition (8), indicating that the tumor was amenable to radical surgical resection. The patient's general condition was stable, liver function was well preserved, the Child-Pugh grade (9) was A, the albumin-bilirubin grade (10) was 1 and there were no severe comorbidities; however, the patient opted for C-ion RT as the initial treatment for the HCC. After completing the schedule of C-ion RT (a dose of 60 Gy in 4 fractions within a 9-day time period), the patient received follow-up CT every 4 months, which confirmed post-treatment changes in the tumor location (Fig. 2A). The tumor lesion shrank to a nodule of ~10-mm with a surrounding low-density area, and a delayed enhancement effect was observed, consistent with changes after C-ion RT. Blood test results showed that levels of both α-fetoprotein and protein induced by vitamin K absence (PIVKAII), which are tumor markers for HCC, were within the normal ranges (α-fetoprotein: 2.0 ng/ml [normal range: 0-10 ng/ml], PIVKAII: 19 mAU/ml [normal range: 0-40 mAU/ml]), and the hepatobiliary enzyme levels were not elevated (AST: 25 IU/l [normal range: 13-30 IU/l], ALT: 9 IU/l [normal range: 10-42 IU/l), ALP: 78 IU/l [normal range: 38-113 IU/l], γ-GTP: 22 IU/l [normal range: 13-64 IU/l]). However, recurrence was suspected, as CT performed 16 months after C-ion RT revealed an area with a distorted shape that was ring-enhanced in the arterial phase and washed out in the delayed phase within the previously irradiated area of S7 (Fig. 2B). Short-term follow-up CT, which was conducted 1 month after the most recent CT and 18 months after C-ion RT, revealed that the area suspected as recurrence had clearly enlarged, and the ring enhancement was stronger compared with that in the previous CT images (Fig. 2C). As another modality, EOB-MRI revealed a mass lesion on the surface of liver S7 that was hyperintense on T2-weighted/fat-suppressed imaging and diffusion-weighted imaging. Moreover, the lesion showed ring enhancement in the early phase and wash out in the delayed phase on dynamic study, and hypointensity, including the area around the lesion, in the hepatobiliary phase, with EOB (Fig. 2D). At the 16-month visit when the recurrence was first observed, both α-fetoprotein and PIVKAII levels in the blood test were within the normal ranges and were not elevated in comparison with previous data (α-fetoprotein, 1.6 ng/ml, PIVKAII: 17 mAU/ml). On the basis of the CT and MRI findings, atypical recurrence of HCC after C-ion RT was diagnosed. At this time, the attending hepatologist recommended a surgical resection for the recurrent HCC, and the patient strongly desired this approach. Regarding preoperative liver function, the indocyanine green (ICG) retention rate at 15 min, whose normal reference range is from 0 to 10%, was 16.2%. Additionally, the Child-Pugh classification and albumin-bilirubin score were grade A and grade 1, respectively, indicating that the patient could tolerate surgery. Therefore, a laparoscopic partial liver resection of S7 was performed in November 2022. The extent of the liver resection was designed to include the area affected by the C-ion RT. Regarding the potential of a biopsy before surgery, firstly the hepatologist determined that a biopsy would be somewhat difficult due to the location of the tumor. Furthermore, as the tumor was small and its boundaries were unclear, the recurrence of HCC could not be ruled out even if malignant cells were not detected by the biopsy. Based on this, a decision was made to judge recurrence based on the imaging findings. Intraoperatively, the liver surface above the tumor in S7 was depressed (delle), and atrophy and fibrosis were observed around the lesion (Fig. 3A). Fluorescence imaging (PINPOINT® Endoscopic Fluorescence Imaging System; Stryker Corporation) revealed that ICG uptake was weaker in the tumor and its surroundings than that in the normal parenchyma, unlike that found in typical HCC (Fig. 3B). The designed liver resection was completed successfully laparoscopically. Blood loss was 50 ml and the operating time was 275 min. The cut surface of the resected specimen revealed a whitish solid tumor with irregular borders measuring 15.3x13.4 mm in diameter (Fig. 4A). The resected specimens were fixed with 10% neutral buffered formalin for 24 h at room temperature. Formalin-fixed paraffin-embedded tissue was sectioned at a thickness of 4 μm and stained with hematoxylin and eosin (H&E). The H&E-stained slides were scanned and converted to digital slides by NanoZoomer S360 (Hamamatsu Photonics K.K.). Presented figures were obtained by digital slides. Histologically, proliferation of moderately differentiated HCC showing marked nuclear atypia was observed (Fig. 4B). The tumor showed an invasive growth pattern without a fibrous capsule between the tumor and the surrounding liver parenchyma, and numerous portal vein invasions were observed (Fig. 4C). The liver parenchyma around the tumor was collapsed owing to the loss of hepatocytes, and abundant infiltration of inflammatory cells in both the portal tract and hepatic lobules, with reactive cholangiolar proliferation, was observed (Fig. 4D). These liver parenchymal findings were considered the effects of C-ion RT. The surgical margins were negative and an R0 resection was confirmed. Based on the pathological findings, the final stage of the tumor was T1aN0M0, stage IA, in accordance with the Union for International Cancer Control 8th edition.

Postoperatively, the patient experienced no complications and was discharged on day 9. The patient visited the outpatient clinic every 3 months thereafter. An enhanced CT was performed each visit to check for recurrence, and tumor markers, such

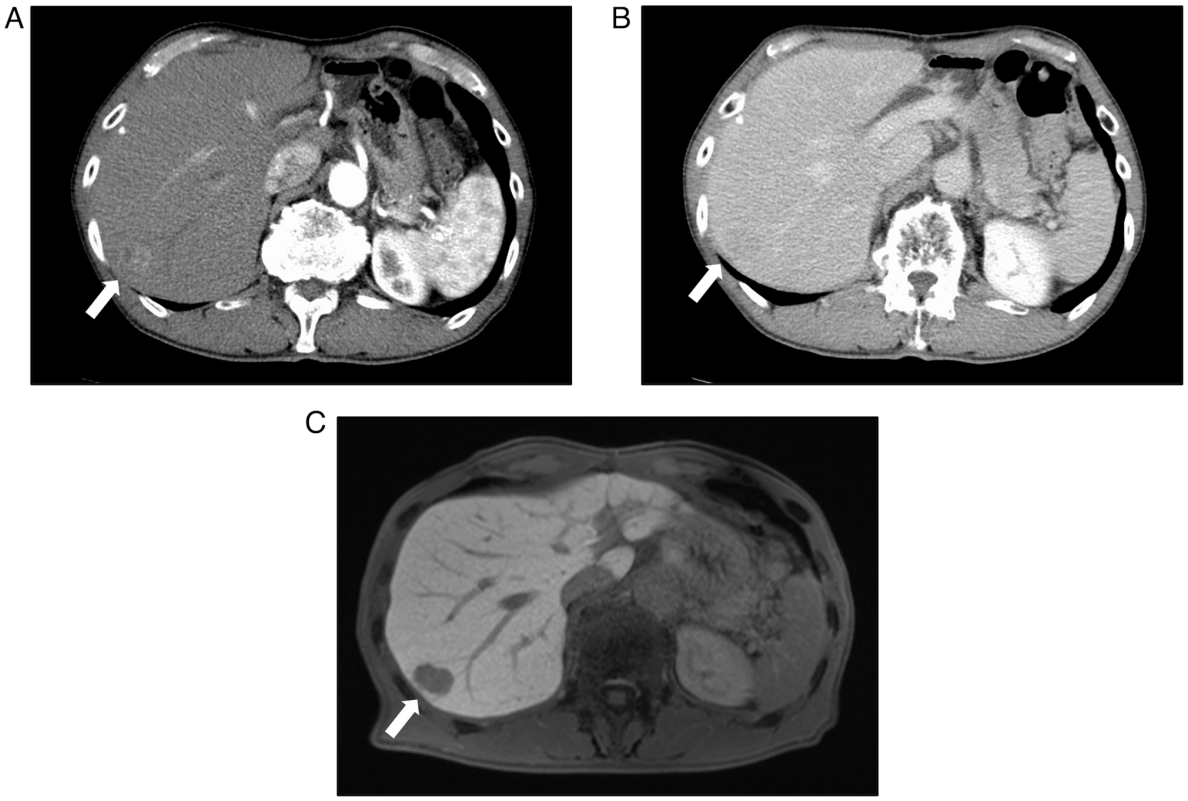

Figure 1. Contrast-enhanced CT and MRI at the initial detection of HCC in March 2021. (A) CT in the arterial phase showing a heterogeneously enhanced HCC in S7 (arrow). (B) CT in the delayed phase showing washed out HCC enhancement (arrow). (C) MRI in the hepatobiliary phase using EOB, showing no EOB uptake in the HCC (arrow). CT, computed tomography; magnetic resonance imaging; HCC, hepatocellular carcinoma EOB, gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid.

Figure 2. Imaging examinations after C-ion RT and at recurrence. (A) Contrast-enhanced CT after C-ion radiotherapy before recurrence showing an unenhanced irradiated area in the arterial phase (arrow). (B) Contrast-enhanced CT at the initial detection of recurrence showing ring-enhancement of the irradiated area in the arterial phase and wash out in the delayed phase (arrow). (C) Contrast-enhanced CT 1 month after detection of recurrence showing clear enlargement of the component suspected of recurrence (arrow). (D) Magnetic resonance imaging 1 month after the detection of recurrence showing hypointensity of the recurrent tumor and the surrounding tissues in the hepatobiliary phase when using gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (arrow). CT, computed tomography.

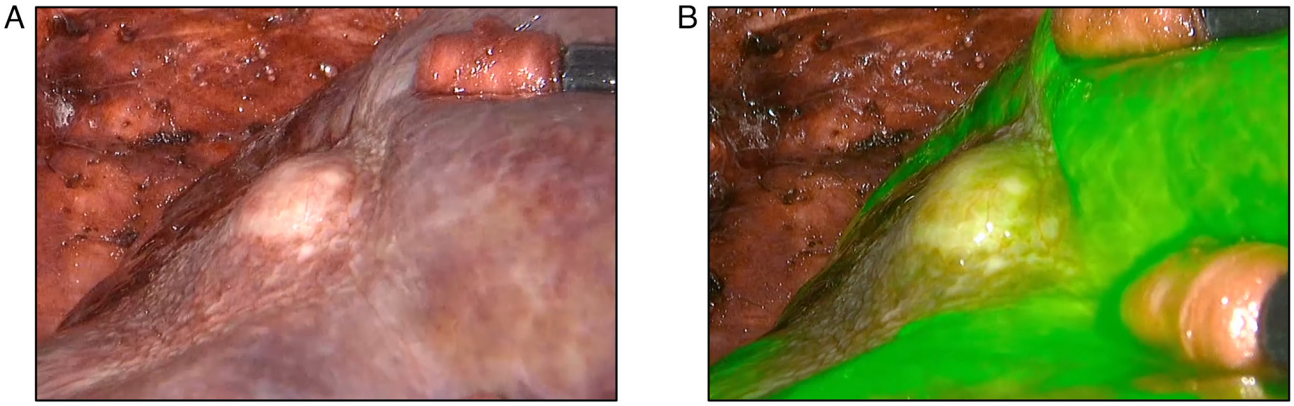

Figure 3. Intraoperative findings. (A) Liver surface above the tumor of segment 7 showing atrophy and fibrotic changes visible around the recurrent tumor. (B) Fluorescence imaging of the liver surface above the tumor showing weaker indocyanine green uptake in the tumor and the surrounding tissues compared with that in the normal parenchyma.

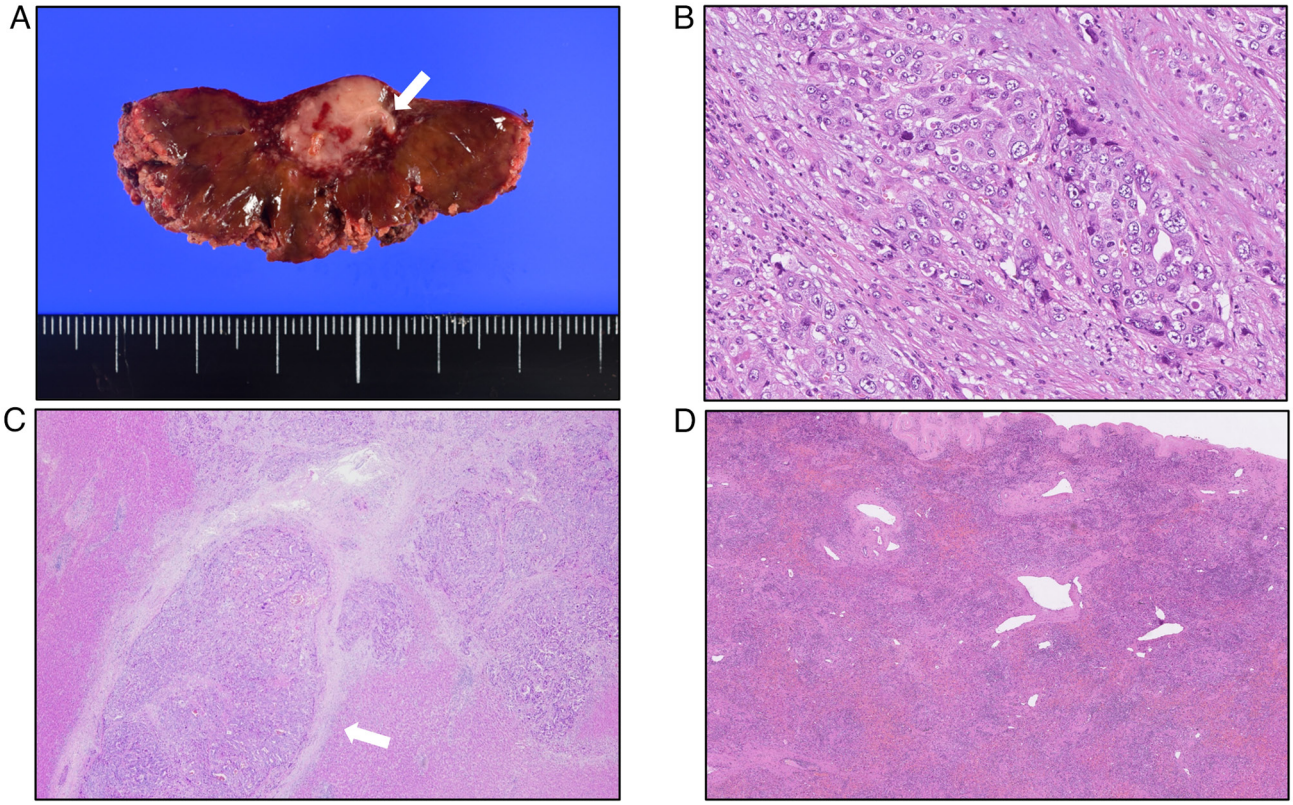

Figure 4. Macroscopic and microscopic findings. (A) Gross appearance of the tumor. The tumor is whitish and solid with irregular borders. Portal vein invasion is visible macroscopically (arrow). (B) Histologically, the tumor shows marked nuclear atypia [hematoxylin and eosin (H&E); x200 magnification]. (C) A typical infiltrating growth pattern and portal vein invasion (arrow) are visible (H&E; x20 magnification). (D) The liver parenchyma around the tumor is markedly collapsed due to the loss of hepatocytes (H&E; x25 magnification).

as α-fetoprotein and PIVKAII, were measured. There was no recurrence up to 13 months after surgery. Patient will continue to be followed up every 3 months to check for recurrence.

Discussion

The present study reports a case of curative laparoscopic liver resection for local recurrence of HCC after C-ion RT as the initial treatment. To the best of our knowledge, this is the first report of such a specific therapeutic process.

C-ion RT is a promising modality in RT that allows higher dose localization and relative biological efficacy compared with X-ray RT (11,12). Additionally, as C-ion RT has a 'Bragg peak', meaning an energy distribution in penetration depth, it is characterized by minimal damage to the normal cells surrounding the treatment target (13). Previous studies have reported that C-ion RT is associated with better sparing of the surrounding normal liver compared with stereotactic body RT (14,15). Considering these physical and biological advantages, C-ion RT is well tolerated in patients with HCC who are

older, fragile, and/or who have severe comorbidities or poor liver function (16,17). Thus, C-ion RT may be a treatment option even for small and solitary HCC, for which surgical resection or RFA is recommended, if the patient cannot tolerate these treatments. Therefore, surgical resection is extremely rare for local recurrence after C-ion RT. From this point of view, the current case is valuable to clarify the long-term outcomes or intraoperative findings and pathological features of locoregional recurrence after initial C-ion RT.

In the present case, CT at recurrence showed a clear increase in tumor size over a short period of time, while depression of the liver surface above the tumor, and communication between the tumor and the portal vein were observed, suggesting HCC with high malignant potential. Huang *et al* (18) reported the surgical findings of two patients who underwent living donor liver transplantation for HCC recurrence after C-ion RT. Severe atrophy of the liver parenchyma was found in the irradiated area, and the tissues adjacent to the irradiated area were strongly adhered, which resulted in difficulty with adhesiolysis during surgery. These changes following C-ion RT increase surgical difficulty, and adhesiolysis to address strong adhesions poses the risk of cancer dissemination. In the present case, severe atrophy and fibrosis were observed in the irradiated area during surgery. However, no adhesions were observed between the irradiated area and the diaphragm, and laparoscopic resection was completed without intraoperative complications. Additionally, in this case, the liver surface above the tumor had a delle. These changes were considered to be effects of C-ion RT and also may have indicated HCC with high malignant potential. Regarding the ICG uptake, it was hypothesized that accumulation did not occur, as the liver parenchyma around the tumor was markedly collapsed by the loss of hepatocytes.

Histopathologically, studies have shown that tumors measuring ≤2 cm have poor growth of the tumor vasculature, and ~10% of cases will have microvascular invasion of portal branches by the tumor (19-22). By contrast, numerous studies have shown that portal vein invasion is one of the strongest prognostic factors for HCC (23). In the present case, numerous portal vein invasions were observed despite the small size of the tumor (15 mm). Several studies have also shown that irradiation augments the invasiveness of some types of cancer cells, such as non-small cell lung cancer cells (24-26). Therefore, although pathological information before C-ion RT was not available in the present case, we hypothesized that the recurrent tumor after C-ion RT gained malignant potential; the tumor showed marked invasive growth with portal vein invasion. In a study where metastatic liver cancer from colon cancer for which C-ion beam therapy was selected even though the tumor was resectable, both local recurrence and massive tumor thrombi in the portal vein and hepatic vein were reported after C-ion beam therapy (27).

Regarding the basic concept of treatment for HCC, radical treatment is indicated for patients with HCC and good liver function, and the absence of high vascular invasion or distant metastasis (1,2,28). To achieve a safe and maximum therapeutic effect in HCC, it is necessary to select the optimal treatment on the basis of the stage of cancer progression and the patient's condition. In fact, liver resection is strongly recommended for HCC measuring ≤3 cm with no vascular invasion, according to the Japan Society of Hepatology HCC Guidelines 2021 (1). Similarly, in the Barcelona Clinic Liver Cancer staging and treatment strategy (2022 version), liver resection is recommended for single HCC without vascular invasion or extrahepatic spread in patients with preserved liver function and no increased portal pressure or bilirubin levels (2). The present case involved an initial single HCC measuring 18 mm in size; therefore, the best indication was a surgical approach. However, the patient selected C-ion RT as the initial treatment for the HCC. This decision was based on the fact that he had special health insurance, which paid for the advanced medical treatment; the national health insurance program in Japan does not cover C-ion RT. It is an important fact that the treatment choice resulted in recurrence with numerous portal vein invasions. Physicians involved in the treatment of HCC should note that such cases exist. Therefore, the present report is valuable in the sense that it warns against the easy selection of C-ion RT for patients with HCC for whom resection is considered optimal surgically and functionally.

It also must be noted that there is insufficient evidence confirming a therapeutic outcome of C-ion RT for early stage HCC, such as Barcelona Clinic Liver Stage 0 and A, and no studies have compared the outcomes of surgical resection and C-ion RT for these stages of HCC. Based on current evidence for the treatment of HCC, the standard treatment for early stage HCC is liver resection or RFA if the patient's general condition and liver function are preserved. In the current information-oriented society, there is a possibility that the number of patients who desire less invasive treatment and have excessive expectations for C-ion RT will increase. The possibility of unusual recurrence after C-ion RT, such as that reported in the present case, should be considered, and sufficient informed consent should be obtained from patients when selecting the treatment for HCC. By contrast, C-ion RT can be a very effective treatment option, with appropriate indications. However, currently, there is no international guideline for the indications for C-ion RT in HCC. Additional understanding must be gained regarding the hepatic biological and histopathological features after C-ion RT to optimize the treatment of HCC.

Finally, we speculate why HCC relapsed after initial C-ion RT in this case in association with clinical and pathological features. CT examination at the time of recurrence revealed a new distorted area at the central region of the irradiated S7. In other words, this clinical feature suggested that the recurrent tumor occurred inside of the irradiated area instead of on its margins. Regarding pathological features, histological examination of the resected specimen showed tumor cells adjacent to scar tissue that was considered to occur by irradiation of C-ion RT. Considering these clinical and pathological features, although the tumor was within the irradiated field of C-ion RT, the delivered radiation dose may have been insufficient to completely destroy the tumor cells. Chen *et al* (29) reported that the center of the irradiated area tends to be hypoxic, which may reduce the effectiveness of irradiation in this region.

In conclusion, the present study described surgery for an unusual recurrence of HCC after C-ion RT, which was successfully treated with a laparoscopic liver resection. Locoregional recurrence of HCC after C-ion RT could result in highly malignant cancer with extensive portal vein

invasion. In addition to hepatocyte atrophy and fibrosis, C-ion RT may cause severe intra-abdominal adhesions, and it is necessary to be aware of these changes when performing surgical resection for recurrence after C-ion RT. The present case may raise concerns about the true efficacy of C-ion RT and indicates the importance of appropriate treatment selection on the basis of individual patient- and tumor-related characteristics.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

TT was responsible for the conception of the study and drafting the case report. TT, TI and KI performed the surgery and perioperative management of the patient and edited the manuscript. TT, KI, KK and TI performed the acquisition and analysis of data. HN advised on patient treatment. TT, TI and HN reviewed the manuscript. TT, TI and HN confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written informed consent for the publication of the data.

Competing interests

The authors declare that they have no competing interests.

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