Proton Irradiation in a Single Fraction for Hepatocellular Carcinoma Patients with Uncontrollable Ascites

Technical Considerations and Results

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Purpose: To present technical considerations and results of proton irradiation in a single fraction for hepatocellular carcinoma (HCC) patients with uncontrollable ascites.
Patients and Methods: Three HCC patients with uncontrollable ascites underwent proton irradiation of 24 Gy in a single fraction. Hepatic tumors were solitary in two patients, and multiple in one, and tumor sizes were 30, 30, and 33 mm in maximum diameter. No patient had lymph node or distant metastases. The center position of radiation fields was determined and the beam range was adjusted, using CT data taken immediately before irradiation to compensate for changes in the volume of ascites. Adjustment of the beam range was within 6 mm in water-equivalent thickness.
Results: All irradiated tumors showed objective responses, and were controlled during the follow-up period. Of the three patients, two were alive with no evidence of disease at 13 and 30 months, respectively, after treatment. The remaining patient died of ruptured esophageal varices 6 months after treatment. No therapy-related toxicity of grade 3 or more was observed.
Conclusion: Proton beams were successfully adjusted immediately before irradiation. Single-dose irradiation with precisely adjusted proton beams may be tolerable for HCC patients with uncontrollable ascites.

Key Words: Ascites · Hepatocellular carcinoma · Proton-beam therapy · Radiation therapy · Single-fraction irradiation

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Protonenbestrahlung in einer einzigen Fraktion bei Patienten mit Leberzellkarzinom und unkontrollierbarem Aszites. Technische Überlegungen und Ergebnisse

Ziel: Vorstellung technischer Überlegungen und der Ergebnisse von Protonenbestrahlungen in einer einzigen Fraktion bei Patienten mit Leberzellkarzinom (HCC [„hepatocellular carcinoma"]) und unkontrollierbarem Aszites.
Patienten und Methodik: Drei HCC-Patienten mit unkontrollierbarem Aszites erhielten eine Protonenbestrahlung von 24 Gy als Einzelfraktion. Bei den Lebertumoren handelte es sich in zwei Fällen um solitäre Tumoren und in einem Fall um multiple Tumoren, deren maximaler Durchmesser jeweils 30, 30 und 33 mm betrug. Bei keinem der Patienten lagen Lymphknoten- oder Fernmetastasen vor. Das Zentrum des Bestrahlungsbereichs wurde anhand der unmittelbar vor der Bestrahlung erhobenen CT-Daten festgelegt, und der Strahlbereich wurde entsprechend eingestellt, um Änderungen im Aszitesvolumen auszugleichen. Die Einstellung des Strahlbereichs lag innerhalb einer wasseräquivalenten Schichtdicke von 6 mm.
Ergebnisse: Bei allen bestrahlen Tumoren wurde eine objektive Veränderung registriert und während der Beobachtungszeit kontrolliert. Zwei der drei Patienten waren jeweils 13 und 30 Monate nach der Behandlung ohne Anzeichen der Krankheit am Leben. Der andere Patient verstarb 6 Monate nach der Behandlung an einer Ruptur ösophagealer Varizen. Therapiebezogene Toxizität eines Schweregrades von 3 oder höher wurde nicht beobachtet.
Schlussfolgerung: Protonenstrahlen wurden unmittelbar vor der Bestrahlung erfolgreich eingestellt. Die Bestrahlung als Einzeldosis mit einem genau eingestellten Protonenstrahl scheint für HCC-Patienten mit unkontrollierbarem Aszites tolerierbar zu sein.

Schlüsselwörter: Aszites · Leberzellkarzinom · Protonentherapie · Strahlentherapie · Einzelfraktionsbestrahlung

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Introduction

Hepatocellular carcinoma (HCC) is a common malignancy and a major contributor to cancer mortality [22]. Many HCC patients are effectively treated with various modalities, such as surgical resection, transcatheter arterial chemoembolization, percutaneous ethanol injection and microwave coagulation, and radiofrequency ablation [2, 15, 20]. However, HCC patients with uncontrollable ascites have limited treatment options.

At our institute in the University of Tsukuba, Japan, proton beams have been used to treat HCC and other malignancies since 1983 [4, 9–12, 25, 29]. Proton beams are theoretically better in dose localization compared with photons, and, consequently, can reduce the irradiated volume and dose given to the hepatic parenchyma and digestive tract of HCC patients, while increasing the dose to the tumor [6, 14, 21, 23, 27, 28]. HCC patients who have ascites due to cirrhosis at the time of diagnosis usually receive proton beam therapy when the ascites is under control. However, there are a few patients with uncontrollable ascites, and it is difficult to irradiate hepatic tumors precisely in daily fractions in such patients. Therefore, three consecutive HCC patients with uncontrollable ascites were treated with high-dose irradiation in a single fraction with precisely adjusted proton beams. Herein, we present a first report on technical considerations and results of this treatment for HCC.

Patients and Methods

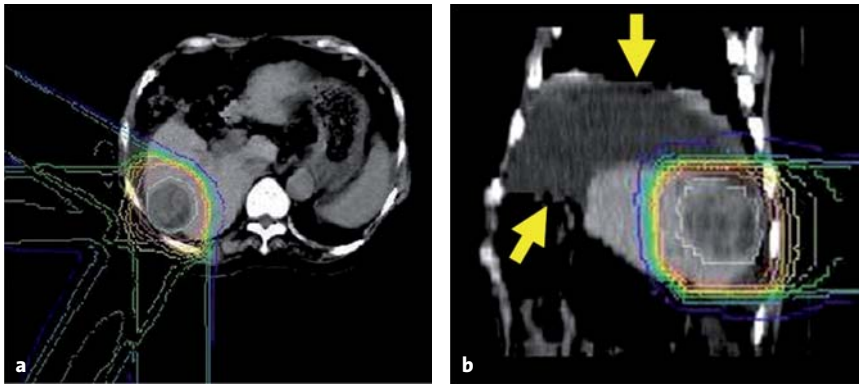
Patients

In September 2001, proton-beam therapy was started at our new facility. A total of 158 HCC patients had undergone proton-beam therapy by September 2004. Of these patients, three were treated with proton irradiation in a single fraction, because other treatment modalities were considered contraindicated or unfeasible because of the existence of uncontrollable ascites due to cirrhosis. Their general condition was Eastern Cooperative Oncology Group performance status 0–2 [24]. Two patients had Child-Pugh class B, and one patient class C cirrhosis, respectively [26]. All patients were clinically diagnosed as HCC based on imaging findings (tumor regions enhanced in arterial phase, and washed out in portal venous phase on multiphase contrast-enhanced computed tomography [CT]), because taking biopsies was considered dangerous due to ascites. Two patients had solitary, and one patient multiple tumors, respectively, in the peripheral regions of the liver. No patient had regional lymph node or distant metastases. Patient and tumor characteristics are summarized in Table 1. Written informed consent was obtained from all patients before treatment.

Table 1. Patient and tumor characteristics. AFP: α-fetoprotein; F: female; HCV: hepatitis C virus; M: male; PS: performance status.

Tabelle 1. Patienten- und Tumorcharakteristika. AFP: α-Fetoprotein; F: weiblich; HCV: Hepatitis-C-Virus; M: männlich; PS: Performance-Status.

Case #	Age (years)	Gender	PS	Etiology of cirrhosis	Child-Pugh class (score)	Tumors (n)	Tumor size (mm)	Baseline serum AFP value (ng/ml)
1	69	F	2	HCV	Class C (11)	1	30	272
2	68	F	1	HCV	Class B (9)	1	30	70
3	78	M	1	HCV	Class B (8)	2	33 and 30	16

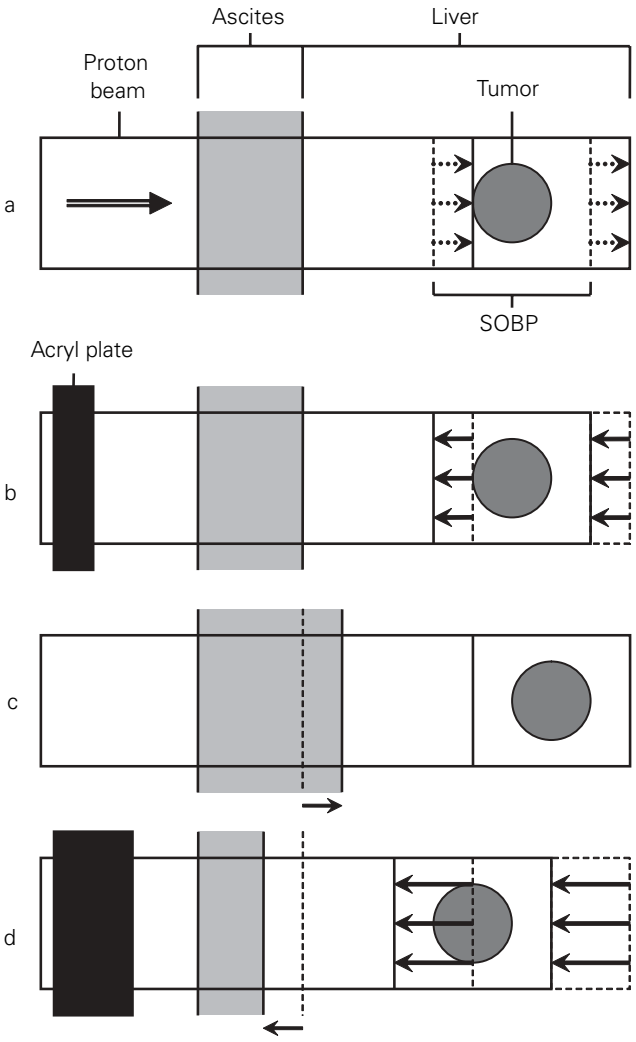


Figures 1a and 1b. Isodose distribution of proton beams in a hepatocellular carcinoma patient. a) Isodose lines on a CT slice demonstrate 100% of the prescribed dose level at the inside center, which decreases by 10% of the dose at the outside. Critical organs such as the heart, digestive tract, and spinal cord are located entirely outside the irradiated volume, due to sharp distal fall-off of the Bragg peak of proton beams. b) Sagittal image reconstructed by treatment-planning CT. Fluid collection indicated by arrows shows ascites.

Abbildungen 1a und 1b. Isodosenverteilung des Protonenstrahls bei einem Patienten mit Leberzellkarzinom. a) Isodosenlinien auf einem CT-Schnitt zeigen innerhalb des Zentrums 100% des vorgeschriebenen Dosispegels, der dann bis auf 10% der Dosis im Randbereich abfällt. Lebenswichtige Organe wie das Herz, der Verdauungstrakt und das Rückenmark liegen aufgrund des scharf abfallenden Bragg-Maximums des Protonenstrahls vollständig außerhalb des bestrahlten Volumens. b) Anhand einer zur Behandlungsplanung angefertigten CT-Aufnahme rekonstruiertes Sagittalbild. Die durch Pfeile markierte Flüssigkeitsansammlung zeigt den Aszites.

Proton-Beam Therapy

The patient's body was immobilized by an individually shaped vacuum pillow (ESFORM; Engineering System, Matsumoto, Japan). Treatment planning for proton-beam therapy was based on respiratory-synchronized CT images at 5-mm intervals in the treatment position. The treatment-planning CT was performed 2–3 days before treatment. Clinical target volume (CTV) was defined as gross tumor volume plus a 5-mm margin. Planning target volume (PTV) included



Figures 2a to 2d. Methods for adjusting the range of proton beams according to changes in the thickness of ascites along the beam path. a) The beam range was intentionally assumed to be 10 mm longer in water-equivalent thickness than that estimated by treatment planning. Accordingly, the spread-out Bragg peak (SOBP) shifts to 10 mm in the deeper area in water-equivalent thickness. b) A case with no change in the thickness of ascites at irradiation. An acryl plate with 10-mm water-equivalent thickness is inserted in the beam line. c) A case with a 10-mm longer beam range than that estimated by treatment planning due to increase in the thickness of ascites at irradiation. No acryl plate is used. d) A case with a shorter beam range than that estimated by treatment planning due to decrease in the thickness of ascites at irradiation. An acryl plate with water-equivalent thickness equal to the shortened range plus 10 mm is inserted in the beam line.

Abbildungen 2a bis 2d. Methoden zur Einstellung des Protonenstrahlbereichs entsprechend den Änderungen in der Schichtdicke des Aszites entlang dem Strahlengang. a) Es wurde unterstellt, dass der Strahlenbereich in einer wasseräquivalenten Schichtdicke 10 mm länger war als bei der Behandlungsplanung angenommen. Dementsprechend verschiebt sich das SOBP („spread-out Bragg peak") bei einer wasseräquivalenten Schichtdicke um 10 mm in die Tiefe. b) Ein Fall ohne Änderung der Schichtdicke des Aszites bei der Bestrahlung. Eine Acrylplatte mit einer wasseräquivalenten Schichtdicke von 10 mm ist in den Strahlengang geschoben. c) Ein Fall, bei dem der Strahlenbereich aufgrund der Zunahme der Schichtdicke des Aszites bei der Bestrahlung in einer wasseräquivalenten Schichtdicke 10 mm länger war als bei der Behandlungsplanung angenommen. In diesem Fall wurde keine Acrylplatte verwendet. d) Ein Fall, bei dem der Strahlenbereich aufgrund der Zunahme der Schichtdicke des Aszites bei der Bestrahlung kürzer war als bei der Behandlungsplanung angenommen. Hier wurde eine Acrylplatte mit einer dem verkürzten Bereich plus 10 mm entsprechenden wasseräquivalenten Schichtdicke in den Strahlengang geschoben.

the CTV with a 5-mm margin, and an additional 5-mm margin in the caudal direction for respiratory movement. The PTV was homogeneously encompassed with the 100% dose level, using the spread-out Bragg peak (SOBP) of proton beams (Figure 1). Multiple hepatic tumors in case 3 were entirely included within a target volume. The dose of proton beams was verified in an acryl phantom for each patient before treatment. The beam range, which was assumed to be 10 mm longer than that estimated by treatment planning, was tentatively set to deal with a possible increase in the thickness of ascites along the beam path.

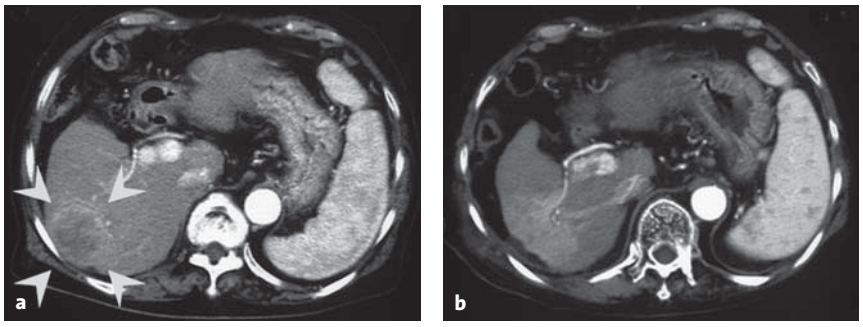
CT was repeated in the treatment position for all patients immediately before irradiation, on the treatment day. The center position of radiation fields was subsequently determined, and the beam range was adjusted based on data obtained from CT, and referring to treatment-planning CT data obtained previously. To adjust the beam range, acryl plates available per millimeter in water-equivalent thickness were inserted in the beam line as compensators (Figure 2). The difference between the beam range estimated by treatment planning and that estimated immediately before irradiation for each port in all patients, ranged from 0 to 6 mm (median, 3 mm) in water-equivalent thickness.

Proton beams of 155–250 MeV generated by an accelerator with a synchrotron were used for treatment. The beams were synchronized with respiration, and were delivered through four or five ports with coplanar angles using a rotational gantry. Respiratory gating was controlled by means of a semiconductor laser irradiated to the abdominal surface of patients, so that proton beams were delivered to the hepatic tumors in the expiratory phase, when the tumor position was considered to be at its most stable and reproducible [30]. The overall treatment time between the beginning of CT scanning and the end of irradiation was approximately 60 min in each patient. A dose of 24 Gy in a single fraction, with 4.8–6.0 Gy equally weighted per port, was used. A relative biological effectiveness value of 1.0 was used in accordance with data obtained from experiments with fibrosarcoma NFSa cells [1].

The dose of 24 Gy in a single fraction was equivalent to 68.0 Gy and 129.6 Gy when given with 2 Gy per fraction according to the linear-quadratic model with α/β ratios of 10 and 3 for early and late responding tissues, respectively [32]. Dose-volume analyses of the liver were performed in all patients.

Follow-Up Procedure

Patients underwent serum α-fetoprotein (AFP) measurements and abdominal CT 1 and 3 months after treatment, respectively, and then were followed up at intervals of 1–3 months. Complete response (CR) and partial response (PR) were defined as complete disappearance of the irradiated tumor and > 50% reduction in tumor volume, respectively. Therapy-related toxicities were evaluated with Common Terminology Criteria for Adverse Events v3.0 [5].



Figures 3a and 3b. Contrast-enhanced CT in the arterial phase of a hepatocellular carcinoma patient before and after treatment. a) Immediately before irradiation. Arrowheads represent the position of the hepatic tumor with inhomogeneous enhancement. b) 11 months after irradiation. The hepatic tumor has disappeared, although the hepatic parenchyma irradiated with a high dose shows enhancement due to radiation hepatitis and atrophic change.

Abbildungen 3a und 3b. Kontrastverstärkte CT-Aufnahme in der arteriellen Phase eines Patienten mit Leberzellkarzinom vor und nach der Behandlung. a) Unmittelbar vor der Bestrahlung. Die Pfeilspitzen zeigen die Position des Lebertumors mit inhomogener Verstärkung. b) 11 Monate nach der Bestrahlung. Der Lebertumor ist verschwunden, obwohl das mit hoher Dosis bestrahlte hepatische Parenchym aufgrund einer Strahlenhepatitis und atrophischer Veränderungen verstärkt erscheint.

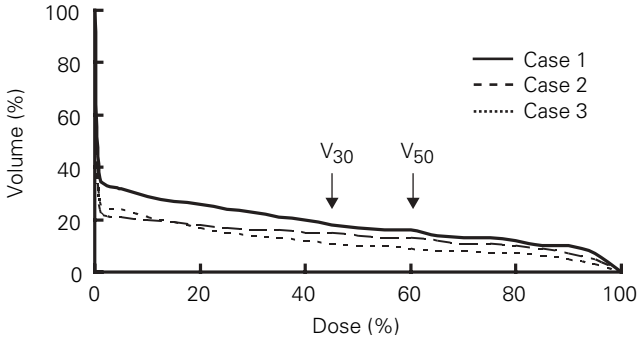


Figure 4. Dose-volume histograms of the liver in three hepatocellular carcinoma patients treated with proton irradiation in a single fraction. V_{30} and V_{50} show %volumes of the liver to which 45% (10.8 Gy) and 60% (14.4 Gy) of the prescribed dose (24 Gy) to the tumors were given, respectively.

Abbildung 4. Dosis-Volumen-Histogramme der drei Patienten mit Leberzellkarzinom, die mit als Einzelfraktion verabreichter Protonenbestrahlung behandelt wurden. V_{30} und V_{50} zeigen das %-Volumen der Leber, zu dem noch etwa 45% (10,8 Gy) und 60% (14,4 Gy) der vorgeschriebenen Dosis (24 Gy) addiert wurden.

Results

Tumor Control and Survival

All three patients showed PR 3 months after treatment. Subsequently, cases 2 and 3 achieved CR, 11 and 9 months after treatment, respectively (Figure 3). No recurrence was observed in any patient. Serum AFP values which were 272 and 70 ng/ml beyond the upper normal limit of 20 ng/ml in cases 1 and 2 before treatment decreased to 88 and 53 ng/ml 1 month after treatment, and to 26 and 7 ng/ml at the last follow-up, respectively.

Case 1 died of rupture of esophageal varices due to cirrhosis 6 months after treatment. This patient had undergone repeated endoscopic sclerotherapy for bleeding from the varices before irradiation. Cases 2 and 3 were alive with no evidence of disease, 30 and 13 months after treatment, respectively.

Dose-Volume Analysis

In cases 1, 2, and 3, CTV was 62, 63, and 78 cm^3, respectively; total liver volume (TLV) amounted to 807, 731, and 1,011 cm^3, respectively. Percentage of CTV in TLV (%CTV) was 7.7% in cases 1 and 3, and 8.6% in case 2. Doses of 10.8 Gy and 14.4 Gy in a single fraction were almost equal to doses of 30 Gy and 50 Gy in terms of 2 Gy per fraction-equivalent dose with an α/β ratio of 3, respectively. Percentages of liver volume to which the doses of ≥ 10.8 Gy and ≥ 14.4 Gy were irradiated in TLV were defined as V_{30} and V_{50}, respectively. V_{30} was 18%, 15%, and 11%, and V_{50} was 16%, 13%, and 9% in cases 1, 2, and 3, respectively. Dose-volume histograms of the liver are shown in Figure 4. The heart and spinal cord were entirely excluded from the irradiated volume in all patients. The irradiated dose to the gastrointestinal tract was < 2.4 Gy (10% of the prescribed dose).

Toxicity

Therapy-related acute toxicities were not observed at all. There was no deterioration in Child-Pugh score 1 month after irradiation.

As for therapy-related late toxicity, case 2 showed a rib fracture with right lateral chest pain 13 months after irradiation. The fracture region was included within > 90% dose volume because it was adjacent to the tumor. This late event, which was categorized as grade 2, improved with conservative

Table 2. Clinical courses of three hepatocellular carcinoma patients treated with proton irradiation in a single fraction. AFP: α-fetoprotein; CR: complete response; CTV: clinical target volume; NED: no evidence of disease; PR: partial response; REV: rupture of esophageal varices; TLV: total liver volume.

Tabelle 2. Klinische Verläufe der drei Patienten mit Leberzellkarzinom, die mit als Einzelfraktion verabreichter Protonenbestrahlung behandelt wurden. AFP: α-Fetoprotein; CR: komplette Remission; CTV: klinisches Zielvolumen; NED: keine Krankheitszeichen; PR: partielle Remission; REV: Ösophagusvarizenruptur; TLV: gesamtes Lebervolumen.

Case #	CTV (cm^3)	TLV (cm^3)	V_{30} (%)	V_{50} (%)	Tumor response	Recurrence	Recent serum AFP value (ng/ml)	Adverse event	Follow-up period (months)	Recent status
1	62	807	18	16	PR	None	26	None	6	Dead of REV
2	63	731	15	13	CR	None	7	Rib fracture, grade 2	30	Alive with NED
3	78	1,011	11	9	CR	None	13	None	13	Alive with NED

therapy, and the symptoms subsequently subsided. The other two patients had no late toxicities after treatment. Liver functions in all patients were well preserved, with no deterioration in Child-Pugh score during the follow-up period.

The clinical courses of all patients are summarized in Table 2.

Discussion

The intraabdominal organs of patients with ascites are unstable in position, and the volume of ascites changes daily. Hence, it is difficult to precisely target hepatic tumors in patients with ascites when treatment is given in daily sessions. Furthermore, it is essential for proton irradiation that the beam range is precisely fitted to the target. Therefore, in our study, all beam ranges were adjusted using CT data taken immediately before irradiation, and high-dose proton irradiation in a single fraction was used to treat the tumors.

Some studies have reported the use of hypofractionated high-dose radiation therapy with photons for hepatic tumors. Blomgren et al. were the first to report on stereotactic radiotherapy for extracranial tumors, including HCCs of eight cases [3]. The patients in their series underwent stereotactic radiotherapy with total mean doses of 16–66 Gy in one to three fractions to PTVs. Tumors decreased in volume in two patients, and disappeared in one patient. However, all patients developed fever up to 38.5 °C and nausea for a few hours after irradiation. Moreover, one patient died of unknown origin 2 days after treatment, and two patients died, probably of liver failure, 1.5 and 2.5 months after treatment. Liang et al. treated 128 patients with primary liver carcinoma using three-dimensional conformal radiotherapy (3D-CRT) with total doses of 40–60 Gy (median, 53.6 Gy) in fractions of 4–8 Gy (median, 4.9 Gy) [18]. The objective response rate was 55% at 3 months after treatment. However, seven (6%) of 108 patients with Child-Pugh class A cirrhosis, and twelve (60%) of 20 patients with Child-Pugh class B cirrhosis developed radiation-induced liver disease (RILD) 4–8 weeks after treatment, and 16 of 19 patients with RILD died of liver failure. Wulf et al. and Wada et al. attempted to control pulmonary and hepatic tumors with 3D-CRT, using total doses of 30–45 Gy in three fractions [31, 33]. Local control rates of hepatic tumors were 61–71.2% at 2 years, and tumor size represented a predictive factor for local control (95.0% for < 3 cm in tumor size vs. 58.3% for ≥ 3 cm at 2 years). Herfarth et al. reported the use of 3D-CRT with a single dose of 14–26 Gy in 37 patients with hepatic tumors that were liver metastases from various origins in most cases and HCC in only one case [13]. The objective response rate was 63% 0.5 years after irradiation, though the median follow-up period was only 5.7 months.

To our knowledge, there has been no detailed report on the outcomes of HCC treatment with radiation therapy using a single fraction. In the current study, all hepatic tumors were controlled during the follow-up period of 6–30 months. Unfortunately, all the present cases were not histologically but clinically diagnosed. However, it is reported that the false-positive rate is ≤ 2% in HCC clinically diagnosed by multiphase (arterial, portal venous and delayed phase) contrast-enhanced CT [19]. Furthermore, the accuracy of diagnosis of HCC becomes better when the patient has cirrhosis or the tumor size is > 3 cm [17]. Therefore, HCC is frequently diagnosed by medical imaging such as multiphase CT without biopsy in our country, especially in patients with ascites, bleeding tendency, or unfavorable tumor location, in whom taking of a biopsy is considered risky. The present cases were diagnosed as HCC using multiphase CT, which showed typical HCC patterns; moreover, all patients had cirrhosis, cases 1 and 2 had abnormally elevated AFP values before treatment, and case 3 had a hepatic tumor of > 3 cm. Accordingly, the diagnosis of HCC in the present cases was considered reliable.

The radiation tolerance of the whole normal liver is reported to be approximately 30 Gy in conventional fractions [8]. Some studies have demonstrated an intimate relationship between radiation tolerance and irradiated volume in the liver. Doses associated with 5% risk of RILD for irradiation volumes of one third and two thirds of the liver are 90 Gy and 47 Gy, respectively [7, 16]. These findings suggest that high-dose irradiation can be delivered safely to a part of the liver including HCC. In the present cases, V_{30} and V_{50} were 11–18% and 9–16%, respectively. These irradiated %volumes of the liver were far smaller than those assumed to be tolerable, though the relationship between dose and volume in single-fraction irradiation cannot be dealt with in the same way as that in conventional-dose irradiation.

Conclusion

Proton beams were successfully adjusted immediately before irradiation. Single-dose irradiation with precisely adjusted proton beams may be tolerable for HCC patients with uncontrollable ascites. However, the safety and efficacy of this treatment must be carefully confirmed by further investigations using a larger number of patients and a longer follow-up period.

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