Proton Beam Therapy for Hepatocellular Carcinoma: A Retrospective Review of 162 Patients

Toshiya Chiba,[1] Koichi Tokuuye,[2] Yasushi Matsuzaki,[1] Shinji Sugahara,[2] Yoshimichi Chuganji,[1] Kenji Kagei,[2] Junichi Shoda,[1] Masaharu Hata,[2] Masato Abei,[1] Hiroshi Igaki,[2] Naomi Tanaka,[1] and Yasuyuki Akine[2]

Abstract

Purpose: We present results of patients with hepatocellular carcinoma (HCC) treated with proton beam therapy.

Experimental Design: We reviewed 162 patients having 192 HCCs treated from November 1985 to July 1998 by proton beam therapy with or without transarterial embolization and percutaneous ethanol injection. The patients in the present series were considered unsuitable for surgery for various reasons, including hepatic dysfunction, multiple tumors, recurrence after surgical resection, and concomitant illnesses. The median total dose of proton irradiation was 72 Gy in 16 fractions over 29 days.

Results: The overall survival rate for all of the 162 patients was 23.5% at 5 years. The local control rate at 5 years was 86.9% for all 192 tumors among the 162 patients. The degree of impairment of hepatic functions attributable to coexisting liver cirrhosis and the number of tumors in the liver significantly affected patient survival. For 50 patients having least impaired hepatic functions and a solitary tumor, the survival rate at 5 years was 53.5%. The patients had very few acute reactions to treatments and a few late sequelae during and after the treatments.

Conclusions: Proton beam therapy for patients with HCC is effective, safe, well tolerable, and repeatable. It is the useful treatment mode for either cure or palliation for patients with HCC irrespective of tumor size, tumor location in the liver, insufficient feeding of the tumor with arteries, presence of vascular invasion, impaired hepatic functions, and coexisting intercurrent diseases.

The estimated number of patients with primary hepatocellular carcinoma (HCC) was ~1 million per year worldwide (1); the average survival for patients with HCC is a few months when untreated (2–4). In Japan, HCC is the third highest cause of cancer-related deaths for men and the fourth for women (5). Patients having long-term hepatitis B or C with liver cirrhosis are frequently found to have HCC; 90% of patients with HCC have had hepatitis C virus infection (6, 7).

Several treatment modalities are currently available for patients with HCC. For 17,885 patients with HCC treated in Japan over the 2-year period (8) from January 1998 to December 1999, proportions of patients with HCC treated with each modality were 51.4% for transarterial chemoembolization (9–13), 42.1% for transcatheter arterial embolization, 29.2% for surgery (14) 25.7% for percutaneous ethanol injection (15, 16), 7.3% for microwave coagulation therapy (17, 18), 2.1% for radiofrequency ablation (19–21), and 1.5% for radiotherapy.

Photon therapy has rarely been used in HCC treatment because the tolerance dose is ~30 Gy per 3 weeks when the entire organ is irradiated, which is considerably lower than that necessary for tumor control (22–26).

Proton beams allow a rapidly increasing dose at the end of the beam range (Bragg peak) with which excellent dose localization to the target is obtained (27). We began proton beam therapy for malignancies of various organs, including the liver, in 1983 (28). We previously reported excellent local tumor controls in patients with HCCs treated with proton beam therapy (26, 28–31). In this report, we present long-term results of proton beam therapy for 162 patients having 192 HCCs treated from 1985 to 1998.

Patients And Methods

Patients. The present study was conducted according to the Helsinki Declaration and approved by the Ethics Committee of the University of Tsukuba. All patients gave their written informed consents.

Patients with at least one of following conditions were eligible for proton beam therapy: (*a*) medically inoperable conditions attributable to coexisting advanced cirrhosis (i.e., indocyanin green R_{15} > 25%, serum total bilirubin level 34.2-59.9 μmol/L) and other intercurrent diseases; (*b*) HCC(s) not suitable for surgical resection and considered difficult to control with nonsurgical treatments, such as transcatheter

Authors' Affiliations: Departments of [1]Gastroenterology and [2]Radiation Oncology, Institute of Clinical Medicine, University of Tsukuba, Ibaraki, Japan

Received 7/9/04; revised 10/28/04; accepted 12/20/04.

Grant support: Grant-in-Aid for Cancer Research (15-9) and Second Term Comprehensive 10-Year Strategy for Cancer Control (H-15-006) from the Ministry of Health, Labour, and Welfare of the Japanese Government.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Note: T. Chiba and K. Tokuuye contributed equally to this work. Presented in part at the 45th Annual Meeting of the American Society for Therapeutic Radiology and Oncology, October 2003, Salt Lake City, Utah.

Requests for reprints: Koichi Tokuuye, Radiation Oncology, Institute of Clinical Medicine, University of Tsukuba, Tennodai 1-1-1, Tsukuba, Ibaraki 305-8575, Japan. Phone: 81-29-853-7124; Fax: 81-29-853-7102; E-mail: ktokuue@pmrc.tsukuba.ac.jp.

arterial embolization and percutaneous ethanol injection; (*c*) patient's refusal of surgery. The patient was required to have three or fewer tumors in the liver to enter the study; when the patient had multiple tumors, they were encompassed in a single irradiation field.

From November 1985 to July 1998, we treated 165 patients with HCCs using proton beam therapy at the Proton Medical Research Center, University of Tsukuba. Three of the 165 patients were excluded from present analysis: one patient discontinued proton beam therapy because of severe cholecystitis not attributable to irradiation; one patient discontinued the treatment for nonmedical reasons; and one patient underwent liver transplantation following proton beam therapy. The remaining 162 patients having 192 HCCs were reviewed with regard to survival rates, local control rates, and treatment sequelae.

Of the 162 patients, 110 underwent ultrasound-guided percutaneous needle (21 Majima needle, Top Co., Ltd., Tokyo, Japan) biopsy, and 100 of the 110 were diagnosed pathologically as having HCC. The remaining 52 patients did not undergo needle biopsy for various reasons: tumor location was considered too dangerous for needle insertion, concomitant illness, and patient's refusal of biopsy. For 100 patients with pathologically diagnosed HCC, 95% of the patients had tumors of grade I and II in the Edmondson and Steiner grade (32). Thirty-nine of the 62 patients without pathologic diagnosis were judged to have HCC based on increased serum α-fetoprotein level of >100 μg/L and imaging studies. The remaining 23 patients were diagnosed solely on imaging studies.

Table 1 shows patient characteristics. The median age was 62.5 years ranging from 41 to 84 years. Patients were categorized retrospectively according to the degree of impairment in the hepatic function using Child-Pugh classification (33). About half of the patients showed class B and C in the classification. Of the patients, 86% had performance status 0 or 1.

Table 1. Clinical characteristics of patients

Characteristics	No. patients (%)
Age (y)	
<60	56 (34.6)
60-69	72 (44.4)
≥70	34 (21.0)
Gender	
Men	124 (76.5)
Women	38 (23.5)
Underlying liver disorders	
Cirrhosis	154 (95.1)
A	82 (50.6)
B	62 (38.3)
C	10 (6.2)
Chronic hepatitis	7 (4.3)
Normal liver	1 (0.6)
Etiology of liver disorders	
Hepatitis B virus	15 (9.3)
Hepatitis C virus	129 (79.6)
Hepatitis B and C viruses	3 (1.9)
Non – hepatitis B, non – hepatitis C	11 (6.8)
Alcoholic	2 (1.2)
Unknown	2 (1.2)
Performance status	
0	61 (37.7)
1	79 (48.8)
2	21 (13.0)
3	1 (0.6)
4	0 (0)

Table 2. Background of hepatic tumor at entry

Characteristics	*n* (%)
No. tumors	
Single	80 (49.4)
Multiple	82 (51.6)
Type of tumor	
Nodular	156 (96.3)
Massive	6 (3.7)
Diffuse	0
Tumor-node-metastasis stage	
I	66 (40.7)
II	70 (43.2)
IIIA	25 (15.4)
IIIB	1 (0.6)
Tumor size (cm)*	
<3.0	51 (26.6)
3.0-5.0	108 (56.3)
>5.0	33 (17.2)
Serum α-fetoprotein (μg/L)	
<20	50 (30.9)
20-99	38 (23.5)
100-500	35 (21.6)
>500	39 (24.1)

*192 tumors treated by proton beam therapy.

Table 2 shows characteristics of 162 tumors. Tumors were categorized retrospectively according to International Union Against Cancer tumor-node-metastasis classifications (34). Of the patients, 60% had advanced tumors (stages II and IIIB). Among the 25 patients with stage IIIA, 10 patients had tumors involving a major branch of the portal vein (portal vein tumor thrombus). Of those 10 patients, 6 had portal vein tumor thrombus in the main trunk. The median maximal diameter of tumors was 3.8 cm ranging from 1.5 to 14.5 cm. Of the 162 patients, 112 (69.1%) had ≥20 μg/L in serum α-fetoprotein levels for which the median value was 227 μg/L (range, 21-12,539 μg/L).

Proton Irradiation. Procedures for proton beam therapy at the University of Tsukuba were reported previously (28, 35). Briefly, proton beams were provided with a booster synchrotron of the High Energy and Accelerator Research Organization. The beam energy was degraded to 250 from 500 MeV before medical use. Proton beams were available for medical use for 4 hours a day on ~120 days a year. The two treatment rooms were equipped with either a horizontal or a vertical port. We irradiated patients once a day, 3 or 4 days a week because of the limited time for using the beam.

Fiducial markers (0.8 mm in diameter and 2 mm long iridium seeds) were implanted adjacent to the tumor under ultrasonography guidance. A clinical target volume was gross tumor volume plus 5 to 10 mm margins at each axial plane on the treatment planning computed tomography images. Irradiation was given mostly with right-angled vertical and horizontal beams. For patients who had a tumor adjacent to the gastrointestinal tract, we irradiated the patient with other angles whenever necessary to avoid irradiating the gastrointestinal tract. We started to use respiration-gated irradiation (36, 37) in December 1992 to reduce the irradiated volume attributable to organ motion that accompanies breathing.

Of the 192 tumors irradiated, 9 tumors were irradiated simultaneously, resulting in a total number of treatment courses of 183. Of the 162 patients, 11 had two courses of treatment at different times, 2 had three courses, and 2 had four courses. The median total dose was 72 Gy

ranging from 50 to 88 Gy with a median fraction dose being 4.5 Gy ranging from 2.9 to 6 Gy. Patients were treated with different fractionation regimens: 72 Gy in 16 fractions over 24 to 43 days for 64 treatment courses, 78 Gy in 20 fractions over 33 to 42 days for 11 courses, 84 Gy in 24 fractions over 33 to 50 days for 10 courses, 50 Gy in 10 fractions over 13 to 21 days for 10 courses, and miscellaneous regimens for the remaining 97 courses. Various fractionation regimens were used especially in the earlier period of the present study. For that reason, equivalent doses with 2 Gy per fraction were calculated using a linear quadratic model with α/β ratios of 10 and 3 for early and late responding tissues (Table 3; ref. 38).

Follow-up. After completion of proton beam therapy, patients were examined every 3 months until 2 or 3 years and every 6 months afterward. Follow-up examinations included the following whenever possible: clinical history; physical examination, including assessing performance status according to the WHO handbook for reporting results of cancer treatment (39); biochemical examination, serum α-fetoprotein values; abdominal computed tomography or magnetic resonance imaging; and percutaneous needle biopsy 3 weeks after the completion of irradiation.

Local tumor control was defined as the situation in which an irradiated tumor showed no sign of regrowing and no new tumor appearing in the treatment volume.

A patient was considered to have died of hepatic failure when the patient died with marked progression of coexisting liver cirrhosis without having marked growing of HCC. Death from tumor progression occurred when the patient died with marked growing of HCC (more than a half volume of the whole liver) and distant metastasis without displaying progressing liver cirrhosis.

Treatment Sequelae. An increase of serum total bilirubin >51.3 μmol/L was considered significant acute toxicity in the hepatic function. Decreases of >20 g/L hemoglobin, $>3 \times 10^9$/L WBC, and $>50 \times 10^9$/L platelet count were considered significant acute treatment sequelae in the hematopoietic systems. Late sequelae were graded retrospectively according to the late radiation morbidity scoring scheme of the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (40).

Statistical Methods. Survival rates and local control rates were calculated with the Kaplan-Meier method (41). Statistical significance of differences for both survival rates and local control rates was examined using the log-rank test (42). The difference between the two values calculated was examined using Student's *t* test or Fisher's exact test. Possible factors affecting survival were assessed with Cox proportional hazards regression analysis (43). Statistical analyses were done with SPSS version 11.0 (SPSS, Inc., Chicago IL).

Results

Patients were followed up until death or June 30, 2003. The median observation period for survival for all patients was 31.7 months ranging from 3.1 to 133.2 months.

Table 3. Dose fractionations and equivalent doses when given 2 Gy per fraction

Total dose (Gy)	No. fractions	Dose/ fraction	Equivalent total doses (2 Gy/fraction)	
			$\alpha/\beta = 10$	$\alpha/\beta = 3$
72	16	4.5	87.0	108.0
78	20	3.9	90.4	107.6
84	24	3.5	94.5	109.2
50	10	5.0	62.5	80.0

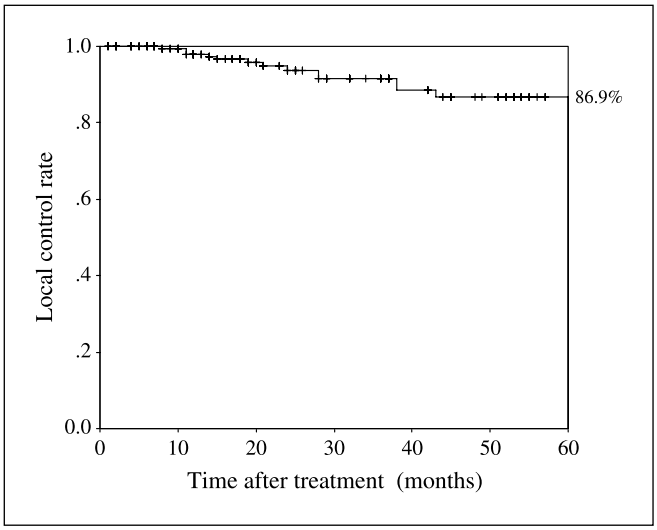

Fig. 1. Local tumor control after proton beam therapy.

Of the 162 patients, 17 were alive at their last follow-up. Their follow-up periods ranged from 32.4 to 133.2 months.

Imaging studies after proton beam therapy for four patients having four HCCs were unavailable; hence, the four patients were considered lost to follow-up for local control analysis at the end of treatment.

Local Tumor Control. The local control rate at 5 years was 86.9% for all of the 192 tumors among the 162 patients (Fig. 1). No significant difference in the local control rate at 5 years was observed between patients with tumors <5 cm in maximal diameter (87.8%) and those with >5 cm (82.1%; $P = 0.40$). Thirteen tumors locally recurred between 7 and 43 months (median, 21 months) after the completion of the irradiation. Maximal diameter of tumors that had recurred were median 4.7 cm ranging from 2.0 to 7.0 cm before irradiation. The tumors were irradiated to median total doses of 72 Gy ranging from 55 to 84 Gy. For locally controlled tumors, the maximal diameter was median 3.5 cm ranging from 1.5 to 14.5 cm and total doses irradiated were median 72 Gy ranging from 50 to 88 Gy. No correlation was found among local control and equivalent doses ($\alpha/\beta = 10$).

No significant difference in local control was observed between those treated with proton beam therapy with other modalities (90.7%) and those treated with proton beam therapy alone (81.3%; $P = 0.22$).

Eight of 68 (11.8%) tumors treated before December 1992, when we started respiratory-gated irradiation, recurred locally. In contrast, only 5 of 124 (4.0%) tumors treated after December 1992 recurred. Notwithstanding, that difference was not statistically significant ($P = 0.07$).

Survival. The overall survival rate for all of the 162 patients at 5 years was 23.5% (Fig. 2). The degree of impairment in the hepatic function attributable to coexisting cirrhosis and the number of tumors affected survival on the Cox regression analysis (Table 4). Tumor size, total irradiated dose given, and prior treatments before proton irradiation were not significant factors.

Survival rates for patients with chronic hepatitis and class A cirrhosis were significantly better than for those with B cirrhosis and those with C cirrhosis ($P < 0.0001$); no significant

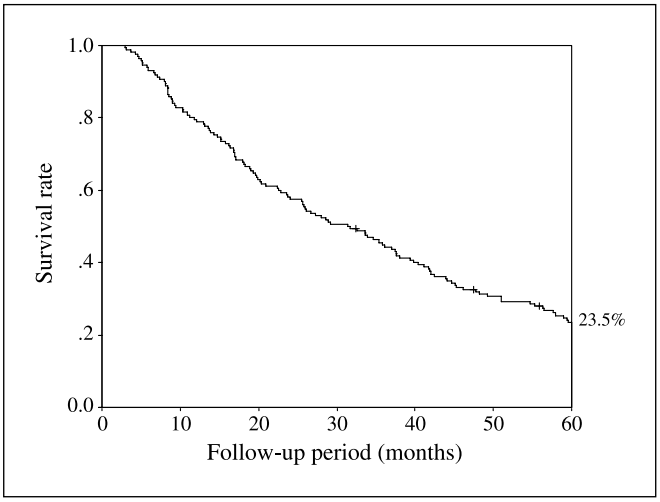

Fig. 2 Actual survival for all the patients.

difference was found between patients with B cirrhosis and those with C cirrhosis (Fig. 3).

Five-year survival rates according to the tumor-node-metastasis classification were as follows: 45.3% for stage I, 11.2% for stage II, and 26.9% for stage IIIA.

The 5-year survival rate for patients without prior therapy (45 patients) and those with prior therapy (117 patients) were 37.7% and 17.9% ($P = 0.02$), respectively.

There were 50 patients with favorable prognostic factors (Child-Pugh class A and solitary tumor) in the present series, and in these patients, the 5-year survival rate was 53.5% (Fig. 4).

Performance Status. Two (1.4%) patients were with performance status 0 before irradiation and performance status 1 after irradiation; another 2 (1.4%) patients were performance status 2 before and performance status 3 after irradiation. All remaining patients had stable performance status before and after irradiation.

Histopathologic Changes. Of the 100 patients who had been diagnosed pathologically as having HCC before irradiation, 47 were unable to undergo biopsy after the irradiation because the tumor was not detected with ultrasound. The remaining 53 patients with 53 tumors underwent biopsy 3 weeks after completion of proton beam therapy. Complete necrosis was observed in 12 (22.6%) tumors, degeneration of the nucleus and vessels in 16 (30.2%), fibrosis in 2 (3.8%), disappearance of tumor cells in 9 (17.0%), and no change in 14 (26.4%).

Vascular Invasion. Vascular invasion of the tumor or portal vein tumor thrombus into the main stem or the primary bifurcation of the portal vein was shown in 10 patients. The median total dose given to portal vein tumor thrombus was 55.3 Gy in 15 fractions over 20 days ranging from 50 Gy in 10 fractions over 13 days to 77 Gy in 22 fractions over 44 days. After irradiation, the tumors in the vessels were reduced in size markedly without impairing the patient's hepatic functions. The median survival period after proton beam therapy for the patients was 26.4 months ranging from 5.1 to 76 months.

Treatment Sequelae. Elevated plasma aspartate transaminase and alanine transaminase values by a factor of 3 at the most were observed in 18 patients on 18 courses (9.7%). However, they subsided quickly without causing any remarkable problems.

Table 5 shows that there were very few acute reactions to the treatment in 162 patients on 185 courses aside from the transient elevation of aspartate transaminase and alanine transaminase. All acute reactions subsided within 2 weeks. No patients discontinued treatment because of the acute reactions.

Five patients had late sequelae of grade II or higher: one patient had fibrotic stenosis of the common bile duct, which was located in the treatment volume, 13 months after irradiation; two patients had biloma with infection adjacent to the irradiated volume 29 and 38 months after irradiation, respectively; one patient had intractable gastric ulcer in the treatment volume 4 months after irradiation; the remaining patient had an ulcer in the ascending colon 6 months after irradiation. All patients who had developed late sequelae were treated before 1995. No patients died of treatment sequelae in the present series.

Outcome. As of June 2003, 145 of the 162 (89.5%) patients were dead. Of all 162 patients, 85% had developed another HCC(s) in the liver within 5 years following proton beam therapy. They underwent transarterial chemoembolization/transcatheter arterial embolization (51.4%), proton beam therapy (13.3%), percutaneous ethanol injection (6.7%), miscellaneous therapies, including systemic chemotherapy (6.7%), and no treatment (22.0%) as treatments for the newly developed HCCs.

Causes of death for the 145 patients were hepatic failure for 55 (37.9%) patients, 12 of whom had gastrointestinal bleeding at their death; tumor progression for 68 (46.9%); intercurrent diseases (renal failure for 4 patients, intracranial hemorrhage for 3, pneumonia for 3, and miscellaneous for 4) for 14 (9.7%); suicide for 1 (0.7%); and unknown for 7 (4.8%).

Table 4. Results of a Cox proportional hazards regression

Variable	Adjusted rate ratio (95% confidence interval of hazard ratio)	*P*
Child-Pugh classification		
A	1.00	
B*	2.22 (1.54-3.19)	<0.0001
C†	3.57 (1.81-7.03)	0.0002
No. tumors		
Solitary	1.00	
Multiple	1.58 (1.09-2.31)	0.02
Tumor size		
<50	1.00	
≥50	1.41 (0.92-2.15)	0.11
Proton doses		
<72	1.00	
≥72	1.01 (0.74-1.46)	0.95
Prior treatment		
Received	1.00	
Not received	0.88 (0.58-1.34)	0.56

*Child-Pugh B compared with those of Child-Pugh A.
†Child-Pugh C compared with those of Child-Pugh A.

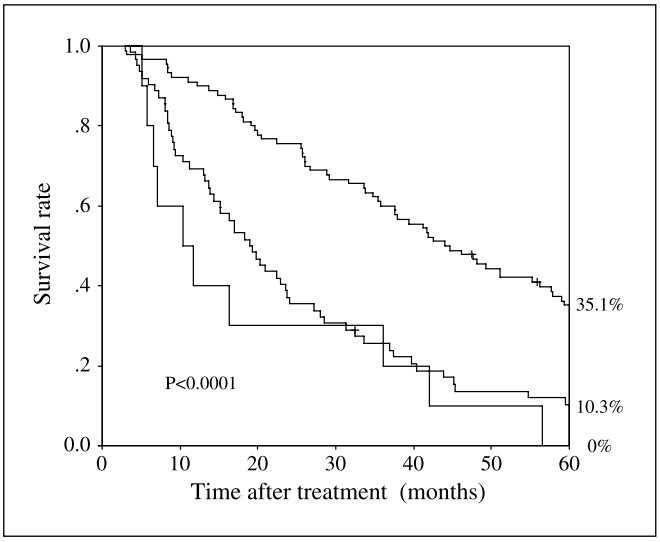

Fig. 3. Survival for the patients according to the degree of hepatic dysfunction. For patients with chronic hepatitis and Child-Pugh class A-C cirrhosis, the 5-year survival rates were 35.1%, 10.3%, and 0%, respectively.

Fifteen of the 162 patients in the present series had two courses or more of proton beam therapy; 13 of these had such treatment for tumors judged as newly developed and 2 for tumors judged as locally recurring.

Discussion

In the present series, the 5-year survival rate for 50 patients with a solitary tumor and with least impaired hepatic function (Child-Pugh class A) was 53.5%. It was 57.9% for 15,453 patients with a solitary HCC who underwent surgery from 1988 to 1999 in Japan (8). It is impossible to simply compare these results because the studied patient populations differ entirely. In fact, we have shown that survival of patients with HCC depends largely on the degree of impairment in hepatic function because of coexisting liver cirrhosis and the number of tumors in the liver. However, it can be inferred that proton beam therapy is as effective as hepatectomy for patients with HCC.

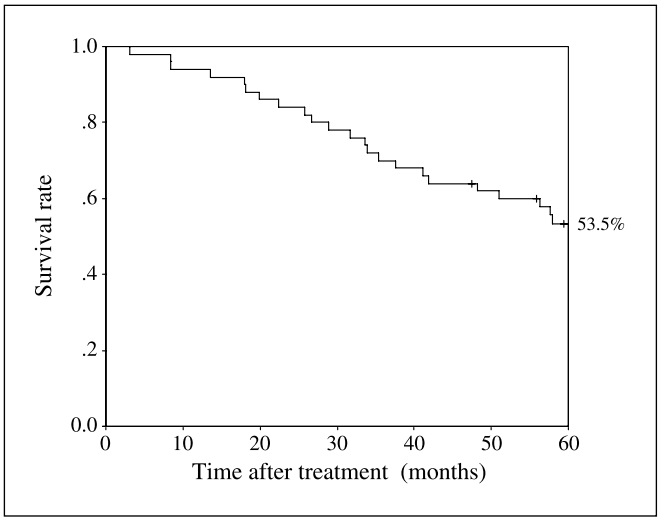

Fig. 4. Survival for patients with least impaired hepatic function (chronic hepatitis or Child-Pugh class A cirrhosis) and a solitary tumor.

Only ~30% of patients with HCC undergo surgery (44). Reasons why patients choose not to undergo surgery include poor medical condition caused by intercurrent diseases to undergo surgery, poor hepatic functions attributable to coexisting liver cirrhosis, advanced age, and too advanced tumor stage. In the present series, 65% of all patients were ages ≥60 years. About half of the patients had multiple tumors and 45% of the patients were class B or C in Child-Pugh classification. Therefore, it seems that the patients with a wider spectrum of general conditions and tumor conditions are treatable with proton beam therapy.

Of patients who underwent percutaneous ethanol injection, microwave coagulation therapy, and radiofrequency ablation from January 1998 to December 1999 in Japan, only a small proportion of the patients had tumors >5 cm (3.5% for percutaneous ethanol injection, 1.8% for microwave coagulation therapy, and 6.4% for radiofrequency ablation; ref. 8). In the present series, 33 of 192 (17.2%) tumors were >5 cm in maximal diameter. The tumor size did not significantly affect local control in the present series, suggesting that proton beam therapy could be used to treat patients with relatively large tumors. We are often unable to detect HCC with ultrasound when it is located at a site adjacent to the lung and the bone. In such cases, we could not treat it with ablative procedures. When a tumor is located at a site adjacent to a larger blood vessel, we are also unable to treat it effectively with radiofrequency ablation because of the heat dissipation through the vessel (45). Smaller (≤3 cm in maximal diameter) multiple tumors are often treated with transcatheter arterial embolization and transarterial chemoembolization. However, it is impossible to use transcatheter arterial embolization/transarterial chemoembolization when the tumor is not fully fed with arteries.

Although we had a better local control rate after initiating the use of respiration gating irradiation (11.8% versus 4.0%), we are unable to assess the degree of its contribution to improvement of local control. Our irradiation techniques, including target delineation, improved considerably during the period. Unfortunately, we have no methodology to distinguish their contributions.

For the same reason, we are unable to identify a tumor that locally recurred because of a geographic miss in treatment planning. Of the 13 tumors that locally recurred in the present

Table 5. Treatment sequelae in 185 courses

Treatment sequelae	No. treatment courses (%)
Acute-subacute	
Elevation of bilirubin	3 (2.1)
Anemia	2 (1.1)
Leukocytopenia	1 (0.5)
Thrombocytopenia	6 (3.2)
Elevation of transaminase level	18 (9.7)
Late	
Infection biloma	2 (1.1)
Common bile duct stenosis	1 (0.5)
Gastrointestinal tract bleeding	2 (1.1)

series, 10 recurred in the central portion of the irradiated volume, whereas the remaining 3 tumors did so at the periphery; some of the 3 tumors that recurred peripherally might have recurred due to a geographic miss.

Of 145 patients who had died as of June 2003, 68 (46.9%) died of tumor progression. On the other hand, the local control rate for all tumor was high (86.9%). The high local control rate with the higher tumor progression rate is explained by the multifocal nature of HCC in the cirrhotic liver; 84% of all patients in the present series developed HCC(s) at a site that was remote from the treated tumor in the liver within 5 years. A significant proportion of them eventually became uncontrollable, engendering patient death. The remaining 77 (53.1%) patients died of various causes unrelated to tumor progression, of whom 55 (37.9% of 145 patient deaths) died of hepatic failure attributable to liver cirrhosis.

No significant difference in local control rate was found between patients with no prior therapy and those previously treated with other modes of therapy, suggesting that a patient with HCC could be treated exclusively with proton beam therapy.

Photon radiotherapy to give 44 to 52 Gy in 4 to 5.5 weeks for patients with HCC yielded a limited improvement in survival and local control rates (46, 47). Robertson et al. (48) and Blomgren et al. (49) recently attempted to increase the dose of irradiation to the hepatic tumors using conformal radiotherapy or stereotactic radiotherapy. Long-term results of their attempts are yet to be shown. In addition, it is unavoidable to have a large portion of the liver and other adjacent organs irradiated with lower doses of deeply penetrating photons. Such treatment may or may not engender late radiation sequelae, including radiation-induced carcinogenesis.

In the present series, most patients were given very high doses compared with those given with photon beams (Table 3), which may explain the higher local control rate obtained in the present series.

Few effective treatments are available for patients having HCC with vascular invasion (50). However, in the present series, 10 patients with a tumor involving major branches of portal veins survived a median 26.4 months after proton beam therapy. Proton beam therapy is the currently preferred treatment for patients having HCC with vascular invasion.

Patients who underwent proton beam therapy had stable performance status before and after irradiation, very few acute reactions to the treatments during and after irradiation, and a few late sequelae after treatment. For those reasons, proton beam therapy seems to be less invasive than any other HCC treatment modalities.

Of the 53 patients who underwent biopsy 3 weeks after completion of irradiation, 14 (26.4%) patients had viable cancer cells. Considering the high rate of local control obtained, second biopsies were undertaken too early after completion of irradiation in the present study.

Fifteen patients had multiple (maximum of four) courses of proton beam therapy, which suggests that proton beam therapy could be given repeatedly at different times. Because HCC in the cirrhotic liver has multifocal carcinogenesis in nature, it renders a great advantage to proton beam therapy in treating patients who often undergo multiple courses of treatments.

Although we could treat most patients with HCC using proton beam therapy, we might not treat a patient who has one or more of the following conditions: poor general condition (performance status 3-4), diffusely infiltrating HCC, multiple HCC (several or more) in both lobes, or an exophytic tumor extensively involving the gastrointestinal tract.

We have started a phase II study in which a proton dose of 60 Gy in 10 fractions over 2 weeks is given to patients having a solitary HCC located not adjacent to the porta hepatis or the gastrointestinal tract. For tumors located adjacent to the porta hepatis and the gastrointestinal tract, we are currently giving 66 Gy in 22 fractions over 4.5 weeks in the hope of avoiding serious late sequelae.

In conclusion, proton beam therapy for patients with HCC is effective, safe, well tolerable, and repeatable. The treatment can apply for cure as well as for palliation to patients with HCC irrespective of tumor size, tumor location in the liver, insufficient feeding of the tumor with arteries, presence of vascular invasion, degree of hepatic dysfunction, and intercurrent diseases.

Acknowledgments

We thank the late Profs. Toshiaki Osuga, Toshio Kitagawa, and Yuji Itai for their dedication to establishing proton beam therapy at Tsukuba.

References

1. Munoz N, Bosch X. Epidemiology of hepatocellular carcinoma, in Okuda K, Ishak KG, editors. Neoplasms of the liver. Tokyo: Springer-Verlag; 1987. p. 3–19.
2. Okuda K, Ohtsuki T, Obata H, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment: study of 850 patients. Cancer 1985;56: 918–28.
3. El-Domeiri AA, Huvos AG, Goldsmith HS, et al. Primary malignant tumors of the liver. Cancer 1971;27: 7–11.
4. Nagasue N, Yukaya H, Hamada T, et al. The natural history of hepatocellular carcinoma: a study of 100 untreated cases. Cancer 1984;54:1461–5.
5. The Research Group for Population-Based Cancer Registration in Japan. Cancer incidence and incidence rates in Japan in 1995. Estimates based on data from nine population-based cancer registries. Jpn J Clin Oncol 2000;30:318–21.
6. Nishioka K, Watanabe J, Furuta S, et al. A high prevalence of antibody to the hepatitis C virus in patients with hepatocellular carcinoma in Japan. Cancer 1991;67:429–33.
7. Tanaka K, Hirohata T, Koga S, et al. Hepatitis C and hepatitis B in the etiology of hepatocellular carcinoma in the Japanese population. Cancer Res 1991;51: 2842–7.
8. Ikai I, Itai Y, Okita K, et al. Report of the 15th follow-up survey of primary liver cancer. Hepatol Res 2004;28: 21–9.
9. Nakamura H, Hashimoto T, Oi H, et al. Transcatheter oily chemoembolization of hepatocellular carcinoma. Radiology 1989;170:783–6.
10. Yamada R, Kishi K, Sonomura T, et al. Transcatheter arterial embolization in unresectable hepatocellular carcinoma. Cardiovasc Intervent Radiol 1990;13: 135–9.
11. Bismuth H, Morino M, Sherlock D, et al. Primary treatment of hepatocellular carcinoma by arterial chemoembolization. Am J Surg 1992;163:387–94.
12. Aoyama K, Tsukishiro T, Okada K, et al. Evaluation of transcatheter arterial embolization with epirubicin-lipiodol emulsion for hepatocellular carcinoma. Cancer Chemother Pharmacol 1992;31 Suppl:S55–9.
13. Nakamura H, Mitani T, Murakami T, et al. Five-year survival after transcatheter chemoembolization for hepatocellular carcinoma. Cancer Chemother Phamacol 1994;33 Suppl:S89–92.
14. Tobe T, Arii S. Improving survival after resection of hepatocellular carcinoma: characteristics and current status of surgical treatment of primary liver cancer in Japan. In: Tobe T, Kameda H, et al., editors. Primary liver cancer in Japan. Tokyo: Springer-Verlag; 1992. p. 215–20.
15. Sheu JC, Huang GT, Chen DS, et al. Small hepatocellular carcinoma: intratumor ethanol treatment using new needle and guidance system. Radiology 1987; 163:43–8.
16. Shiina S, Yasuda H, Muto H, et al. Percutaneous ethanol injection in the treatment of liver neoplasms. AJR Am J Roentgenol 1987;149:949–52.
17. Seki T, Wakabayashi M, Nakagawa T, et al. Ultrasonically guided percutaneous microwave coagulation

therapy for small hepatocellular carcinoma. Cancer 1994;74:817–25.

18. Sato M, Watanabe Y, Ueda S, et al. Microwave coagulation therapy for hepatocellular carcinoma. Gastroenterology 1996;110:1507–14.

19. Rossi S, Fornari F, Buscarini L. Percutaneous ultrasound-guided radiofrequency electrocautery for the treatment of small hepatocellular carcinoma. J Intervent Radiol 1993;8:97–103.

20. Rossi S, Buscarini L, Garbagnati F, et al. Percutaneous treatment of small hepatic tumors by an expandable RF needle electrode. AJR Am J Roentgenol 1998;170:1015–22.

21. Buscarini L, Buscarini E, Di Stasi M, et al. Percutaneous radiofrequency ablation of small hepatocellular carcinoma: long-term results. Eur Radiol 2001;11:914–21.

22. Phillips R, Murikami K. Primary neoplasms of the liver. Results of radiation therapy. Cancer 1960;13:14–20.

23. Cochrane AMG, Murray-Lyon IM, Brinkley DM, et al. Quadruple chemotherapy versus radiotherapy in treatment of primary hepatocellular carcinoma. Cancer 1977;40:609–14.

24. Friedman MA, Volberding PA, Cassidy MJ, et al. Therapy of hepatocellular carcinoma with combined intrahepatic arterial chemotherapy and whole liver irradiation. Ann Acad Med Singapore 1980;9:260–3.

25. Russell AH, Clyde C, Wasserman TH, et al. Accelerated hyperfractionated hepatic irradiation in the management of patients with liver metastases: result of the RTOG dose escalating protocol. Int J Radiat Oncol Biol Phys 1993;27:117–23.

26. Osuga T, Matsuzaki Y, Chiba T, et al. Radiatiotherapy. In: Okuda K, Tabor E, editors. Liver cancer. London: Churchill Livingstone; 1997. p. 481–96.

27. Suit H, Urie M. Proton beams in radiation therapy. J Natl Cancer Inst 1992;84:155–64.

28. Tsujii H, Tsuji H, Inada T, et al. Clinical results of fractionated proton therapy. Int J Radiat Oncol Biol Phys 1992;25:49–60.

29. Tanaka N, Matsuzaki Y, Chuganji Y, et al. Proton irradiation for hepatocellular carcinoma. Lancet 1992;340:1358.

30. Matsuzaki Y, Osuga T, Saito Y, et al. A new, effective, and safe therapeutic option using proton irradiation for hepatocellular carcinoma. Gastroenterology 1994;106:1032–41.

31. Tsujii H, Tsuji H, Okumura T, et al. Proton therapy of thoraco-abdominal tumors. In: Linz U, editor. Ion beams in tumor therapy. London: Chapman & Hall; 1995. p. 127–32.

32. Edmondson HA, Steiner PE. Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. Cancer 1954;7:462–503.

33. Pugh RNH, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60:646–9.

34. International Union Against Cancer (UICC). TNM classification of malignant tumours. 6th ed. New York: Wiley-Liss; 2002. p. 81–3.

35. Inada T, Hayakawa Y, Maruhashi A, et al. Vertical proton beam irradiation control system for cancer therapy. Nippon Acta Radiol 1984;44:844–53.

36. Inada T, Tsuji H, Hayakawa Y, et al. Proton irradiation synchronized with respiratory cycle. Nippon Acta Radiol 1992;52:1161–7.

37. Ohara K, Okumura T, Akisada M, et al. Irradiation synchronized with respiration gate. Int J Radiat Oncol Biol Phys 1989;17:853–7.

38. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. Br J Radiol 1989;62:679–94.

39. WHO handbook for reporting results of cancer treatment. WHO offset publication No. 48. Geneva: WHO; 1979.

40. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995;31:1341–6.

41. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.

42. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Br J Cancer 1977;35:1–39.

43. Cox DR. Regression models and life tables. J Roy Stat Soc Sec 1972;B34:187–220.

44. Hassoun Z, Gores GJ. Treatment of hepatocellular carcinoma. Clin Gastroenterol Hepatol 2003;1:10–8.

45. Yamasaki T, Kurokawa F, Shirahashi H, et al. Percutaneous radiofrequency ablation therapy for patients with hepatocellular carcinoma during occlusion of hepatic blood flow. Cancer 2002;95:2353–60.

46. Cheng JCH, Chuang VP, Cheng SH, et al. Local radiotherapy with or without transcatheter arterial chemoembolization for patients with unresectable hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 2000;47:435–42.

47. Yasuda S, Ito H, Yoshikawa M, et al. Radiotherapy for large hepatocellular carcinoma combined with transcatheter arterial embolization and percutaneous ethanol injection therapy. Int J Oncol 1999;15:467–73.

48. Robertson JM, Lawrence TS, Dworzanin LM, et al. Treatment of primary hepatobiliary cancers with conformal radiation therapy and regional chemotherapy. J Clin Oncol 1993;11:1286–93.

49. Blomgren H, Lax I, Göranson H, et al. Radiosurgery for tumors in the body: clinical experience using a new method. J Radiosurg 1998;1:63–74.

50. Yamada K, Izaki K, Sugimoto K, et al. Prospective trial of combined transcatheter arterial chemoembolization and three-dimensional conformal radiotherapy for portal vein tumor thrombus in patients with unresectable hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 2003;57:113–9.