Proton beam therapy for large hepatocellular carcinoma

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Conflict of Interest Notification

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Note

S. Sugahara and Y. Oshiro contributed equally to this work.

Abstract

Object: To investigate the safety and efficacy of proton beam therapy (PBT) in patients with large hepatocellular carcinoma (HCC).

Materials/Methods: Twenty-two patients with HCC larger than 10 cm were treated with proton beam therapy at our institution between 1985 and 2006. Twenty-one of the 22 patients were not surgical candidates due to advanced HCC, intercurrent disease, or old age. Median tumor size was 11 cm (range: 10-14cm) and median clinical target volume was 567 cm^3 (range: 335-1398cm^3). HCC was solitary in 18 patients and multifocal in 4 patients. Tumor types were nodular and diffuse in 18 and 4 patients, respectively. Portal vein tumor thrombosis was present in 11 patients. Median total dose delivered was 72.6 GyE in 22 fractions (range: 47.3-89.1 GyE in 10-35 fractions).

Results: The median follow-up period was 13.4 months (range: 1.5–85 months). Tumor control rate at 2 years was 87%. One-year overall and progression free survival rates were 64% and 62%, respectively. Two-year overall and progression-free survival rates were 36% and 24%, respectively. The

predominant tumor progression pattern was new hepatic tumor development outside the irradiated field. No late treatment-related toxicity of grade 3 or higher was observed.

Conclusions: The Bragg peak properties of proton beam therapy allow for improved conformality of the treatment field. As such, large tumor volumes can be irradiated to high doses without significant dose exposure to surrounding normal tissue. PBT therefore represents a promising modality for the treatment of large volume HCC. Our study shows that indeed, PBT is an effective and safe method for the treatment of patients with large HCC.

Key Words: Large hepatocellular carcinoma, Proton beam therapy, Radiotherapy

Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers in the world and is especially prevalent in Southeast and East Asia.[1] Between 10-20% of newly diagnosed HCCs are larger than 10 cm in diameter.[2] Tumor size plays an important role in determining which treatment modalities are appropriate in patients with HCC. For example, patients with large tumors are not candidates for ablation therapies,[3-9] such as percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA), or for liver transplantation.[10,11] These treatments were not listed in the guidelines of the European Association for the Study of the liver[12] or the American Association for Study of the Liver Disease.[9, 13] Currently, surgery appears to confer the best outcome in patients with HCC larger than 10 cm.[14-20] However, less than 20% of patients with HCC are candidates for resection.[7,21]

We have treated HCC with proton beams at our facility since 1985.[22-27] Proton beams have a unique physical property called the Bragg peak which allows for excellent dose localization. This property makes proton beam therapy (PBT) a promising modality for the treatment of patients with HCC. In this report, we analyze 22 patients with HCC larger than 10cm in diameter

who were treated with proton beam therapy at our institution.

Method and Materials

Patients

A total of 507 HCC patients with no regional lymph node involvement or distant metastases received PBT at our institution between 1985 and 2006. Twenty-three of these patients had large HCCs measuring over 10 cm in greatest dimension. Of these 23 patients, 1 was excluded from the present review because of poor general condition (World Health Organization performance status of 3[28] prior to proton beam therapy). Outcomes for the 22 remaining patients are reviewed below.

Six patients were histopathologically diagnosed with HCC by needle biopsy. The remaining 16 were clinically diagnosed using CT and/or MRI findings in conjunction with elevated serum alpha-fetoprotein (AFP) or protein-induced by vitamin K absence or antagonists–II (PIVKA II) values.

Patient and tumor characteristics are shown in Table 1. Twenty-one patients were deemed inoperable. Eleven tumors were inoperable because of

extensive tumor invasion. The remaining 10 were medically inoperable; severe liver cirrhosis in 1 patient, small remnant liver volume after liver resection in 2 patient, old age of 80 years or greater with Child-Pugh B class liver cirrhosis in 3 patients, and intercurrent disease in 4 patients. The remaining 1 patient included in this study voluntarily refused surgical treatment.

AFP was elevated in 18 patients and PIVKA II was elevated in 15 patients prior to PBT. Thirteen patients had pursued other therapies (transarterial chemoembolization (TACE) (n=7), hepatic arterial infusional chemotherapy (HAI) (n=3), percutaneus ethanol injection (PEI) (n=2) and oral chemotherapy with uracil-tegafur (n=1)) prior to PBT, while the remaining 9 patients received PBT as the primary treatment modality. Written informed consent was obtained from all patients prior to treatment onset.

Treatment

Between April 1985 and July 2000, PBT was administered at the National Laboratory for High Energy Physics. 250MeV proton beams which were generated by a booster synchrotron and degraded were scattered through a double scattering system for clinical use. At this facility, clinical use of the

proton beam was limited to 4 hours per day for 120 days per year. Additionally, treatment planning at the National Laboratory facility was limited by fixed vertical and horizontal gantries. Starting in September 2001, patients were treated at our new hospital-based facility at the University of Tsukuba with rotational gantries capable of releasing proton beams in a respiration-gated fashion. At the new facility, 155-, 200-, 230-, or, 250-MeV proton beams were generated with a dedicated accelerator with a double scattering system. This facility was available for use Monday through Friday, and treatments were delivered 5 days / week if necessary.

Patients were considered suitable for PBT when the number of viable tumors was one or two. TACE was firstly performed if the number was three or more, and considered suitable if the number reduced to one or two by the treatment.

Prior to the initiation of treatment, metallic fiducial markers were implanted percutaneously into hepatic parenchyma adjacent to tumor, except in cases where materials such as embolic iodine or a surgical clip could be seen fluoroscopically. Immobilization of the patient on the treatment table was achieved using individualized body casts (ESFORM; Engineering System, Matsumoto).

CT images obtained at 5mm intervals in the treatment position during the expiratory phase were transferred directly to a treatment planning system

(Hitachi Co. Ltd. Tokyo). The gross tumor volume (GTV) was defined as an enhanced area in an arterial phase on contrast enhanced CT images. A clinical target volume (CTV) was contoured as GTV plus a 5-10 mm margin on serial CT images using the treatment system. A 5 mm caudal margin for respiratory movement was added to CTV as an internal margin. The planning target volume (PTV) was defined as an internal target volume (ITV) with an 8 mm margin in all directions. Proton beams were delivered during the expiratory phase using the respiration-gated system.[29]

After defining the number of beams and beam directions for each beam, the following parameters were automatically calculated by the treatment-planning software (Hitachi planning Ver.1.72, Hitachi Co. Ltd. Tokyo): dose distributions, beam delivery device parameters such as a length of spread-out Bragg peak (SOBP), a proton beam energy for each port, a range-shifter thickness, a shape of compensating chemical wood bolus and a brass collimator shape). The CTV was homogeneously encompassed with more than 95% and less than 108% of the prescribed dose of the isocenter by selecting adequate ports and margins. Prior to the initiation of treatment for each patient, reliability of the proton beam dose distributions was confirmed using a water phantom.

A median total dose of 72.6 gray equivalents (GyE) in 22 fractions (range: 47.3-89.1 GyE in 10-35 fractions) was given with a relative biological effectiveness value of 1.1. At present, our protocol is as follows: 72.6 GyE in 22 fractions for tumors adjacent to hepatic portal fissure, 74 GyE in 37 fractions for

tumors adjacent to the digestive tract, and 50-60 GyE in 25-30 fractions for palliative intent. Fractionation schemes utilized in this study were variable due to restricted clinical use of the proton beam at the National Laboratory facility.

Because various fractionation regimens were used for treatment, the equivalent dose when delivered at 2.0 GyE per fraction was calculated for comparison using the linear quadratic model, with α/ß ratios of 10 and 3 for early and late responding tissues.[30] Median total equivalent doses for 2.0 GyE per fraction were 91.5 GyE (range: 49.7–125.9 GyE) when the α/ß ratio was assumed to be 3, and 80.5 GyE (range: 48.3–98.8 GyE) when the α/ß ratio was 10. The median overall treatment time was 34 days (range: 16–73 days). Dose-volume histogram (DVH) analyses were performed for 12 patients.

Follow-up and evaluation criteria

Patients underwent abdominal imaging studies (CT or MRI) 1 to 4 months after completion of treatment. Additionally, patients were monitored at 1-3 month intervals for recurrence or late radiation toxicities via follow-up visits to our department, to the referring physician, or by mail and/or phone.

Acute and late toxicities associated with treatment were evaluated using the National Cancer Institute - Common Toxicity Criteria (NCI-CTC) version 3 and the Radiation Oncology Study Group/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme.[31]

Statistical analysis

Actuarial survival and disease control rates were calculated from the beginning of PBT using the Kaplan-Meier method.[32] Differences in survival were evaluated with the log-rank test.[33] A p-value of 0.05 or less was considered statistically significant. All statistical analyses were performed using statistical software (SPSS Inc., Chicago, IL, USA).

Results

The median follow-up period was 13.4 months for all 22 patients (range: 1.5–85 months). Nineteen patients died between 1.5 and 85 months after treatment, and 3 were alive with no evidence of recurrence at last follow up in December 2007. Causes of death included progressive HCC outside the irradiated volume in 10 patients, liver failure with viable HCC in 3 patients,

liver failure without viable HCC in 2 patients, cerebral infarction in 2 patients, cardiac arrest in 1 patient and cerebral hemorrhage in 1 patient. The overall survival rates at 1 and 2 years were 64% (95% confidence interval [CI], 44-84) and 36% (95% CI, 15-56), respectively (Fig 1). Age, Child-Pugh class, use of more than one treatment modality, tumor size, and tumor number did not affect survival rates.

Six patients survived for greater than 2 years following treatment. All 6 of these patients had single focus, nodular-type disease. By the time of analysis, five of these six patients had died from cerebral hemorrhage, cerebral infarction, liver failure (n=1 each), and uncontrolled HCC (n=2).

Fourteen patients (64%) suffered from disease progression outside the irradiated volume after PBT. Eleven developed new hepatic tumors, one developed lymph node metastasis, and six developed distant metastasis. Of the six patients with metastases, three developed bone involvement and concomitant new hepatic tumors while the remaining three had lung metastases without new hepatic tumor development. Of the 11 patients who developed new hepatic tumors, two patients received second course of PBT; One patient developed a new hepatic tumor outside the irradiated volume and

received a second course of PBT 4 months after the first PBT. The other patient, who had right portal vein thrombosis, underwent surgical resection and second course of PBT for new hepatic tumors 9 and 19 months after the first PBT. The progression free survival rates at 1 and 2 years were 62% (95% CI, 42-82) and 24% (95% CI, 4-45), respectively (Fig 1).

Eleven patients (50%) demonstrated a complete response to PBT with no evidence of viable tumor on follow-up imaging studies. Seven patients (32%) showed tumor shrinkage, while 2 patients (9%) showed no change in tumor size 3-6 months after the completion of PBT. The remaining 2 patients (9%) developed local recurrences 7 and 13 months after PBT. Therefore, the objective response rate to PBT was 82%, and the two-year local control rate was 87% (95% CI, 65-100) (Fig. 2).

The 2 years overall survival rates were 38% (95% confidence interval [CI], 12-65) for the 13 patients who received definitive proton therapy at the new facility and 33% (95% CI, 3-64) for the nine patients treated at the old facility or at the new facility with palliative intent, respectively. No significant deference between these groups was obseerved (p=0.91). The 2 years progression free survival rates were 29% (95% CI, 3-42) for 13 patients and 22%

(95% CI, 0-49) for nine patients, respectively. There was no significant deference between these groups (p=0.75).

Increased serum levels of AFP, PIVKA II, or both markers were noted in 18, 16, and 13 patients prior to PBT. Median serum AFP levels decreased from 1251 ng/ml (range: 33 - 32597 ng/ml) before PBT to 146 ng/ml (range: 2-11832 ng/mL) after PBT, and PIVKA II levels decreased from 11523 mAU/ml (range: 54-335000 mAU/ml) to 303 mAU/ml (range: 16-75000 mAU/ml) during the course of treatment. Of the 18 patients with elevated AFP levels prior to treatment, 3 patients (2 of whom eventually suffered from bone metastases 6 and 21 months after PBT) maintained high levels of AFP throughout the treatment period. The remaining one patient developed a new lesion outside the irradiated volume on CT scan 4.3 months following the completion of treatment, and also demonstrated increased levels of PIVKA II throughout PBT. With the exception of this patient, serum PIVKA II levels decreased in all other patients during PBT.

Dose volume histograms were available for 14 patients. CTV ranged from 335 - 1398 cm^3 (median: 567 cm^3), and non-cancerous liver volume (NLV), defined as total liver volume minus CTV, was 451–1292 cm^3 (median: 992 cm^3).

As noted above, these values are all reported using the calculated equivalent dose when delivered at 2.0 GyE per fraction. A summary of dose-volume analysis is shown in Table 2 and typical dose distributions and DVHs are shown in figure 3.

Toxicity

Acute non-hematological toxicities involving the skin were observed in 3 patients (grades 1-2). There were five patients who experienced grade 1 deterioration in white blood cell count and eight with grade 1 reduction in platelet and WBC counts. Hemoglobin levels were unaffected in all patients. All cases of myelosuppression recovered spontaneously in one month. No late complications were observed. Of the 5 patients who died within 6 months of PBT, 4 died of cancer progression and the remaining 1 died of liver failure. Autopsy of the latter showed no evidence of radiation-induced liver disease (RILD), which is typically characterized by liver congestion and hepatic vein occlusion.[34] Finally, five patients developed liver failure. As three of the five patients had no viable HCC, the cause of death of the three patients might be liver failure.

Discussion

There are few treatment modalities available to address large foci of HCC. Trans-arterial chemoembolization (TACE) is an effective treatment of HCC and can be used if multiple tumor foci are present so long as no single lesion exceeds 3 cm in greatest dimension.[35-37] TACE is indicated for patients who are not candidates for curative treatment but have a good performance status, acceptable liver and renal function, and no portal hypertension or portal thrombosis. PEI results in complete destruction of 90% of lesions less than 3 cm in size,[38] but is ineffective for tumors larger than 3 cm.[3] RFA is more effective than PEI for tumors greater than 3 cm[39-41], however, it is usually ineffective for tumors larger than 5 cm or for tumors located adjacent to the hilum, where large vessels such as the portal vein or IVC can dissipate the heat intended to ablate the tumor.[37] Mok et al. reported overall response rates and overall survival rates at 1 year and 3 years in patients with HCC larger than 10 cm of only 27%, 23.3%, and 9.6%, respectively, when multimodality non-surgical therapies were employed.[20] In contrast, the overall survival rates at 1 year and 3 years after surgery are markedly better at 64% and 24.5%,

respectively. In our series, 21 of 22 patients were not suitable for surgery because of liver impairment (n=13), limited residual liver volume (n=2), intercurrent diseases (n=4), and old age (n=2). However, because of improved dose localization related to the Bragg peak properties of the proton beam, we were able to safely deliver high doses of radiation (median: 72.6 GyE in 22 fractions) and achieve a high local control rate of 87% during the limited observation period. Based on these results, PBT appears a potential comparable, less-invasive alternative to surgery for patients with large tumors that are poor candidates for surgical resection.

Traditionally, radiation therapy has played a minor role in the treatment of HCC because antiquated dose localization techniques required the delivery of lower doses to larger volumes and did not routinely achieve tumor eradication. However, improvements in radiological imaging and radiotherapy techniques have made it possible to irradiate smaller, well-defined targets within the liver. Emami et al. estimated liver doses associated with a 5% risk of RILD with uniform irradiation of one third (D_{33}), two thirds (D_{66}), and the entire volume of the liver (D_{100}) at 50 Gy, 35 Gy and 30 Gy, respectively.[42] Lawrence et al. presented a normal tissue complication

probability (NTCP) model and estimated D_{33}, D_{66} and D_{100} to be 75 Gy, 45 Gy and 35 Gy, respectively.[43] According to this model, high dose RT up to 90Gy can be delivered safely if a substantial part of normal liver is spared. In our study, D_{33}, D_{66}, and D_{100} (dose equivalent if given in 2 Gy per fraction (α/β = 10)) were low at 30.1 GyE, 0.8 GyE, and 0 GyE, thereby minimizing the risk of RILD.

Liang et al. reported that a target volume over 500 ml is a risk factor for RILD, and the tolerance volumes for 5 Gy (V_5), 10 Gy (V_{10}), 20 Gy (V_{20}), 30Gy (V_{30}), and 40Gy (V_{40}) are 86%, 68%, 49%, 28%, and 20% of the normal liver volume.[44] For our patients, V_0, $V_{10,}$ $V_{20,}$ $V_{30,}$ V_{40}, if doses are calculated in in 2 GyE per fraction equivalents, were 53%, 39.5%, 36%, 33.5%, 23%, respectively. Our V_0, $V_{10,}$ and V_{20} values were sufficiently low but V_{30} and V_{40} values were high compared to the tolerance volumes delineated by Liang et al. Additionally, we delivered high doses to large target volumes (median: 992 ml), yet found no evidence of RILD.

The improved dose localization of sophisticated techniques such as intensity modulated radiotherapy (IMRT) or stereotactic body radiotherapy (SBRT) permit dose escalation to tumor tissue with sparing of surrounding

functional liver.[21, 44-46] However, these doses are generally insufficient to eradicate very large lesions, in which case, PBT may be the radiotherapy modality of choice.

The majority of patients who develop HCC have concurrent HBV and/or HCV viral infections.[27] In this study, approximately half of the patients showed no evidence of active viral infection. Therefore, these patients may have fared better than their HCC counterparts in the general population due to a relatively lower prevalence of coexistent viral hepatitis.

Tateishi et al. reported that tumor markers for HCC, such as AFP or PIVKA-II, can complement imaging modalities in the evaluation of treatment efficacy.[47] In our study, tumor marker levels in most patients markedly decreased during PBT, suggesting a response to therapy.

A major limitation of the present investigation involves the small number of patients treated over a protracted period. Thus, additional studies incorporating large numbers of patients are necessary to more clearly define the role of proton beam therapy in HCC greater than 10 cm in maximal dimension.

In the present cases, twenty out of 22 had large hepatocellular carcinoma located adjacent to the porta hepatis. According to our current

protocols, we recommend a protocol of 72.6GyE/22 fractions to reduce the risk of bile duct stenosis for large hepatocellular carcinoma except adjacent to the gastrointestinal tract. If the tumor was located adjacent to the gastrointestinal tract, we choose a protocol of 74.0GyE/37 fractions at present.

Recently, novel regimens such as systemic chemotherapy, and interferon and molecular targeted therapy have improved progression free survival or overall survival in patients with HCC.[48, 49] Further study will be necessary to determine whether these strategies can be used in conjunction or in sequence with PBT to improve HCC outcomes.

Conclusion

Proton beam therapy is an effective and safe intervention for patients with HCC greater than 10 cm in maximal dimension.

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Figure legends

Fig.1 Overall survival and progression-free survival rates for 22 patients with hepatocellular carcinoma exceeding 10 cm.

Fig 2. Local control rates in 22 patients with hepatocellular carcinoma exceeding 10 cm treated with proton beam therapy

Fig 3. Typical dose distributions and dose-volume analyses are shown.