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Research Article

Proton beam therapy for intrahepatic cholangiocarcinoma: A multicenter prospective registry study in Japan

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Short title: Multicenter registry study of PBT for ICC in Japan

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Abstract

Introduction: Intrahepatic cholangiocarcinoma (ICC) can be treated with chemotherapy in unresectable cases, but outcomes are poor. Proton beam therapy (PBT) may provide an alternative treatment and has good dose concentration that may improve local control.

Methods: Fifty-nine patients who received initial PBT for ICC from May 2016 to June 2018 at nine centers were included in the study. The treatment protocol was based on the policy of the Japanese Society for Radiation Oncology. Forty patients received 72.6-76 Gy (RBE) in 20-22 fr, 13 received 74.0-76.0 Gy (RBE) in 37-38 fr, and 6 received 60-70.2 Gy (RBE) in 20-30 fr. Overall survival (OS) and progression-free survival (PFS) were estimated by Kaplan-Meier analysis.

Results: The 59 patients (35 men, 24 women; median age 71 years; range 41-91 years) had PS of 0 (n=47), 1 (n=10) and 2 (n=2). Nine patients had hepatitis and all 59 cases were considered inoperable. The Child-Pugh class was A (n=46), B (n=7), and unknown (n=6); the median maximum tumor diameter was 5.0 cm (range 2.0-15.2 cm); and the clinical stage was I (n=12), II (n=19), III (n=10), and IV (n=18). At the last follow-up, 17 patients were alive (median follow-up 36.7 months; range 24.1-49.9 months) and 42 had died. The median OS was 21.7 months (95% CI 14.8-34.4 months). At the last follow-up, 37 cases had recurrence, including 10 with local recurrence. The median PFS was 7.5 months (95% CI 6.1-11.3 months). In multivariable analyses, Child-Pugh class was significantly associated with OS and PFS, and Child-Pugh class and hepatitis were significantly associated with local recurrence. Four patients (6.8%) had late adverse events of Grade 3 or higher.

Discussion/Conclusion. PBT gives favorable treatment outcomes for unresectable ICC without distant metastasis and may be particularly effective in cases with large tumors.

Introduction

The prevalence of intrahepatic cholangiocarcinoma (ICC) is high in Asia [1, 2]. The age-adjusted prevalence in Japan is 1.25 per 100,000 person-years for men and 0.77 per 100,000 person-years for women [3]. The standard treatment for intrahepatic bile duct cancer is resection and chemotherapy, and the appropriate combination is selected based on liver function and clinical variables such as distant metastasis, lymph node metastasis, and multiple lesions [4]. The 5-year survival rates are 90-100% for Stage I, 60-70% for Stage II / III, and 20% for Stage IV cases [5]. The outcome of surgical resection depends on the tumor size, lymph node metastasis, and portal vein tumor invasion, and the 5-year survival rate for patients with lymph node metastasis is thought to be 20% or less [5, 6].

Unresectable ICC is treated with chemotherapy such as gemcitabine, cisplatin and TS-1, but the therapeutic effect is poor and the median survival time is only about 1 year [7-9]. Particle therapy provides an alternative treatment and has good dose concentration that is likely to result in a high local control rate compared to that with X-ray therapy. However, only a few phase I/II trials and retrospective studies have examined this therapy for intrahepatic cholangiocarcinoma [10-13]. In Japan, a prospective study was started in May 2016 to evaluate the efficacy and safety of proton beam therapy (PBT) for malignant carcinoma. Here, we evaluate the preliminary results of this study for cases of ICC.

Patients and Methods

Patients who received PBT from May 2016 to June 2018 at nine participating centers were registered in the study database. This study protocol was reviewed and approved by [Ethical Review Board for Life Science and Medical Research, Hokkaido University Hospital], approval number [016-0106]. Prior approval for the study was obtained from the ethics committee at each center and written informed consent was provided by all patients. The initial registration items are as below: name of the irradiation facility, gender, age, PBT (initial treatment, second or later), tumor localization (localized, with metastasis), surgical indication (operable, inoperable), initial treatment (initial, recurrence), diagnostic method (histological diagnosis, clinical diagnosis), double cancer (with, without), radiotherapy history (yes, no), Karnofsky performance status (KPS), PS, treatment policy (radical, non-radical), tumor location (hepatic portal, gastrointestinal proximity), PBT method (broad beam, spot scanning), PBT start/end date, total dose, number of fractions, treatment period (days), extent of completion of PBT (completion, completion with a break of ≥ 8 days, discontinuation at $\geq 50\%$ of the schedule, discontinuation at $< 50\%$ of the schedule), Child-Pugh classification (A, B, C), hepatitis (none, alcohol, type B, type C, autoimmune), maximum tumor diameter (cm), ICG_{15min} value, portal vein tumor thrombosis (PVTT) (VP0-2, 3-4), hepatic vein tumor thrombosis (Vv0-1, 2-3), and clinical stage (TNM, UICC, JPS) on the end date of PBT.

The following items were added to the registry at least once each year: late adverse events (yes, no), date of confirmation of late adverse events, classification of late adverse events, grade of late adverse events (CTCAE, Grade 3 or higher), status (death from ICC, survival with recurrence, survival without recurrence, unknown), date of confirmation of survival status, recurrence (yes, no), date of confirmation of recurrence, site of recurrence (inside irradiated field, outside irradiated field and inside liver, affiliated lymph nodes, distant metastasis, unknown), secondary cancer (yes, no), and date of confirmation of secondary cancer.

Eligibility for this registry study was defined as unresectable ICC and all active tumors amenable to PBT. Therefore, lymph node metastasis close to the primary tumor that could be irradiated with PBT and cases with distant metastasis that were judged to be controlled by other treatments were acceptable indications for treatment. In PBT, local irradiation was performed on areas with obvious lesions. No prophylactic irradiation of lymphatic areas was performed. Treatment CT was recorded after fasting for at least 3 hours after eating, and irradiation was performed using a respiratory-gated system or a motion tracking system.

Data analysis

Overall survival (OS) and progression-free survival (PFS) were estimated with the Kaplan-Meier method. The cumulative incidence for local recurrence with the competing risk of death without local recurrence was estimated with the ordinary nonparametric method. Multivariable Cox regression models were applied for OS and PFS and a multivariable Fine-Gray regression model [14] was used for local recurrence. The candidate covariates in these models were age, tumor size, gender, prior treatment, performance status, tumor location, Child-Pugh score, history of hepatitis, portal vein tumor thrombus and clinical stage. Variable selection for multivariable models was conducted using the stepwise method with AIC. The significant level for statistical tests was set at 0.05 and the confidence level for confidence intervals was set at 95%. Analyses were conducted using the survival, prodlm,

cmprsk, and crstep packages in R software v.4.2.0 [15-19]. Local recurrence was defined as tumor progression within the PBT irradiation range.

Results

A total of 81 patients who received PBT for ICC were registered between May 2016 and June 2018. Of these cases, 59 (Table 1) that underwent initial PBT, had no double cancer and no metastasis outside the irradiated area, and received curative treatment were included in this analysis. The 59 patients (35 men, 24 women) had a median age of 71 years old (range 41-91 years old) and a PS of 0 (n=47), 1 (n=10) and 2 (n=2). None of the patients had received radiotherapy before PBT. The tumor location was close to the hepatic portal vein (n=44) and the gastrointestinal tract (n=15). Nine patients had hepatitis. All 59 cases were considered inoperable. The Child-Pugh class was A (n=46), B (n=7), and unknown (n=6); the median maximum tumor diameter was 5.0 cm (range 2.0-15.2 cm); PVTT was VPO-2 (n=51) and VP3-4 (n=8); and the clinical stage was I (n=12), II (n=19), III (n=10), and IV (n=18). The treatment protocol was selected based on the unified treatment policy stipulated by the Japanese Society for Radiation Oncology (JASTRO). This policy indicates 72.6-76 Gy (RBE) in 20-22 fractions (fr) for tumors adjacent to the porta hepatis and 74.0-76.0 Gy(RBE) in 37-38 fr for those adjacent to the gastrointestinal tract (20). In this study, 40 patients received 72.6-76 Gy (RBE) in 20-22 fr, 13 received 74.0-76.0 Gy (RBE) in 37-38 fr, and 6 received another treatment schedule of 60-70.2 Gy (RBE) in 20-30 fr. Only the irradiation dose is specified in this policy, and setting of the irradiation range and margin depends on the standard approach at each facility. An irradiation dose outside this protocol is acceptable when the treatment period has to be adjusted due to the patient's circumstances or adjustment is necessary based on the tolerable dose of organs at risk. The acceptable dose to such organs is not specified in the policy. However, in a survey of participating centers, a spinal cord dose <45 Gy (RBE), gastrointestinal dose <50 Gy (RBE), and minimizing the liver volume receiving 0-30 Gy (RBE) or more were considered to be acceptable doses to at risk organs.

At the last follow-up, 17 patients were alive and 41 had died. The median follow-up period for survivors was 36.7 months (24.1-49.9 months). The causes of death are listed in Table 2. There were 16 deaths due to recurrence in the liver, including local recurrence (n=4), intrahepatic recurrence other than local recurrence (n=10), and both (n=2). Eleven patients died of metastases (peritoneum=6, lung=1, bone=1, multisite=3), 8 deaths were due to other disease (infection=5, kidney failure=1, pneumonitis=1, unclassifiable=1), and 6 were of unknown cause (4 of 6 had tumor progression, and 2 cases had no information other than death).

The median OS period for all 59 patients was 21.7 months (95% CI 14.8-34.4 months) and the 1-, 2-, 3-, and 4-year OS rates were 71.2% (95% CI 57.8-81.0%), 45.8% (32.8-57.8%), 36.1% (23.9-48.6%), and 18.6% (7.5-33.6%), respectively. At the last follow-up, 37 cases had recurrence, including distant metastasis (n=19), recurrence in the liver outside the irradiation field (n=8), and local recurrence (n=10). The median PFS of the 59 patients was 7.5 months (95% CI 6.1-11.3 months); the 1-, 2-, 3-, and 4-year PFS rates were 35.6% (95% CI 23.7-47.7%), 23.7% (13.9-35.1%), 15.3% (7.2-26.2%), and 9.2% (2.9-20.2%), respectively; and the 1-, 2-, 3-, and 4-year local recurrence rates were 8.8% (0.4-17.0%), 22.6% (8.2-37.0%), 34.1% (14.5-54.0%), and 34.1% (14.5-54.0%), respectively. OS and PFS rates are shown in Figure 1 and the local recurrence rate is shown in Figure 2.

Multivariable analyses were performed to evaluate factors related to OS, PFS and local recurrence. Age, tumor size, gender, prior treatment, PS, tumor location, Child-Pugh class, history of hepatitis, PVTT and clinical stage were evaluated as prognostic factors. Only Child-Pugh class was significantly associated with OS and PFS. Child-Pugh class and hepatitis were significantly associated with local recurrence, and tumor size also showed a tendency to be related to local recurrence. The results of multivariable analysis are shown in Table 3. These results suggest that the excluded variables were at least not important prognostic factors.

At the last follow-up, 4 patients (6.8%) had late adverse events of Grade 3 or higher for which a relationship with PBT could not be excluded. These events were bile duct stenosis (n=2), dermatitis (n=1) and gastric hemorrhage (n=1) (Table 4). No grade 3 or higher hepatic dysfunction occurred during the observation period.

Discussion/Conclusion

This study was performed in cases of ICC with no distant metastasis that was inoperable or for which the patient refused surgery. The PBT schedule was selected in accordance with the unified treatment policy indicated by JASTRO [20]. In a multicenter phase 2 trial of PBT in 39 patients with unresectable ICC treated with 67.5 GyE or 58.05 GyE in 15 fr, Hong et al. [12] reported median survival of 23 months and 1- and 2-year survival rates of 70% and 43%, respectively. There were adverse events of Grade 3 or higher in 3 cases (8%). In PBT at a median dose of 72.6 Gy (RBE) in 22 fr for 25 patients with unresectable ICC, Shimizu et al. achieved median survival of 25 months,

1- and 2-year survival rates of 66% and 52%, and 1- and 2-year local control rates of 100% and 72%, respectively [10, 11]. Three cases (12%) had cholangitis as an adverse event of Grade 3 or higher. In a multicenter prospective observational study of PBT for 25 cases with unresectable ICC, Parazen et al. reported a 1-year survival rate of 82%, a 1-year local control rate of 91%, and a rate of adverse events of Grade 3 or higher of 5% [21]. In the current study, median OS was 21.7 months, the 1- and 2-year OS rates were 71.2% and 45.8%, and the 1- and 2-year local control rates were 91.2% and 77.4%, respectively, all of which are similar to those in previous reports.

The results of this analysis showed that the local control rate was significantly lower in patients with poor liver function. The treatment protocol was the same for patients with poor and good liver function. However, a survey conducted at participating centers suggested that the irradiation range in patients with poor liver function may be minimized to reduce irradiation to the normal liver, and thus, the possibility of an increased recurrence rate due to an insufficient margin cannot be ruled out. Also, in this analysis, 6 patients received PBT outside the JASTRO treatment policy. The lowest dose in these 6 patients was 60 Gy (RBE) in 30 fractions and the median dose was 68.9 Gy (RBE). The median OS of the 6 cases tended to be slightly shorter at 16.9 months (2.5-30.2 months), but due to the small number of cases, it was difficult to judge the impact of choosing a treatment protocol outside the policy. In previous studies, the incidence of late adverse events of Grade 3 or higher was 5-12% [10-13]. In our study, late Grade 3 adverse events occurred in 4 cases, giving a similar incidence of 6.8%, and the nature of these events was also similar to previous findings.

Radiotherapy has been used in combination with TACE for unresectable ICC, normally with irradiation of 50 Gy in 1.8-2.0 Gy fractions. The median survival using this approach is 10-14 months and the rate of adverse events of Grade 3 or higher is about 10% [22-27]. In recent years, stereotactic body radiotherapy (SBRT) has also been examined for unresectable ICC, with irradiation of about 45 Gy in 3 fr giving median survival of about 10-15 months and a rate of adverse events of Grade 3 or higher of about 10-20% [28-31]. ICC is a rare tumor, which makes it difficult to make comparisons among cases with the same patient background. However, radiotherapy and PBT are basically performed for unresectable ICC. Based on the median survival time, PBT shows good treatment outcomes of >20 months compared to that of 10-15 months with X-ray therapy. Photon radiotherapy and PBT are performed for hepatocellular carcinoma (HCC) and ICC [32-35]. For small HCCs of 2-3 cm or less, PBT and SBRT have almost the same effect on local control, but PBT is superior for cases with poorer conditions, such as those with large tumors [36-39]. The tumor size in unresectable ICC usually exceeds 2-3 cm (the median maximum tumor diameter in this study was 5 cm), which suggests that PBT may be more effective. Furthermore, the extent of ICC is often unclear and the wider irradiation range in PBT may be important in this respect.

With reference to the JASTRO treatment policy, the same dose fractionation was indicated for HCC and ICC. However, the local control rate of ICC tends to be lower than that of HCC, since ICC has a tendency to infiltrate and radiotherapy may simply be less effective. ICC cases were also thought to have a larger tumor size at the time of PBT. The irradiation range is not specified in the protocol, so different margins were used at each facility. However, in the survey conducted at the participating centers, the irradiation target was commonly indicated to have a margin of about 1 cm from the range where the tumor was clearly confirmed on diagnostic imaging. In addition, multiple centers responded that the margin may be set wider for ICC than for HCC, especially in ICC cases with unclear boundaries. In the future, there is a need to conduct a clinical trial with a standardized irradiation dose and range to determine the optimal dose fractionation for control of ICC.

Surgical resection is most effective for ICC [4] and treatment outcomes of surgery for early intrabiliary tumors are very good [5, 6]. However, the mass-forming type has a high recurrence rate and the 5-year survival rate is only 30-40% [5, 6, 40]. T4 and N1 cases also have poor treatment outcomes, with a median survival time of about 20 months [5]. The median survival time of PBT in this study and a previous report was ≥ 20 months, which indicates a favorable treatment outcome given that all cases were unresectable or the patient refused surgery. Chemotherapy with gemcitabine, cisplatin and TS-1 is performed for unresectable ICC, but the median survival time is only about 12 months [7-9]. Patients indicated for chemotherapy include those with distant metastasis and lymph node metastasis, so a simple comparison is difficult, but PBT appears to be effective treatment for unresectable and non-metastatic cases. In Japan, chemotherapy is the standard treatment for unresectable ICC, and as mentioned above, GEM, CDDP, and TS-1 are used in combination. In a randomized phase 2 trial, Okusaka et al. reported median survival times (MSTs) of 11.2 months (GC; GEM+CDDP) and 7.7 months (GEM alone), respectively (41). Morizane et al. conducted a randomized controlled trial of GC therapy and GEM + TS-1 therapy and obtained MSTs of 15.1 months (GC) and 13.4 months (GS), respectively (9). In a comparative study of GC and GCS, Ioka et al. found MSTs of 13.5 (GCS) and 12.6 (GC), indicating the superiority of GCS (42). Based on these results, the MST of chemotherapy for unresectable ICC in Japan is presently about 13-15 months. The MST in our registry is 21.7

months, which seems to be a good result compared to chemotherapy alone, but these data do not include cases with active distant metastases and the conditions were good even among unresectable ICC cases. De et al. have recently described the advantages of radiotherapy for ICC with metastases (43). In a comparison of chemotherapy alone with radiotherapy, 82% of deaths with chemotherapy alone were found to be caused by liver recurrence, but after radiotherapy this rate dropped to 47%, with distant metastasis becoming the leading cause of death (43). It was concluded that radiotherapy is associated with a lower rate of death caused by liver recurrence and with longer survival (43). In the current study, the main cause of death was liver recurrence, but most deaths were due to recurrence in the liver outside the irradiated area (24%) and only a small number were due to local recurrence (15%). Distant metastasis (27%) and death from another disease (20%) were the second and third causes of death. Local recurrence alone was the cause of death in 10% of cases, and this rate was only 15% if cases with local recurrence plus other recurrence in the liver were added. This suggests that local control by PBT changes the main cause of death from local recurrence to progression to another site (distant metastasis, intrahepatic recurrence outside the irradiated field), and this may contribute to prolongation of survival time. Thus, a strict comparison is difficult due to the selection of cases. In addition, only 10 of 59 patients received chemotherapy in this registry. Given that >70% of the recurrence types in the study were outside the radiation range, the combination of chemotherapy appears to be effective. However, to fully resolve these questions, a comparative study of PBT plus chemotherapy and chemotherapy alone for unresectable ICC is required. In conclusion, ICC is a rare cancer and this makes it difficult to perform large prospective or randomized trials. Patient backgrounds were not standardized in this registry trial, but PBT was found to give favorable treatment outcomes for unresectable ICC without distant metastasis.

Statement of Ethics

Study approval statement: This study protocol was reviewed and approved by [Ethical Review Board for Life Science and Medical Research, Hokkaido University Hospital], approval number [016-0106].

Consent to participate statement: Written informed consent was obtained from all participants in the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conception/design: MaMi, KS, HS. Provision of study material or patients: KT, HM, MS, TaO, TW, HI, HT, YU, TA, TO, TI, MaMu. Collection and/or assembly of data: NK. Data analysis and interpretation: MaMi, KM, KS. Manuscript writing: MaMi, KS. Final approval of manuscript: HS

All authors (1) made substantial contributions to the study concept or the data analysis or interpretation; (2) drafted the manuscript or revised it critically for important intellectual content; (3) approved the final version of the manuscript to be published; and (4) agreed to be accountable for all aspects of the work.

Data Availability Statement

Data is not publicly available due to ethical reasons. Further enquiries can be directed to the corresponding author

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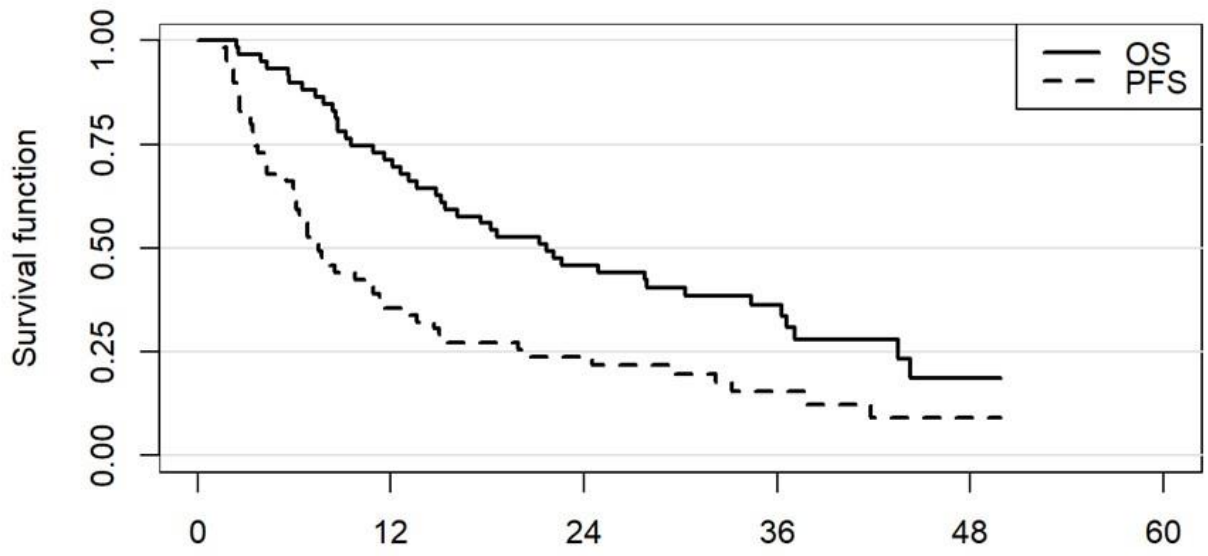
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Figure Legends

Fig. 1. Overall survival and progression-free survival rates in all patients.

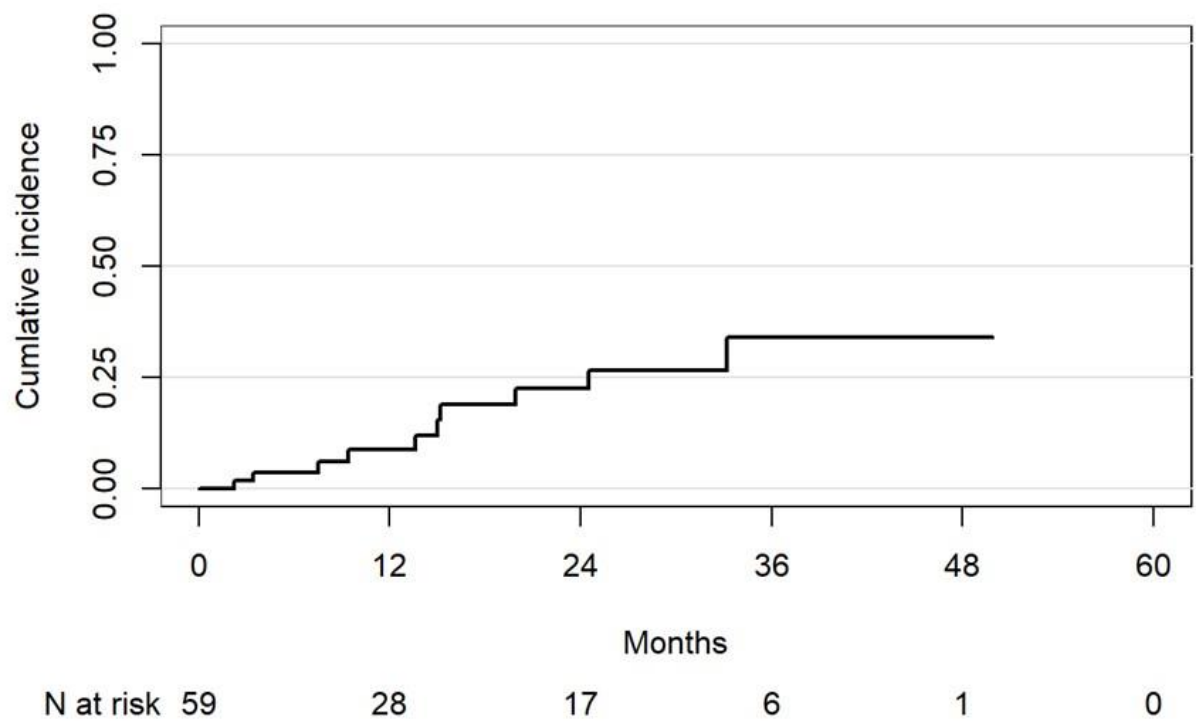
Fig. 2. Local recurrence rate in all patients.

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N at risk		Months					
		0	12	24	36	48	60
OS:	59	42	27	14	1	0	
PFS:	59	21	13	6	1	0	

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Table 1. Characteristics of patients and tumors.

Characteristics	Number	%
Age (years)	41-91	71 (median)
Gender		
Male	35	59.3
Female	24	40.7
Surgical indication		
Operable	0	0
Inoperable	59	100
ECOG performance status		
0	47	79.7
1	10	16.9
2	2	3.4
History of hepatitis		
Yes	9	15.3
No	50	84.7
Child-Pugh classification		
A	46	78.0
B	7	11.9
Unknown	6	10.2
Tumor location		
Hepatic portal	44	74.6
Gastrointestinal proximity	15	25.4
Tumor size (mm)		
	20-152	50 (median)
< 50	26	44.1
50-99	26	44.1
≥ 100	7	11.9
Portal vein tumor thrombus		
Vp 0-2	51	86.4
Vp 3-4	8	13.6
Prior treatment		
No	48	81.4
Yes	11	18.6

Prior radiotherapy

Yes	0	0
No	59	100

Clinical stage

I	12	20.3
II	19	32.2
III	10	16.9
IV	18	30.5

ECOG, Eastern Cooperative Oncology Group

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Table 2. Causes of death after proton beam therapy.

Cause of death	n	
	Local recurrence	4
Liver	Recurrence outside irradiated field in liver	10
	Recurrence locally and outside irradiated field	2
	Peritoneum	6
Distant metastasis	Lung	1
	Bone	1
	Multiple	3
Other disease		8
Unknown reason	With tumor progression	4
	No information other than death	2

Table 3. Multivariable analysis of potential predictive factors for overall survival, progression-free survival and local recurrence.

Factors	PT Number	2-year (%)	Hazard Ratio	HR range	z-value	p-value
<i>Overall survival</i>						
Prior treatment						
No	48	41.7				
Yes	11	63.6	0.536	0.225-1.277	-1.407	0.159
Child-Pugh class						
A	46	54.3				
B/C/unknown	13	15.4	2.715	1.329-5.544	2.741	0.006
<i>Progression-free survival</i>						
Child-Pugh class						
A	46	30.4				
B/C/unknown	13	7.7	2.741	1.389-5.411	2.906	0.004
<i>Local recurrence</i>						
Child-Pugh class						
A	46	18.0				
B/C/unknown	13	52.4	4.573	1.395-14.990	2.509	0.012
History of hepatitis						
No	50	25.0				
Yes	9	0	0.000	0.000-0.000	-18.723	0.000
Tumor size (cm)						
≤5.0	31	36.0				
>5.0	28	10.2	0.273	0.070-1.056	-1.881	0.060

Table 4. Proton beam therapy-related late toxicities of Grade 3 or higher.

Grade	3	4	5	Total
Bile duct stenosis	2	0	0	2
Dermatitis	1	0	0	1
Gastric hemorrhage	1	0	0	1

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