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Respiratory-gated proton beam therapy for intrahepatic cholangiocarcinoma without fiducial markers

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Abstract

Background Intrahepatic cholangiocarcinoma (ICC) is a challenging primary liver cancer with a poor prognosis, especially in unresectable cases. Traditional palliative irradiation is limited in reducing liver doses. This study aimed to evaluate the efficacy and toxicity of respiratory-gated proton beam therapy without fiducial markers for intrahepatic cholangiocarcinoma.

Methods Between October 2011 and February 2022, 24 patients (median [range] age, 71 [41–88] years) were evaluated at our institution. Twelve patients were pathologically diagnosed with ICC. All patients underwent respiratory-gated proton beam therapy at a dose of 48–83.6 (relative biological effectiveness) in 20–38 fractions with four-dimensional computed tomography planning. The median follow-up period was 18.5 (range, 2.0–74.0) months. The median tumor size was 41 (range, 10–134) mm. Twenty-one patients were classified as having Child–Pugh class A, and three patients were classified as having Child–Pugh class B. Local progression was defined as any growth of the irradiated tumor.

Results The median survival time was 28 months for all patients. The Kaplan–Meier estimates of the 2-year overall survival, progression-free survival, and local tumor control rates were 51%, 26%, and 73%, respectively. Local tumor control rates were non-inferior to those reported in previous studies using fiducial markers. One patient had grade 4 pleural effusion; however, whether this was an adverse event due to the proton beam therapy was unclear.

Conclusions Respiratory-gated proton beam therapy without fiducial markers is an effective and less invasive treatment option for ICC, showing potential for improved local control and tolerable adverse effects.

Keywords Proton beam therapy, Cholangiocarcinoma, 4D-CT, Respiratory-gated irradiation

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Background

Intrahepatic cholangiocarcinoma (ICC) accounts for 10–20% of primary liver cancers and is the second common tumor after hepatocellular carcinoma [1]. Intrahepatic and hilar cholangiocarcinomas, including advanced unresectable lesions, are associated with a poor prognosis, with a 5-year survival rate of 5–10% [2], and complete surgical resection is considered the only treatment for long-term survival [3]. However, Nagorney et al. reported that 50–90% of patients with cholangiocarcinoma presented with unresectable disease [4].

Palliative irradiation is the mainstay radiotherapy for ICC because of the difficulty in reducing the dose to the liver [4, 5]. However, in recent years, techniques, such as stereotactic body radiotherapy and particle beam therapy, have been developed to increase the dose while protecting the surrounding normal liver, and local control (LC) by external radiation has been reported. Tao et al. reported prolonged survival in patients treated with enhanced dose-intensive radiation therapy [6]. However, in photon therapy, large tumors are poor candidates for stereotactic body radiotherapy to avoid radiation-induced liver damage. Tumor size limits the protection of the background liver area, especially in inoperable ICC [7–10].

Proton beam therapy has a slightly higher biological effectiveness (approximately 1.1 times) than photon therapy and reduces the adverse effects on the normal liver because of the nature of the Bragg peak [11, 12]. The liver is a movable organ due to respiratory motion. Therefore, specific techniques must be used to reduce the internal margin of the liver. In proton beam therapy, percutaneous physical marker implantation is often required in organs, such as the liver [13–15], with its high mobility due to respiration. In such cases, there are risk of adverse events, such as pneumothorax and hemorrhage, and reports of marker migration, albeit with a small probability. Several studies have reported the outcomes of proton beam therapy for ICC, and it is considered an effective treatment method when combined with fiducial marker insertion [16–18].

In our hospital, we have been performing proton beam therapy for the liver without fiducial markers using four-dimensional computed tomography (4D-CT) for treatment planning and respiratory synchronized proton beam irradiation combined with daily CT image-guided positioning [19, 20]. In this study, we investigated the outcomes and adverse events of proton beam therapy for ICC at our hospital and compared them with those reported in the literature.

Materials and methods

Patients and methods

Between October 2011 and February 2022, we irradiated 24 patients and 24 lesions at our institution (median patient age, 70.5 [range, 41–88] years). Patients with intrahepatic lesions were exclusively enrolled in this study. Twelve (50%) patients had a pathological diagnosis of cholangiocarcinoma, and other patients were diagnosed based on clinical information, such as imaging findings and tumor markers. The median tumor size was 4.1 (range, 1.0–12.5) cm. In four patients, regional lymph node metastasis was clinically diagnosed, and none of the patients had distant metastases. Regarding background liver disease before proton beam therapy, one patient had hepatitis B, two hepatitis C, two alcoholic cirrhosis, and one non-alcoholic steatohepatitis. Three patients had a Child–Pugh class B classification, and the other patients had a Child–Pugh A classification. This study was approved by the Institutional Review Board of the Proton Therapy Center, Fukui Prefectural Hospital (no. 20-35).

Planning of proton beam therapy

We previously reported the use of 4D-CT planning at our institution [19, 20]. Similarly, we developed a treatment plan using respiration-synchronized 4D-CT (Aquilion LB TSX-201A; Toshiba Medical Systems Co., Tochigi, Japan). Tumor movement in the terminal expiratory phase observed with 4D-CT.A metronome was used to induce the patients to breathe at a steady rate of 10–15 breaths per minute, and the patients' breathing was measured by monitoring the abdominal wall movement with a laser sensor of the respiratory gating system (AZ-733V; Anzai Medical Co., Tokyo, Japan). Irradiation was performed with narrow gating at 17–25% of the duty cycle at end expiration (approximately 1 s).

Balter et al. reported that the diaphragm is an acceptable anatomic landmark for estimating liver movement [21]; therefore, we used it as a fiducial marker and evaluated its interfractional reproducibility for abdominal tumors with our technique. While this method effectively manages intra-fractional motion, inter-fractional variations can degrade tumor positional reproducibility since the respiratory gating system provides only relative respiratory phase information. Therefore, we ensured irradiation accuracy by using serial CT imaging during the treatment course to monitor and adjust for any interfractional changes.

CT data were reconstructed at a section thickness of 2 mm and a section interval (gap) of 0.4 mm. The field of view was adjusted to match the patients' physique.

Target contouring was performed on 4D-CT images of the expiratory phase, where the gross tumor volume was defined by contrast-enhanced magnetic resonance imaging (MRI) and CT, and the clinical target volume was approximately 5-mm in all directions from the gross tumor volume, taking into account the extent of lesion reach [22]. The amount of movement due to respiration, calculated by analyzing the 4D-CT images, was added to the clinical target volume and designated as the internal target volume. The planning target volume was determined by adding a 5-mm margin in all directions to the clinical target volume. For this calculation, the proton therapy planning system XiO®-N (Elekta Corp., Stockholm, Sweden) was used. This system calculates the proton dose based on a pencil beam algorithm and forms the target geometry using a passive scattering method, which involves a patient-specific collimator or a multi-leaf collimator, and a patient bolus.

Two or more proton beams were used, and the total dose at the isocenter was prescribed to cover 95% of the planned target volume. In cases with close proximity to the gastrointestinal tract, we replanned the delivery of radiation at 30–40 Gy relative biological effectiveness (RBE) to ensure that the maximum dose to the gastrointestinal tract did not exceed 50 Gy (RBE). The prescribed doses were selected from 10 patterns of 48.0–83.6 Gy (RBE) per 10–38 fractions (Fr) in this study (Table 1). Proton therapy was performed five times per week.

Chemotherapy

Eight (33%) patients received concurrent chemotherapy. This included three patients treated with titanium silicate-1 and titanium silicate-5 with gemcitabine chemotherapy. The remaining 16 (67%) patients received only proton beam therapy. Thirteen (54%) patients received chemotherapy after proton beam therapy. The major systemic agent used in a neoadjuvant (adjuvant) setting was a combination of cisplatin and gemcitabine.

Table 1 Patterns of dose prescription

Prescription	Number of cases
76 Gy(RBE)/20Fr (BED:104.9 Gy)	11
76 Gy(RBE)/38Fr(BED:91.2 Gy)	2
72.6 Gy(RBE)/22Fr(BED:96.6 Gy)	2
72 Gy(RBE)/12Fr(BED:115.2 Gy)	2
66 Gy(RBE)/10Fr(BED:109.6 Gy)	2
83.6 Gy(RBE)/22Fr(BED:115.4 Gy)	1
74.8 Gy(RBE)/34Fr(BED:91.3 Gy)	1
Others 57.68 < BED < 88.8)	3

RBE: Rerative biological effectiveness Fr: fractions

BED: biological effective dose ($\alpha/\beta = 10$)

Follow-up and toxicity evaluation

For follow-up, CT scanning or MRI was performed at approximately 3-month intervals for 3–5 years after the completion of proton beam therapy. Local progression was defined as growth of the irradiated tumor. Toxicity was graded according to the Common Terminology Criteria for Adverse Events version 5.0 (National Cancer Institute, Bethesda, MD, USA) [23].

Analyses

The LC, progression-free survival (PFS), and overall survival (OS) rates were calculated using the Kaplan–Meier method. Multivariate analysis was performed using Cox regression analysis with or without pathological diagnosis, sex stratification, T classification (T1–2 vs. T3–4), combination chemotherapy, and the presence of background liver disease. Hazard ratio with 95% confidence interval (CI) was calculated for each independent variable. The Kaplan–Meier method and Cox regression analysis were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [24]. A p value < 0.05 was considered statistically significant.

Results

Efficacy

Ninety-six percent of the patients (23/24) completed proton beam therapy and were followed up until death or March 31, 2022. In one patient, treatment was discontinued because of brain metastasis. The median follow-up period was 18.5 (range, 2.0–74.0) months. The other characteristics are listed in Table 2.

The 1- and 2-year OS rates after proton beam therapy were approximately 67% (95% CI, 44–82%) and 51% (95% CI, 29–70%), respectively. The median survival time was 28 months. The 1- and 2-year PFS rates after proton beam therapy were 33% (95% CI, 13–55%) and 26% (95% CI, 9–48%), respectively, and the 1- and 2-year LC rates were 74% (95% CI, 48–89%) and 66% (95% CI, 38–84%), respectively (Fig. 1). Six (13%) patients had local recurrence in the irradiated field. Ten (42%) patients had no local recurrence or disease progression outside the field. Liver, lymph node, and both liver and lymph node metastases were observed in three, two, and three patients, respectively. Lymph node and lung metastases were observed in one patient, and multiple bone metastases were observed in one patient.

Table 2 Patient characteristics

Characteristic	n
Number of patients	24
Gender; male/female	15/9
Age (years); median (range)	70.5(41–88)
Pathological diagnosisi/clinical diagnosis	12/12
Tumor size; median (range)	4.1(1.0–13.4)
Chronic hepatitis	
HCV	2
HBV	1
Alcholic	2
NASH	1
Normal liver	19
Child Pugh category	
Normal-A	21
B	3
C	0
UICC Tstage T1-2/T3-4	19/5
Distance from GI-tract ≧ 20 mm, < 20 mm	16/8
Chemothrapy	
Yes	14
Neoadjuvant	5
Concurrent	9
Adjuvant	15
No	11

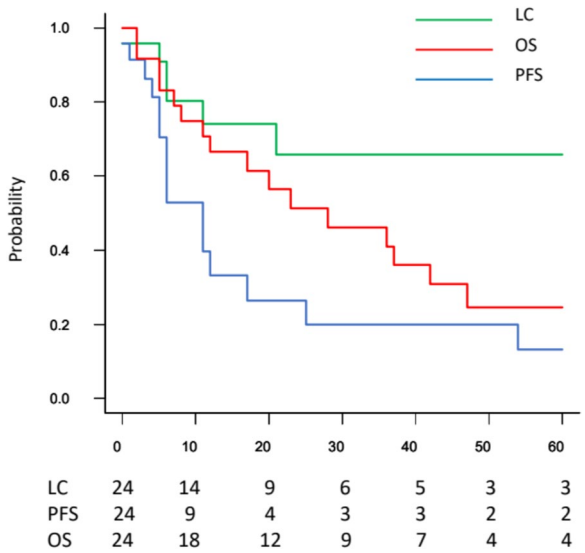

Fig. 1 Kaplan–Meier curves of overall survival (OS). Kaplan–Meier estimates of OS, progression-free survival (PFS), and local control (LC) rates for patients. The median follow-up period was 27.1 (range, 4–69) months. The median OS period was 42 months. The 2-year OS, PFS, and LC rates were 62%, 33%, and 66%, respectively

Furthermore, Table 3 lists the results of the univariate stratified analysis of factors potentially associated with OS. However, no clear correlation was observed.

Toxicity

Regarding acute toxicities, grade 2 dermatitis occurred in four patients, and grade 1 pneumonia was observed in two patients. Among the late toxicities, rib fractures were observed in two patients, and grade 2 pleural effusion was observed in two patients (Fig. 2). Notably, one patient had grade 4 pleural effusion, and its association with proton beam therapy was unclear (Fig. 3).

Discussion

Nakeeb et al. reported that the 5-year survival rate for hilar cholangiocarcinoma was higher than 30–40% in cases of hilar cholangiocarcinoma that were microscopically negative for surgery and that complete surgical resection has been the mainstay of radical treatment for cholangiocarcinoma [3, 25]. However, most ICC cases are unresectable, and the prognosis of patients with unresectable ICC is poor [2, 4].

Adjuvant radiation therapy has often been used as radiotherapy for cholangiocarcinoma with resectable lesions or as palliative radiation for unresectable lesions. However, the effectiveness of radiation therapy in cholangiocarcinoma remains controversial, as reported by Pitt et al. [26]. Moreover, a meta-analysis by Horgan et al. [27] demonstrated that postoperative adjuvant radiotherapy did not result in a significant survival benefit.

It is difficult to deliver high doses of radiation with conventional radiotherapy because of some factors, such as an increased dose to the surrounding normal liver. However, technological advancements in radiotherapy have made it possible to deliver high doses of radiation to large unresectable lesions. Tao et al. [6] attempted to increase the dose using intensity-modulated radiotherapy for unresectable ICC. The 3-year OS rate for patients who received biological equivalent dose (BED) > 80.5 Gy was 73%, compared with the 38% in the low-dose group. Moreover, the LC rates were significantly higher in patients who received BED > 80.5 Gy, and the authors reported the possibility of curative treatment with external radiation. In addition, Mahadevan et al. [28] reported a favorable outcome of stereotactic body radiotherapy at 30 Gy/3 Fr in 42 lesions of intrahepatic and hilar cholangiocarcinoma, including 32 unresectable cases, with an LC rate of 71%.

Thus, there have been reports on the curative treatment of ICC using photon therapy and several reports on the outcomes of proton beam therapy (Table 4). Shimizu

Table 3 Univariate analysis for overall survival rate using Cox proportional hazards model

Variables	Strata	Patient number	Univariate analysis		
			HR	95%CI	p-value
Sex (M = 1, F = 0)	F	8	1	(referent)	–
	M	16	0.835	0.301–2.310	0.728
Age > = 75 ~ 1, < 75 ~ 0	< 75	16	1	(referent)	–
	75 < =	8	1.118	0.405–3.088	0.83
C-P A = 0, BorC = 1	normal-A	21	1	(referent)	–
	B-C	3	3.12	0.614–15.86	0.17
Distance from GI-tract > 20 mm = 1, < 20 mm = 0	< 2 cm	8	1	(referent)	–
	2 cm < =	16	0.932	0.329–2.639	0.895
Tumor diameter > = 5 ~ 1, < 5 ~ 0	< 5 cm	16	1	(referent)	–
	5 cm < =	8	0.742	0.252–2.181	0.587
T1 or T2 = 0, T3 or T4 = 1	T1–T2	19	1	(referent)	–
	T3–T4	5	1.368	0.439–4.260	0.589
N	0	20	1	(referent)	–
	1	4	1.747	0.493–6.190	0.388
Stage (1, 2 = 0, 3,4 = 1)	Stage1–2	15	1	(referent)	–
	Stage3–4	9	1.53	0.567–4.130	0.401
Concurrent Chemo Yes = 1, No = 0	No	16	1	(referent)	–
	Yes	8	1.25	0.431–3.623	0.681
Adjuvant	No	11	1	(referent)	–
	Yes	13	0.795	0.296–2.135	0.649

CI = confidence interval; HR = hazard ratio

et al. [16] reported a 2-year OS rate of 41.4% and an LC rate of 71.5%, and Hong et al. [17] reported a 2-year OS rate of 46.5% and an LC rate of 94.1%, which can be considered good results with regard to the LC of the lesions. This study shows similar results, with a 2-year LC rate of 66%. However, owing to intrahepatic and lymph node metastases, the 2-year PFS rate was as low as 33%. Thus, we believe that LC alone is insufficient to control ICC and that proton beam therapy as a local treatment is insufficient as a curative treatment.

There are several reports on chemoradiotherapy for biliary tract cancer, including 5-fluorouracil-, gemcitabine-, and oral titanium silicate-1-based chemoradiotherapy [29–33]. Sumiyoshi et al. [32] reported 15 patients with unresectable biliary tract cancers who received chemoradiotherapy, including 14 who received titanium silicate-1; 11 of these patients were assessed to have re-resectable lesions after chemoradiotherapy, and 9 of these patients underwent curative resection (R0 resection). Hogan et al. [27] reviewed 20 studies on chemotherapy, radiotherapy, and chemoradiotherapy as adjuvant therapies and reported an overall benefit of adjuvant therapy in node-positive or resection margin-positive (R1 resection) patients and a significant improvement in survival with chemotherapy alone or chemoradiotherapy, depending on the treatment. According to a review by Rizvi et al. [34], several molecularly targeted drugs and immunotherapies for cholangiocarcinoma are currently under investigation for their usefulness. For a complete treatment of ICC, including prevention of distant metastasis, adjuvant therapies, such as chemotherapy and other newer molecular targeted drugs and immunotherapy, as reported in these reports, are indispensable. However, future multicenter prospective studies are required to establish the validity of the novel therapies.

Regarding the adverse events after proton therapy, Shimizu et al. [16] reported grade 3 cholangitis in 3 of 37 patients, and Hong et al. [17] reported grade 3 or higher adverse events, such as liver dysfunction, ascites, and gastric ulcer in 3 of 39 patients. None of these reports reported grade 4 or higher levels of serious adverse reactions. In our institution, irradiation does not involve the use of a fiducial marker, and respiratory synchronization with narrow gating at 17–25% of the duty cycle at end expiration (approximately 1 s) is performed. CT imaging is performed after each irradiation and is compared with the CT scan images

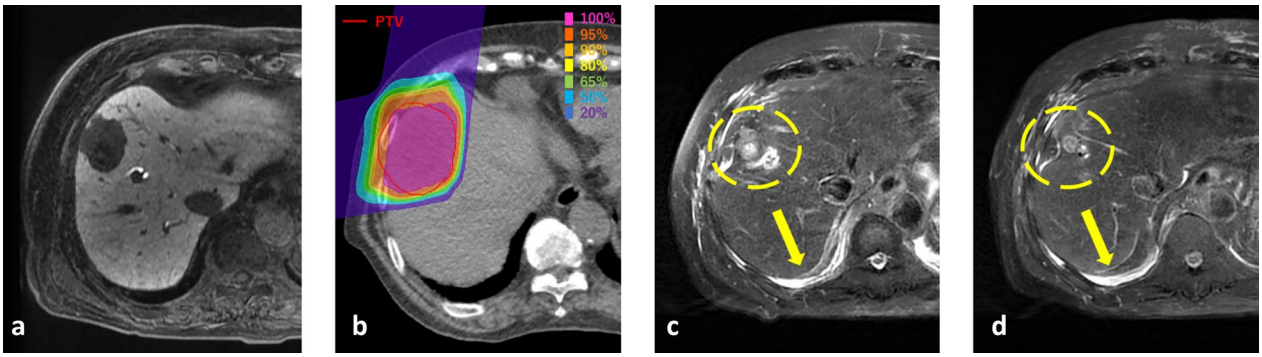

Fig. 2 An 80-year-old man, who was incidentally found to have a 47 × 38 × 38-mm large mass in the S5 liver, was pathologically diagnosed with intrahepatic cholangiocarcinoma (ICC). The patient had a liver reserve classified as Child–Pugh A. The tumor showed hypointensity in the hepatobiliary phase of gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging (MRI) before treatment (**a**). Subsequent imaging studies, such as computed tomography (CT), MRI, and fluorodeoxyglucose positron emission tomography-CT, revealed a diagnosis of T1aN0M0 stage IA cholangiocarcinoma (Union for International Cancer Control 8th edition). The isodose lines are displayed on the images obtained from the planning CT (**b**). This lesion was treated with proton beam therapy with respiratory synchronization and without the use of fiducial markers. No combination chemotherapy was administered. The proton therapy plan was prepared with two beams of 10° and 260°, and a dose of 83.6 relative biological effectiveness/22 fractions was prescribed. At 1 year post-irradiation, the lesion size had reduced (**c**). Subsequently, a small right-sided pleural effusion appeared, with a gradual increase at the 3-year post-irradiation follow-up examination (**d**). The patient complained of shortness of breath and was medically treated, and the dyspnea was judged to be grade 2 according to the Common Terminology Criteria for Adverse Events version 5. Five years after the completion of irradiation, the lesion is under control, and recurrence has not been observed. The patient's pleural effusion has decreased as the patient continues to be followed up

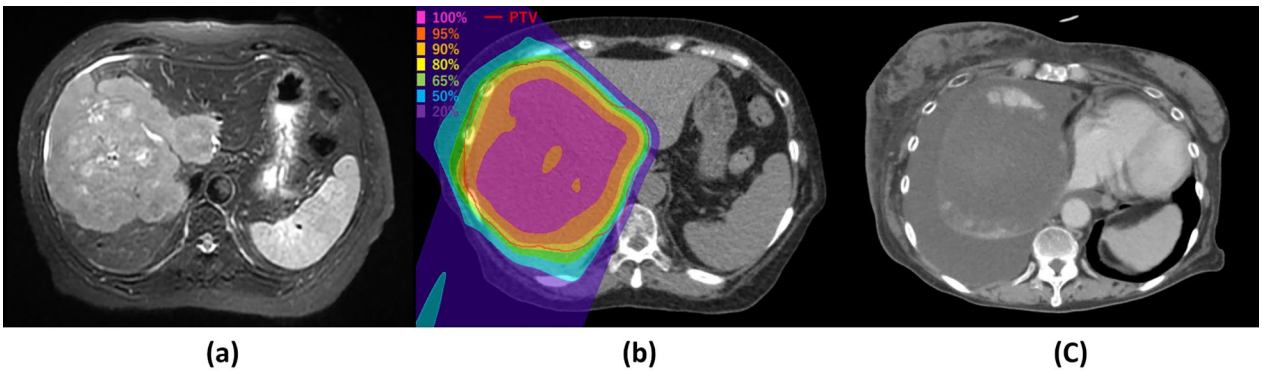

Fig. 3 A 64-year-old woman was treated with 76 (relative biological effectiveness [RBE])/20 fractions of proton beam therapy for cholangiocarcinoma. Despite no pathological diagnosis, the patient was diagnosed with cholangiocarcinoma based on clinical, including imaging, findings. Chronic liver disease was not observed, and liver reserve was noted with Child–Pugh class A. The tumor is large, 134 × 128 × 125 mm, and shows hyperintense signals on magnetic resonance imaging fat-suppressed T2-weighted images (**a**). We diagnosed the patient with a T4N0M0 stage IIIB (Union for International Cancer Control 8th edition) cancer. Isodose lines are observed on treatment planning computed tomography (**b**). The proton therapy plan was prepared and incorporated two beams of 200° and 315°, and 76 relative biological effectiveness/20 fractions was prescribed. Eight months after proton beam therapy, a tendency for local recurrence was observed, and 10 months after proton beam therapy, the patient developed dyspnea due to right-sided predominant pleural effusion and was intubated (grade 4 Common Terminology Criteria for Adverse Events version 5.0)

obtained at the time of treatment planning; alternatively, the diaphragm observed under fluoroscopy is used as a landmark for respiratory movement to perform accurate irradiation. Dawson et al. [35] reported the diaphragm position closely correlates with the position of liver tumors implanted with microcoils, with a discrepancy of approximately 0.2 cm. This supports the use of diaphragm motion as a surrogate marker for liver tumor positioning. We believe that the irradiation accuracy is not poor because no high-grade adverse events were observed in the reports from our hospital, which used the same technique to irradiate hepatocellular carcinoma [19, 20]. However, in this study, grade 4 pleural effusion was observed in one patient. The patient presented

Table 4 Reports of proton beam therapy for intrahepatic cholangiocarcinoma

Authors	Study design	Cases	Tumor size (cm) Median (range)	Treatment dose/ fraction	Follow-up period (median)	Fiducial marker	Breathing method	OS 2Y	PFS 2Y	LC 2Y	Adverse effects grade3 (number of patient)	Adverse effects grade4 (number of patient)
This study	Retro	24	4.1 (1.0–13.4)	48-76 Gy(RBE)/10-37Fr	18.5 months	None	Respiratory gating system	62%	33%	66%	None	4%(1):pleural effusion(1)
Shimizu et al 2019 Radiat Oncol [16]	Retro	37	5.7 (1.5–14.0)	66-74 Gy(RBE)/10-37Fr	37.5 months	(+)	Respiratory gating system	41%	38%	72%	8%(3):cholangitis(3)	None
Theodores S. Hong et al 2016 Pract Radiat Oncol [17]	Pros	39	6.0 (2.2–10.9)	58.05–67.5 Gy(RBE)/15Fr	19.5 months	Not reffered	NR	47%	26%	94%	8%(3):liver failure and ascites(1), stomach ulcer(1), elebated bilirubin(1)	None
Kim et al 2022 Cancers [36]	Retro	47	5.2 (1.0–11.0)	45-80 Gy(RBE)/10Fr	18.3 month	None	Respiratory gating system	43%	17%	87%	8.5%(4):WBC decrease(2), Bilirubin increase(2)	None
Mizumoto et al 2023 Liver Cancer [37]	Pros	59	5.0 (2.0–15.2)	60-76 Gy(RBE)/20-38Fr	36.7 month	Not reffered	Respiratory-gated system or a motion tracking system	46%	24%	77%	6.8%(4):Bile duct stenosis(2), Dermatitis(1), Gastric hemorrhage(1)	None

with dyspnea due to a right-sided predominant pleural effusion and required tracheal intubation 10 months after proton beam therapy. However, the patient had a large pre-irradiated tumor (134 mm) and local recurrence after irradiation, which resulted in a large lesion extending into the diaphragm. In addition, neither a detailed examination of the properties nor cytology of the pleural effusion was performed. Therefore, the possibility of cancerous pleurisy cannot be ruled out. No other high-grade adverse events, including radiation pneumonia, liver damage, gastrointestinal problems, or cholangitis, were observed. However, the local control rates observed in this study, as well as those reported previously, are not yet satisfactory. It suggests that dose escalation may be necessary in next approaches. Accurately quantifying errors related to the actual tumor location remains a challenging issue, requiring further investigation.

This study has some limitations. The study sample was small, the follow-up period was short, and a pathological diagnosis was not established in half of the patients. If the number of patients and follow-up period had increased, different trends may have emerged in the multivariate analysis that did not show significant differences in this study.

Conclusions

We present the reported series of proton beam therapy for ICC. Respiratory-gated proton beam therapy without fiducial markers is an effective and less invasive treatment method for ICC.

Abbreviations

ICC	Intrahepatic cholangiocarcinoma
4D-CT	Four-dimensional computed tomography
PBC	Proton beam therapy
CT	Computed tomography
RBE	Relative biological effectiveness
LC	Local control
PFS	Progression-free survival
OS	Overall survival
CI	Confidence interval
BED	Biological equivalent dose

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13014-024-02550-2.

Additional file1.

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Author contributions

AO, SM, ST, TG, and SK contributed to the study concept and design. SM wrote the initial draft of the manuscript. ST, KY, and SK assisted in manuscript preparation. AO, SM, and ST contributed to the data collection and assembly. SM, ST, SS, SA, HT, YS, KY,HS,HA, and HT contributed to the patient care. KM,YT, YM, and MS contributed to the proton beam therapy treatment planning. AO contributed to the critical revision of the manuscript. SK provided the final approval for the article. All the authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Availability of data and materials

Research data are stored in an institutional repository and will be shared upon request by the corresponding author.

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the Institutional Review Board of the Proton Therapy Center, Fukui Prefectural Hospital (no. 20-35).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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