Proton Beam Therapy for Unresectable Perihilar Cholangiocarcinoma

SungChul Park (psungchul0413@gmail.com)
Hyogo Ion Beam Medical Center
Kazuki Terashima
Hyogo Ion Beam Medical Center
Masaki Suga
Hyogo Ion Beam Medical Center
Daiki Takahashi
Hyogo Ion Beam Medical Center
Yoshiro Matsuo
Hyogo Ion Beam Medical Center
Nor Shazrina Sulaiman
Hyogo Ion Beam Medical Center
Yusuke Demizu
Hyogo Ion Beam Medical Center
Sunao Tokumaru
Hyogo Ion Beam Medical Center
Kyoji Furukawa
Kurume University Graduate School of Medicine
Tomoaki Okimoto
Hyogo Ion Beam Medical Center

Research Article

Keywords: perihilar cholangiocarcinoma, biliary tract cancer, unresectable, proton beam therapy, radiotherapy, particle therapy, prognostic factors, overall survival

Posted Date: February 15th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1345424/v1

Abstract

Background: The outcomes of chemotherapy for patients with perihilar cholangiocarcinoma (PHC) are unsatisfactory, and photon therapy for unresectable PHC reportedly results in improved outcomes. Proton beam therapy (PBT) can be a treatment option for these patients; however, the role of PBT in these patients is poorly defined as PHC is rare. Herein, we evaluated the efficacy and safety of PBT for unresectable PHC.

Methods: This observational retrospective cohort study conducted at a single institution included patients with unresectable PHC who received definitive PBT. Patients who had nodal metastasis at presentation or those who underwent surgery or other radiation therapies before PBT were excluded. To compare different dose fractionations, biologically equivalent doses with α/β=10 [BED10] were calculated.

Results: Overall, 26 patients were eligible. The commonly prescribed doses were 67.5 Gy (relative biological effectiveness [RBE]) in 25 fractions or 70.2 Gy (RBE) in 26 fractions. The median follow-up period was 19.4 months (range, 4.2-137.4 months). The Kaplan–Meier estimates of the 1-, 2-, and 5-year overall survival (OS) rates were 72.9%, 47.7%, and 17.4%, respectively, and the median survival time was 23.7 months. The multivariate analysis demonstrated that Child–Pugh classification B was a significant prognostic factor for unfavorable OS (hazard ratio [HR] 4.92; p=0.009) and that a mean gross tumor volume dose of ≥79.2 Gy (RBE) [BED10] was a significant prognostic factor for favorable OS (HR 0.19; p=0.025). Grade ≥3 late adverse events were observed in seven patients (26.9%).

Conclusions: We demonstrated that definitive PBT for patients with unresectable PHC might improve the prognosis. Further large-scale prospective studies are warranted to validate our findings.

Background

Biliary tract and gallbladder cancer is uncommon and is the 16th leading cause of cancer-related death worldwide [1]. Perihilar cholangiocarcinoma (PHC) accounts for approximately 60% of cholangiocarcinomas [2], which originate from the bile duct epithelia, and surgical resection is the only curative option [3]; however, approximately 30% of patients with PHC have unresectable disease at initial presentation [4]. Liver transplantation (LT) results in the best prognosis for patients with unresectable PHC, although patients with early stage PHC form the primary eligible group for this treatment option [3]. The typical treatment for patients with PHC who are not eligible for surgical resection or LT is chemotherapy. The median survival time (MST) of patients with locally advanced or metastatic biliary tract cancer after chemotherapy is reported to be 4.6-11.7 months [5-7], and the outcome of chemotherapy for these patients is unsatisfactory.

The role of radiotherapy in patients with unresectable, nonmetastatic PHC appears to be important. Photon therapy for these patients reportedly results in improved outcomes with MST of 6.7-16.7 months [8-11]. Proton beam therapy (PBT)—owing to its physical property resulting due to the Bragg peak—can provide more favorable distributions than photon therapy and deposits almost no dose in the normal tissue beyond the Bragg peak [12]. Retrospective studies on PBT for unresectable biliary tract or gallbladder cancer reported an improved MST of 15.0-19.3 months [13, 14]. The role of PBT for patients with unresectable PHC is poorly defined as PHC is rare, resulting in the small number of patients in reported analyses. Herein, we present the results of PBT for PHC to analyze the outcomes in a single-institution.

Methods

Study design and patients

This was an observational retrospective cohort study performed in a single institution. Patients with unresectable PHC who underwent PBT between January 2002 and August 2020 were eligible for the study. Patients were excluded if they had nodal metastasis at presentation or if they underwent surgery or other radiation therapies before PBT. Before the initiation of PBT, all patients were diagnosed based on biopsy or “radiologic studies and detection of elevated tumor markers (carbohydrate

antigen 19-9 [CA19-9] and/or carcinoembryonic antigen [CEA])". The location of tumor origin was determined based on radiologic and endoscopic studies. Staging was according to the TNM Classification of Malignant Tumors, 8th edition (Union for International Cancer Control) and Bismuth–Corlette classification. PHC was deemed unresectable by individual surgeons due to extensive hilar invasion, and/or bilateral liver involvement, and/or vascular encasement, and/or greater age, and/or severe pre-existing disease, such as chronic obstructive pulmonary disease. Acute adverse events (AAEs) and late adverse events (LAEs) were evaluated using the Common Terminology Criteria for Adverse Events (version 5.0). Written informed consent was obtained from all patients. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the local institutional review board, identification number 2-16. We collected data pertaining to age, sex, performance status (PS) on the Eastern Cooperative Oncology Group scale, Child–Pugh classification, stent treatment for biliary stenosis before PBT, surgical spacer placement before PBT, chemotherapy before PBT, underlying liver disease, involvement of the portal vein, concurrent chemotherapy, chemotherapy before PBT, CA19-9, and CEA as risk factors.

Surgical spacer placement for PBT

When the tumor was widely adjacent to the gastrointestinal tract, it was difficult to administer a curative-intent PBT. In such cases, a spacer was placed between the inferior surface of the liver and gastrointestinal tract. Greater omentum and/or Gore-Tex sheets (W.L. Gore and Associates, Newark, DE, USA) were superimposed and applied as spacers [15].

PBT

Each patient was immobilized using a custom-made thermoplastic cast in the supine or prone position, and images were acquired by computed tomography (CT) at slice thicknesses of 2 mm and magnetic resonance imaging (MRI) at a slice thicknesses of 2-5 mm. All three-dimensional treatment planning was performed using the XiO-M treatment planning system (Mitsubishi Electric, Tokyo, Japan). The gross tumor volume (GTV) included the primary tumor; the clinical target volume (CTV) was defined as the GTV plus a 10 mm basic margin, and adjacent structures were not included. The CTV margin, which was defined by the radiation oncologist according to the degree of microscopic extension of the tumor, was poorly defined in PHC. It was reported that microscopic extension of PHC was usually <10 mm [16, 17]. The CTV margin was defined as 10 mm in our study. The planning target volume (PTV) was defined as the CTV plus a setup margin (5 mm) and a respiratory gating margin (1-3 mm), which was measured on CT images between inspiratory and expiratory phases. The stomach; small bowel, including the duodenum; liver; kidneys; and spinal cord were defined as organs at risk (OAR). The target volumes and OAR were delineated on the CT-MRI fusion images.

Dose was expressed as Gy (relative biological effectiveness [RBE]). The RBE of the proton beam had been determined to be 1.1. The dose prescription for curative intent was selected as follows: 72.6 Gy (RBE) in 22 fractions, 70.2 Gy (RBE) in 26 fractions, and 67.5 Gy (RBE) in 25 fractions were selected to the tumor adjacent to the main trunk of the portal vein; 76 Gy (RBE) in 20 fractions and 66.0 Gy (RBE) in 10 fractions were selected to the tumors adjacent only to the first branch of the portal vein; and 60.0 Gy (RBE) in 30 fractions was selected to reduce the risk of gastrointestinal adverse events because total gastrectomy was performed before the initiation of PBT. The prescribed dose was decided based on the earlier experience of soft tissue sarcoma treatment in our institution, because there were few reliable reports on PHC.

To compare different dose fractionations, we used the linear quadratic model; we assumed α/β of 10 Gy (RBE) for the tumor response, which was expressed as biologically effective dose 10 (BED10), and a/b of 3 Gy (RBE) for the late effect, which was expressed as biologically effective dose 3 (BED3) [18]. The maximum dose restrictions for the stomach, small bowel, and spinal cord were 50 Gy (RBE), 50 Gy (RBE), and 45 Gy (RBE), respectively, at a standard fraction of 2 Gy (RBE) per fraction with a 3 Gy (RBE) α/β value [19, 20]. Additionally, irradiated volumes of the stomach, small bowel, liver, and kidney were made to be as low as possible. Typical dose distribution is shown in Figure 1.

Dosimetric analysis

Detailed dose volume histogram (DVH) data were retrospectively obtained using MIM Maestro version 6.9.6. (MIM Software Inc., Cleveland, OH, USA). The following dosimetric variables for BED10 of the GTV, CTV, and PTV were generated from the DVH, respectively: the maximal absolute dose (Dmax) and that covering 2 ml (D2 ml) of the GTV, CTV, or PTV; maximal absolute dose covering 50% (D50) of the GTV, CTV, or PTV; mean dose (Dmean); and minimum absolute dose (Dmin) and that covering 95% (D95) or 98% (D98) of the GTV, CTV, or PTV. To evaluate the dose of GTV, CTV, and PTV, we adopted the value of 79.2 Gy (RBE) [BED10] and 84.0 Gy (RBE) [BED10]) as indexes: the former was equal to the value of BED10 in 66 Gy (RBE) in 33 fractions, and the latter was equal to the value of BED10 in 70 Gy (RBE) in 35 fractions. These dose fractionations are commonly used for definitive radiotherapy in solid cancers.

Statistical analyses

The follow-up of each patient started on the date on which PBT was initiated. The Kaplan–Meier method was used to estimate overall survival (OS), MST, and progression-free survival (PFS) of the eligible subjects. We defined PFS as evidence of neither tumor regrowth nor other recurrence.

Univariable differences in Kaplan–Meier curves for OS were evaluated using the log-rank test. Cox regression was also used to assess the effects of the potential risk factors for OS in multivariate analysis, including those covariates that appeared to be significantly associated with OS ($p<0.05$) in univariate analysis. Statistical analyses were performed using R software version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study patients

Patients were followed until either death or until August 2021. A total of 36 patients with PHC received PBT. Among them, 26 patients were included in this study. The other 10 patients were excluded for the following reasons: seven had recurrent tumors after surgical resection; two had nodal metastases at presentation; and one had an operable disease.

The characteristics of the patients included in our study are shown in Table 1. All the patients had a single nodular tumor. The commonly prescribed dose was 67.5 Gy (RBE) in 25 fractions or 70.2 Gy (RBE) in 26 fractions. Concurrent chemotherapy was administered to seven patients: five received S-1, which was an oral fluoropyrimidine derivative; one received gemcitabine; and one received cisplatin. Spacers were placed in three patients: Gore-Tex sheets, which were non-absorbable spacers, were placed in two patients, and the greater omentum was placed in the other.

[Insert Table 1 here]

Survival and patterns of failure

The median follow-up period was 19.4 months (range, 4.2 to 137.4 months). Generally, patients were followed up at 3- to 6-month intervals.

The Kaplan–Meier estimate of the 1-, 2-, and 5-year OS rates and MST were 72.9% (95% confidence interval [CI], 57.5 to 92.2%), 47.7% (95% CI, 30.4 to 74.7%), 17.4% (95% CI, 5.4 to 55.8%), and 23.7 months (95% CI, 18.9 to NA months), respectively (Figure 2). Twenty patients died of the following: four of respiratory failure due to pleural dissemination; four died of other causes; three of treatment-related adverse events; one of simple obstruction due to peritoneal dissemination; and eight died with unknown cause. The Kaplan–Meier estimates of the 1- and 2-year PFS rates and median PFS were 78.4% (95% CI, 63.1 to 97.6%), 49.8% (95% CI, 29.5 to 83.9%), and 22.9 months (95% CI, 14.1 to NA months), respectively.

Local recurrence was diagnosed in five patients: four had local progression, and one had regional lymph node recurrence. Distant metastasis was diagnosed in ten patients: four had paraaortic lymph node recurrence; three had peritoneal

dissemination; one had pleural dissemination; one had both peritoneal dissemination and pleural dissemination; and one had intrahepatic metastasis.

Toxicity

AAEs and LAEs are shown in Table 2. There were no grade ≥3 AAEs. The numbers of grade 3, grade 4, and grade 5 LAEs were observed in three, one, and three patients, respectively. Regarding four patients with grade 3 or 4 LAE, they were diagnosed as cholangitis due to bile duct stenosis associated with PBT. Three patients presented with grade 5 LAE: one died of radiation-induced liver disease (RILD) 4 months after the completion of PBT; one died of duodenal bleeding due to spacer perforation 8 months after the completion of PBT; and one was free from treatment related complication >10 years after the completion of PBT and in the end died of obstructive cholangitis by radiation-induced bile duct stenosis 136 months after the completion of PBT.

The median latent period of grade ≥3 any LAEs was 13.2 months (interquartile range, 2.8 to 25.6), and that of grade ≥3 obstructive cholangitis was 24.0 months (interquartile range, 13.2 to 27.3). The number of grade ≥3 obstructive cholangitis was five. In grade 4 or 5 obstructive cholangitis cases, the value of BED3 was 172.2 Gy (RBE); in grade 3 obstructive cholangitis cases, the value was 128.2 or 133.3 Gy (RBE) (Additional file 1).

Risk factors for survival

Child–Pugh classification (A or B), mean dose of GTV (< or ≥79.2 Gy (RBE) [BED10]), mean CTV dose (< or ≥79.2 Gy (RBE) [BED10]), and CTV D50 (< or ≥84.0 Gy (RBE) [BED10]) were found to significantly affect OS in univariate analysis (Additonal file 2 and Table 3). The three dosimetric factors indicated the same patient cohort. We, therefore, included the mean GTV dose among the three factors in the multivariate analysis, because the dose distribution of the GTV might be theoretically critical in terms of local control. Finally, we included Child–Pugh classification (A or B) and the mean GTV dose (< or ≥79.2 Gy (RBE) [BED10]) in multivariate analysis; Child–Pugh classification B was a significant prognostic factor for unfavorable OS (hazard ratio [HR], 4.923; 95% CI, 1.478 to 16.401; p=0.009), and a mean GTV dose of ≥79.2 Gy (RBE) [BED10] was a significant prognostic factor for favorable OS (HR, 0.1925; 95% CI, 0.0450 to 0.8170; p=0.025) (Table 3).

[Insert Table 3 here]

Discussion

This study evaluated the efficacy and safety of definitive PBT for 26 patients with unresectable PHC. We found that the MST of these patients was 23.7 months; that the Child–Pugh classification B was a significant prognostic factor for unfavorable OS in the multivariate analysis; that a mean GTV dose ≥79.2 Gy (RBE) [BED10] was a significant prognostic factor for favorable OS in the multivariate analysis; and that grade ≥3 LAEs were observed in seven patients. Although the outcomes of patients with biliary tract or gallbladder cancer who received PBT have been previously reported, these studies included patients with different types of cancers other than PHC [13, 14, 21]. To the best of our knowledge, this is the first study to investigate the efficacy and safety of PBT in a cohort that only included patients with unresectable PHC.

Not all the patients with PHC are eligible for surgical resection, for reasons such as extensive tumor infiltration, greater age, severe pre-existing diseases, and poor PS. Although LT following neoadjuvant chemoradiotherapy is regarded as an alternative treatment for these unresectable PHCs, the number of patients with unresectable PHC eligible for LT is limited because it is too invasive and not as effective. The MST of chemotherapy for patients with unresectable PHC containing locally advanced or metastatic cancer was 4.6 to 11.7 months [5-7]; the MST of 23.7 months in our study was longer than their outcomes. PBT might be an alternative option for patients with PHC ineligible for surgical resection or LT.

We present the comparison of outcomes for PHC treated with radiotherapy in Table 4. The MST of photon therapy, including stereotactic body radiotherapy, for patients with unresectable PHC ranged from 6.7 to 23.6 months in most reports [8, 10, 11, 22-26]; the MST of 23.7 months in our study appeared to be superior to that reported in previous studies. Favorable dose

distributions in PBT might contribute to improved survival outcomes. Although intraluminal brachytherapy (ILBT) had been conventionally performed for PHC to achieve dose escalation in addition to photon radiotherapy, Yoshioka et al. revealed that the addition of ILBT to external beam photon therapy for unresectable biliary tract cancer had no impact on OS in a multi-institution study [27]. Additionally, because we thought that it was possible to administer a sufficient curative dose with PBT alone, we did not combine ILBT in this study. The MST of carbon-ion radiotherapy (CIRT) for patients with resectable or unresectable PHC was reported to be 12.6 months [28]. The result was much lower than ours. Dose distribution of CIRT is as favorable as that of PBT. The value of BED10, which affected local control, of the report of CIRT was higher than ours. We cannot surmise the reason for the difference between the results. Large-scale prospective studies are required to compare PBT with CIRT for patients with unresectable PHC.

LAEs of the biliary tract and gastrointestinal tract adjacent to the PHC are important in radiotherapy, because it can be fatal at times. However, assessing biliary stenosis as LAE is clinically very difficult, because it is difficult to distinguish between LAE and tumor recurrence. We experienced five patients (19.2%) who presented with grade ≥3 obstructive cholangitis, which appeared to be caused by biliary stenosis. Kopek et al. [11] reported that the incidence of grade ≥3 hyperbilirubinemia was 29.6%. Hyperbilirubinemia could be caused by severe obstructive cholangitis or tumor recurrence. In contrast, grade ≥3 LAEs related to obstructive cholangitis was not reported in other reports of CIRT or photon therapy [8, 10, 22-26, 28]. In our study, the median latent period of grade ≥3 obstructive cholangitis was 24.0 months, which was longer than the MST of these reports [8, 10, 11, 22-26, 28]. This may be why the risk of grade ≥3 obstructive cholangitis was underestimated. Compared with that reported by Kopek et al., the incidence of grade ≥3 obstructive cholangitis in our study might be not high. High-dose irradiation to the biliary tract is theoretically thought to cause biliary stenosis, although to the best of our knowledge, there are no reports that reveal an association between irradiation dose and biliary stenosis. We should at least make the value of BED3 172.2 Gy (RBE) or less because the value of BED3 was 172.2 Gy (RBE) in patients presenting with grade 4 or 5 obstructive cholangitis.

The incidence of grade ≥3 gastrointestinal bleeding in radiotherapy for PHC was reported to be 0 to 22.2% [10, 11, 25, 26, 28, 29]. Contrastingly, the incidence in our study was 0%. To reduced LAEs of gastrointestinal tract, spacers were placed in three patients: Gore-Tex sheets were placed in two patients, and the greater omentum was placed in one. However, one patient died from duodenal bleeding owing to Gore-Tex sheets perforation. If Gore-Tex sheets, which are non-absorbable artificial spacers, remain for a long time and become rigid in the patient's body, they might cause severe LAEs. To reduce severe LAEs related to the non-absorbable spacer, we currently adopt a new absorbable spacer, which was used in PBT or CIRT for abdominal or pelvic tumors adjacent to the intestines and caused no severe adverse events [30]. In the future, we hope to report the efficacy and safety of the absorbable spacers in patients with unresectable PHC.

One patient died of RILD regardless of Child-Pugh classification A. Regarding the liver function of the patient before PBT, ICGR15 (percentage of retained ICG at 15 min) was 43%. ICG is routinely used in Asia and parts of Europe to evaluate liver function before and after transplantation, as well as after hepatic resection [31]. Kawashima et al. [32] reported that patients with an ICGR15 of <20% were free from RILD in patients with hepatocellular carcinoma who underwent PBT; that three of four patients with an ICGR15 of ≥50% experienced fatal RILD; and that the multivariate analysis demonstrated that an ICGR15 of >40% was a significant prognostic factor for unfavorable OS. In the subcohort of 16 patients with ICGR15 data available in our study, the median ICGR15 was 16.5% (interquartile range, 8.2 to 29.0). The patient who developed grade 5 RILD presented with ICGR15 43%, which was much higher than the median value. ICGR15 could be useful to evaluate liver function before PBT. In future studies, we hope to report the association between ICGR15 and RILD in patients with unresectable PHC.

OS was significantly better in patients with Child–Pugh class A than in those with Child-Pugh class B in the multivariate analysis. This was comparable with the finding of a study on CIRT for cholangiocarcinoma [28].

The multivariate analysis revealed that a mean GTV dose of ≥79.2 Gy (RBE) [BED10] was significant for favorable OS. High dose radiotherapy was reported to improve local control and OS in patients with intrahepatic cholangiocarcinoma [33]. Elganainy et al. [10] suggested that high dose photon therapy did not improved OS in patients with extrahepatic

cholangiocarcinoma, and inferred that unfavorable dose distribution to the GTV was unable to improve OS because the GTV was almost always close to the bowel. Our results indicated that favorable distributions to the GTV due to the physical property of PBT result in favorable prognosis.

Concurrent chemotherapy did not improve survival in our study. Chemoradiotherapy was reported to be associated with better survival than radiotherapy alone [34]. Further large-scale prospective studies are necessary to determine the effectiveness of concurrent chemotherapy with PBT. Underlying liver disease (Yes or No) was not included in our univariate analysis because only one patient had an underlying liver disease.

Our study had two limitations. First, we adopted a retrospective design owing to the rarity of PHC. Second, we used several treatment protocols: several dose fractionations were included, and several concurrent chemotherapy regimens were included.

Conclusions

This study indicated that definitive PBT for patients with unresectable PHC was tolerable and may improve the prognosis. Further large-scale prospective studies are required to validate our findings.

List Of Abbreviations

PHC - Perihilar cholangiocarcinoma

LT – Liver transplantation

MST - Median survival time

PBT – Proton beam therapy

CA19-9 - Carbohydrate antigen 19-9

CEA - Carcinoembryonic antigen

AAE – Acite adverse events

LAE – Late adverse events

PS – Performance status

CT - Computed tomography

MRI – Magnetic resonance imaging

GTV - Gross tumor volume

CTV - Clinical target volume

PTV - Planning target volume

RBE - Relative biological effectiveness

DVH - Dose volume histogram

OS – Overall survival

PFS – Progression free survival

CI - Confidence interval

RILD - Radiation-induced liver disease

HR - Hazard ratio

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from all patients. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the local institutional review board, identification number 2-16.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

Not applicable.

Funding

Not applicable.

Authors' contributions

SungChul Park designed the study. SungChul Park, Kazuki Terashima, Masaki Suga, Daiki Takahashi, Yoshiro Matsuo, Nor Shazrina Sulaiman, Yusuke Demizu, Sunao Tokumaru, Kyoji Furukawa, and Tomoaki Okimoto collected and reviewed the data, and reviewed the manuscript. SungChul Park, Kazuki Terashima, and Kyoji Furukawa collected, reviewed, and analyzed the data, and wrote the manuscript. All the authors have read and approved the final version of the manuscript.

Acknowledgments

We would like to thank Editage (www.editage.com) for English language editing.

References

1. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Akinyemiju TF, Al Lami FH, Alam T, Alizadeh-Navaei R, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2016: a systematic analysis for the global burden of disease study. JAMA Oncol. 2018;4:1553–68. https://doi.org/10.1001/jamaoncol.2018.2706
2. Aljiffry M, Walsh MJ, Molinari M. Advances in diagnosis, treatment and palliation of cholangiocarcinoma: 1990–2009. World J Gastroenterol. 2009;15:4240–62. https://doi.org/10.3748/wjg.15.4240
3. Rizvi S, Khan SA, Hallemeier CL, Kelley RK, Gores GJ. Cholangiocarcinoma—evolving concepts and therapeutic strategies. Nat Rev Clin Oncol. 2018;15:95–111. https://doi.org/10.1038/nrclinonc.2017.157
4. Jarnagin WR, Fong Y, DeMatteo RP, Gonen M, Burke EC, Bodniewicz BS J, et al. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. Ann Surg. 2001;234:507–17; discussion 517–9. https://doi.org/10.1097/00000658-200110000-00010

5. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010;362:1273–81. https://doi.org/10.1056/NEJMoa0908721
6. Nehls O, Oettle H, Hartmann JT, Hofheinz RD, Hass HG, Horger MS, et al. Capecitabine plus oxaliplatin as first-line treatment in patients with advanced biliary system adenocarcinoma: a prospective multicentre phase II trial. Br J Cancer. 2008;98:309–15. https://doi.org/10.1038/sj.bjc.6604178
7. Park I, Lee JL, Ryu MH, Kim TW, Chang HM, Lee SS, et al. Efficacy and safety of s-1 monotherapy in patients with advanced biliary tract adenocarcinoma: retrospective analysis of 162 patients. Oncology. 2009;76:126–32. https://doi.org/10.1159/000195538
8. Chen SC, Chen MH, Li CP, Chen MH, Chang PM, Liu CY, et al. External beam radiation therapy with or without concurrent chemotherapy for patients with unresectable locally advanced hilar cholangiocarcinoma. Hepato-Gastroenterology. 2015;62:102–7
9. Ghafoori AP, Nelson JW, Willett CG, Chino J, Tyler DS, Hurwitz HI, et al. Radiotherapy in the treatment of patients with unresectable extrahepatic cholangiocarcinoma. Int J Radiat Oncol Biol Phys. 2011;81:654–9. https://doi.org/10.1016/j.ijrobp.2010.06.018
10. Elganainy D, Holliday EB, Taniguchi CM, Smith GL, Shroff R, Javle M, et al. Dose escalation of radiotherapy in unresectable extrahepatic cholangiocarcinoma. Cancer Med. 2018;7:4880–92. https://doi.org/10.1002/cam4.1734
11. Kopek N, Holt MI, Hansen AT, Høyer M. Stereotactic body radiotherapy for unresectable cholangiocarcinoma. Radiother Oncol. 2010;94:47–52. https://doi.org/10.1016/j.radonc.2009.11.004
12. Schulz-Ertner D, Tsujii H. Particle radiation therapy using proton and heavier ion beams. J Clin Oncol. 2007;25:953–64. https://doi.org/10.1200/JCO.2006.09.7816
13. Shimizu S, Okumura T, Oshiro Y, Fukumitsu N, Fukuda K, Ishige K, et al. Clinical outcomes of previously untreated patients with unresectable intrahepatic cholangiocarcinoma following proton beam therapy. Radiat Oncol. 2019;14:241. https://doi.org/10.1186/s13014-019-1451-5
14. Hung SP, Huang BS, Hsieh CE, Lee CH, Tsang NM, Chang JT, et al. Clinical outcomes of patients with unresectable cholangiocarcinoma treated with proton beam therapy. Am J Clin Oncol. 2020;43:180–6. https://doi.org/10.1097/COC.0000000000000646
15. Komatsu S, Terashima K, Matsuo Y, Takahashi D, Suga M, Nishimura N, et al. Validation of combination treatment with surgical spacer placement and subsequent particle radiotherapy for unresectable hepatocellular carcinoma. J Surg Oncol. 2019;120:214–22. https://doi.org/10.1002/jso.25495
16. Ebata T, Watanabe H, Ajioka Y, Oda K, Nimura Y. Pathological appraisal of lines of resection for bile duct carcinoma. Br J Surg. 2002;89:1260–7. https://doi.org/10.1046/j.1365-2168.2002.02211.x
17. Sakamoto E, Nimura Y, Hayakawa N, Kamiya J, Kondo S, Nagino M, et al. The pattern of infiltration at the proximal border of hilar bile duct carcinoma: a histologic analysis of 62 resected cases. Ann Surg. 1998;227:405–11. https://doi.org/10.1097/00000658-199803000-00013
18. Fowler JF. The first james kirk memorial lecture. What next in fractionated radiotherapy? Br J Cancer Suppl. 1984;6:285–300
19. Kavanagh BD, Pan CC, Dawson LA, Das SK, Li XA, Ten Haken RK, et al. Radiation dose-volume effects in the stomach and small bowel. Int J Radiat Oncol Biol Phys. 2010;76;Suppl:S101–7. https://doi.org/10.1016/j.ijrobp.2009.05.071
20. Kirkpatrick JP, van der Kogel AJ, Schultheiss TE. Radiation dose-volume effects in the spinal cord. Int J Radiat Oncol Biol Phys. 2010;76;Suppl:S42–9. https://doi.org/10.1016/j.ijrobp.2009.04.095
21. Makita C, Nakamura T, Takada A, Takayama K, Suzuki M, Ishikawa Y, et al. Clinical outcomes and toxicity of proton beam therapy for advanced cholangiocarcinoma. Radiat Oncol. 2014;9:26. https://doi.org/10.1186/1748-717X-9-26
22. Tan Y, Zhu JY, Qiu BA, Xia NX, Wang JH. Percutaneous biliary stenting combined with radiotherapy as a treatment for unresectable hilar cholangiocarcinoma. Oncol Lett. 2015;10:2537–42. https://doi.org/10.3892/ol.2015.3589

23. Pollom EL, Alagappan M, Park LS, Whittemore AS, Koong AC, Chang DT. Does radiotherapy still have a role in unresected biliary tract cancer? Cancer Med. 2017;6:129–41. https://doi.org/10.1002/cam4.975
24. Takamura A, Saito H, Kamada T, Hiramatsu K, Takeuchi S, Hasegawa M, et al. Intraluminal low-dose-rate 192Ir brachytherapy combined with external beam radiotherapy and biliary stenting for unresectable extrahepatic bile duct carcinoma. Int J Radiat Oncol Biol Phys. 2003;57:1357–65. https://doi.org/10.1016/s0360-3016(03)00770-3
25. Isayama H, Tsujino T, Nakai Y, Sasaki T, Nakagawa K, Yamashita H, et al. Clinical benefit of radiation therapy and metallic stenting for unresectable hilar cholangiocarcinoma. World J Gastroenterol. 2012;18:2364–70. https://doi.org/10.3748/wjg.v18.i19.2364
26. Momm F, Schubert E, Henne K, Hodapp N, Frommhold H, Harder J, et al. Stereotactic fractionated radiotherapy for klatskin tumours. Radiother Oncol. 2010;95:99–102. https://doi.org/10.1016/j.radonc.2010.03.013
27. Yoshioka Y, Ogawa K, Oikawa H, Onishi H, Kanesaka N, Tamamoto T, et al. Impact of intraluminal brachytherapy on survival outcome for radiation therapy for unresectable biliary tract cancer: a propensity-score matched-pair analysis. Int J Radiat Oncol Biol Phys. 2014;89:822–9. https://doi.org/10.1016/j.ijrobp.2014.04.020
28. Kasuya G, Terashima K, Shibuya K, Toyama S, Ebner DK, Tsuji H, et al. Carbon-ion radiotherapy for cholangiocarcinoma: a multi-institutional study by and the Japan carbon-ion radiation oncology study group (j-cros). Oncotarget. 2019;10:4369–79. https://doi.org/10.18632/oncotarget.27028
29. Polistina FA, Guglielmi R, Baiocchi C, Francescon P, Scalchi P, Febbraro A, et al. Chemoradiation treatment with gemcitabine plus stereotactic body radiotherapy for unresectable, non-metastatic, locally advanced hilar cholangiocarcinoma. Results of a five year experience. Radiother Oncol. 2011;99:120–3. https://doi.org/10.1016/j.radonc.2011.05.016
30. Sasaki R, Demizu Y, Yamashita T, Komatsu S, Akasaka H, Miyawaki D, et al. First-in-human phase 1 study of a nonwoven fabric bioabsorbable spacer for particle therapy: space-making particle therapy (smpt). Adv Radiat Oncol. 2019;4:729–37. https://doi.org/10.1016/j.adro.2019.05.002
31. Hemming AW, Scudamore CH, Shackleton CR, Pudek M, Erb SR. Indocyanine green clearance as a predictor of successful hepatic resection in cirrhotic patients. Am J Surg. 1992;163:515–8. https://doi.org/10.1016/0002-9610(92)90400-l
32. Kawashima M, Furuse J, Nishio T, Konishi M, Ishii H, Kinoshita T, et al. Phase II study of radiotherapy employing proton beam for hepatocellular carcinoma. J Clin Oncol. 2005;23:1839–46. https://doi.org/10.1200/JCO.2005.00.620
33. Tao R, Krishnan S, Bhosale PR, Javle MM, Aloia TA, Shroff RT, et al. Ablative radiotherapy doses lead to a substantial prolongation of survival in patients with inoperable intrahepatic cholangiocarcinoma: a retrospective dose response analysis. J Clin Oncol. 2016;34:219–26. https://doi.org/10.1200/JCO.2015.61.3778
34. Koo T, Park HJ, Kim K. Radiation therapy for extrahepatic bile duct cancer: current evidences and future perspectives. World J Clin Cases. 2019;7:1242–52. https://doi.org/10.12998/wjcc.v7.i11.1242

Tables

Table 1. Patient and tumor characteristics (n=26)

Characteristic	No.	(%)
Age, years		
Median (range)	72.5	(40-84)
Sex		
Male	15	(57.7)
Female	11	(42.3)
ECOG Performance status		
0	16	(61.5)
1	10	(38.5)
Child-Pugh classification		
A	17	(65.4)
B	9	(34.6)
Stent treatment for biliary stenosis before PBT		
Yes	23	(88.5)
No	3	(11.5)
Surgical spacer placement before PBT		
Yes	3	(11.5)
No	23	(88.5)
Chemotherapy before PBT		
Yes	5	(19.2)
No	21	(80.8)
Underlying liver disease		
Yes*	1	(3.8)
No	25	(96.2)
Diagnosis		
Pathological	15	(57.7)
Imaging+tumor markers	11	(42.3)
TNM classification†		
T1N0M0	2	(7.7)
T2aN0M0	7	(26.9)
T3N0M0	4	(15.4)
T4N0M0	13	(50.0)
Bismuth-Corlette classification		
II	5	(19.2)
IIIa	8	(30.8)

IIIb	4	(15.4)
IV	9	(34.6)
Involvement of portal vein		
Yes	14	(53.8)
No	12	(46.2)
Concurrent chemotherapy		
Yes	7	(26.9)
No	19	(73.1)
CEA, mg/ml		
Median (range)	2.3	(0.9-68.0)
CA19-9, U/ml		
Median (range)	67.6	(0.1- over 10000)
Dose/fractionation [BED10]		
60.0 Gy (RBE)/30 fr. [72.0]	1	(3.8)
66.0 Gy (RBE)/10 fr. [109.6]	1	(3.8)
67.5 Gy (RBE)/25 fr. [85.7]	9	(34.6)
70.2 Gy (RBE)/26 fr. [89.2]	9	(34.6)
72.6 Gy (RBE)/22 fr. [96.6]	1	(3.8)
76.0 Gy (RBE)/20 fr. [104.9]	5	(19.2)

ECOG, Eastern Cooperative Oncology Group; PBT, proton beam therapy; TNM: tumor, nodes, metastases; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; BED10, biological effective dose when α/β=10 is applied; Gy, gray; RBE, relative biological effectiveness.

*Autoimmune hepatitis

†Staging was according to the TNM Classification of Malignant Tumors, 8th edition (Union for International Cancer Control).

Table 2. Acute and late adverse events for all patients (n=26)

Acute adverse events	Grade 2	(%)	Grade 3	(%)	Grade 4	(%)	Grade 5	(%)
Dermatitis	3	(11.5)	0	(0.0)	0	(0.0)	0	(0.0)
Late adverse events	Grade 2	(%)	Grade 3	(%)	Grade 4	(%)	Grade 5	(%)
Gastrointestinal bleeding	2	(7.7)	0	(0.0)	0	(0.0)	0	(0.0)
Gastrointestinal perforation	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.8)
Obstructive cholangitis	0	(0.0)	3	(11.5)	1	(3.8)	1	(3.8)
Radiation-induced liver disease	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.8)

Table 3. Prognostic factors for overall survival

		No. Of patients	Univariate analyses		Multivariate analyses				
			MST (months)	p	HR	95% CI			p
Age, years	<70	9	30.8	1.000					
	≥70	17	23.7						
Sex	Male	15	22.9	0.200					
	Female	11	50.2						
ECOG Performance status	0	16	30.8	0.900					
	1	10	30.8						
Child-Pugh classification	A	17	30.8	0.004*	Reference				
	B	9	12.1		4.923	1.478	-	16.401	0.009†
Stent treatment for biliary stenosis before PBT	Yes	23	23.7	0.300					
	No	3	NA						
Surgical spacer placement before PBT	Yes	3	22.9	0.200					
	No	23	30.8						
Chemotherapy before PBT	Yes	5	26.9	0.800					
	No	21	23.7						
CEA, mg/ml	<2.3	13	28.7	0.500					
	≥2.3	13	19.9						
CA19-9, U/ml	<67.6	13	23.7	0.500					
	≥67.6	13	22.9						
Distance between tumor and gastrointestinal tract, mm	<1	9	18.9	0.070					
	≥1	17	30.8						
T factor	T1-2	9	23.7	0.700					
	T3-4	17	22.9						
Bismuth-Corlette classification	II	5	NA	0.400					
	III-IV	21	23.7						
Involvement of portal vein	Yes	14	28.7	0.900					
	No	12	22.9						
Concurrent chemotherapy	Yes	7	30.8	0.600					
	No	19	23.7						
Mean dose of GTV, Gy (RBE) [BED10]	<79.2	3	10.6	0.010*	Reference				

≥79.2	23	28.7		0.1925	0.0450	-	0.8170	0.025†

ECOG, Eastern Cooperative Oncology Group; PBT, proton beam therapy; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; GTV, gross tumor volume; Gy, gray; RBE, relative biological effectiveness; BED10, biological effective dose when α/β=10 is applied; MST, median survival time.

*p-value <0.05 by univariate analyses were defined to be significant

†p-value <0.05 by multivariate analysis was defined to be significant

Table 4. Comparison of outcomes for perihilar cholangiocarcinoma treated with various types of radiotherapy

Treatment	Author	Year	No.	Median total EBRT dose [Gy or Gy (RBE)]	Median EBRT fraction	Median BED10	Overall survival (%) 1 year	2 years	5 years	MST (months)
Photon therapy										
EBRT ± ILBT										
	Ghafoori et al. [9]*	2011	37‡	45	NA	NA	59††	22††	NA	14††
	Isayama et al. [25]*	2012	28	54	30	64 (EBRT alone) 123 (EBRT+BT)	74††	45††	6††	22.2††
EBRT										
	Chen et al. [8]	2015	16	54	NA	65¶	41††	NA	NA	13.5†† (CCRT) 6.7†† (RT alone)
	Tan et al. [22]	2015	25	37-40.7‖	10-11‖	56**	NA	NA	NA	12‡‡
SBRT										
	Kopek et al. [11]	2010	27§	45	3	112	NA	NA	NA	10.6††
	Momm et al. [26]	2010	13	48	4	106	NA	NA	NA	23.6§§
	Polistina et al. [29]	2011	10	30	3	60	NA	80§§	NA	35.5§§
Carbon ion radiotherapy										
	Kasuya et al. [28]	2019	29	76	20	105	63.5††	27.3††	NA	12.6††
Photon therapy or proton beam therapy										
	Elganainy et al. [10]†	2018	62	50.4	NA	60	NA	NA	NA	16.7††
Proton beam therapy										
	Present study		26	70.2	26	89	69.6††	47.6††	14.3††	22.9††

*Some patients in this study received ILBT.

†The number of patients who received PBT and photon therapy were not available.

‡Six patients only received BT.

§One case of intrahepatic cholangiocarcinoma was included in this study.

‖Median dose and median fraction were not available.

¶Calculated according to 2 Gy/fr.

**Calculated according to 40.7 Gy/11 fr.

††Survival time was measured from the start of radiotherapy.

‡‡Survival time was measured from the time of biliary stent placement.

§§Survival time was measured from the time of diagnosis.

MST, median survival time; EBRT, external beam radiotherapy; BED, biological effective dose; Gy, gray; RBE, relative biological effectiveness; ILBT, intraluminal brachytherapy; NA, not available; RT, radiotherapy; CCRT, concurrent chemoradiotherapy SBRT, stereotactic body radiotherapy; fr, fraction; PBT, proton beam therapy

Figures

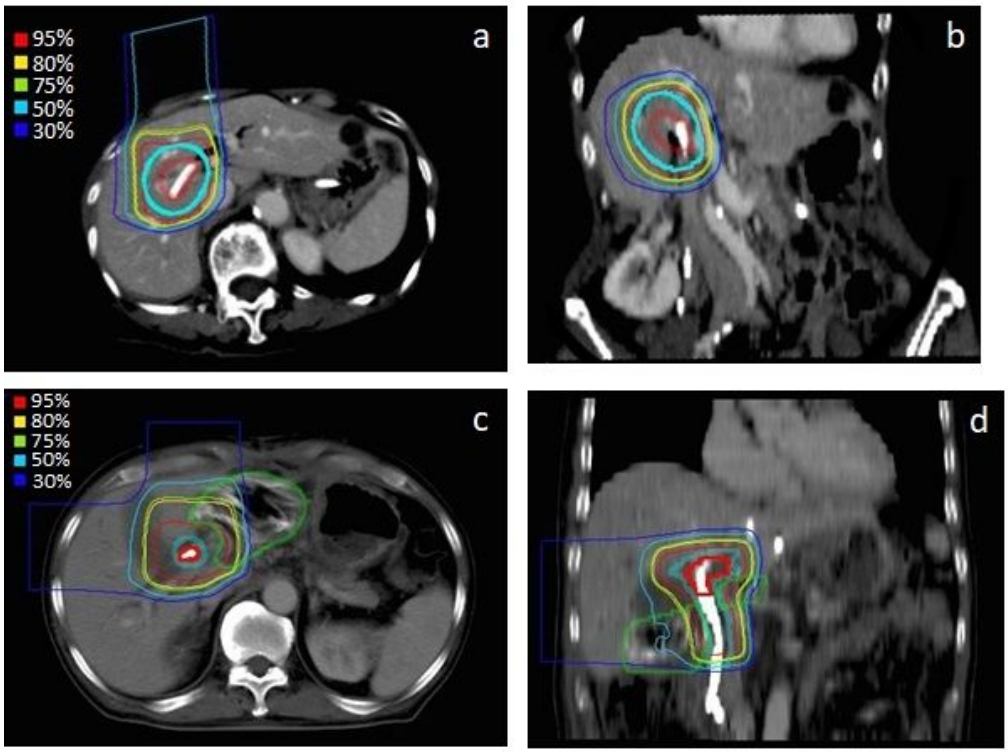

Figure 1

a, b. Images from proton beam therapy plan of a patient. c, d. Images from proton beam therapy plan of a patient who received a non-absorbable spacer.

The prescribed dose was 76 Gy (relative biological effectiveness [RBE]) in 20 fractions. Structures: thick red contour, gross tumor volume; thick cyan contour, clinical target volume; thick green contour, non-absorbable spacer. Colored isodose lines: red, 95%; yellow, 80%; light green, 75%; light blue, 50%; blue, 30%.

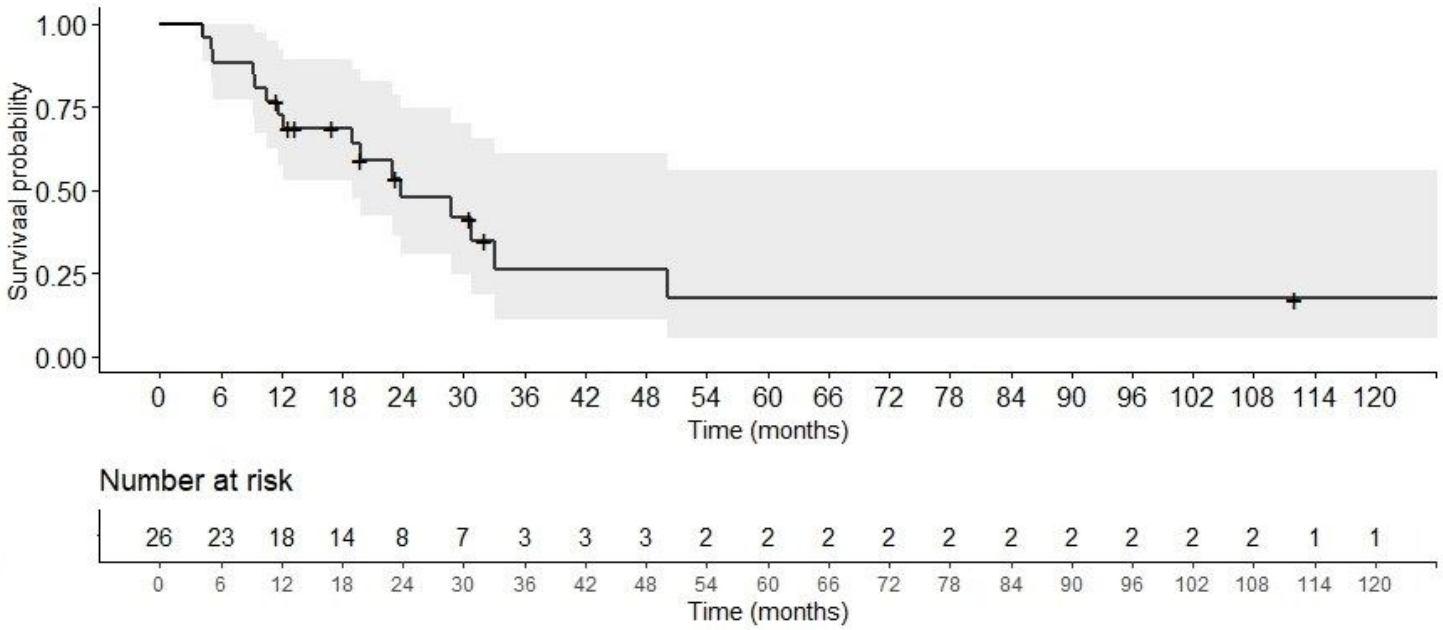

Figure 2

Overall survival curve for all patients (n=26) with perihilar cholangiocarcinoma treated with proton beam therapy.

The corresponding 95% confidence intervals are presented in gray. The median survival time was 22.9 months.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile1.doc
- Additionalfile2.doc