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Proton beam therapy for extrahepatic biliary tract cancer: Analysis with prospective multi-institutional patients' registration database, Proton-Net

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ABSTRACT

Background and purpose: To examine the role of proton beam therapy (PBT) in the treatment of extrahepatic biliary tract cancer (EBC).
Methods and materials: We analyzed the data accumulated in the Proton-Net database, which prospectively registered all individual patient data treated with PBT in all Japanese proton institutions from May 2016 to June 2019. The primary endpoint was overall survival (OS), and the secondary endpoints were local control (LC), progression-free survival (PFS), and toxicity.
Results: Ninety-three patients with unresectable and/or recurrent EBC were treated with PBT using a median prescribed dose of 67.5 Gy (RBE) (range, 50–72.6 Gy) in 25 (22–30 fractions). With a median follow-up of 16.3 months, the median survival time was 20.1 months and the 2-year OS was 37.8%. Two-year PFS and LC rates were 20.6% and 66.5%, respectively. Poor liver function (Child-Pugh B, C), a narrower distance between the tumor and digestive tract (2 cm >), and a larger tumor diameter (2 cm <) were identified as poor prognostic factors for OS. PBT-related grade 3 ≤ acute and late adverse events occurred in 5.4% and 4.3% of patients, respectively, including one gastrointestinal late toxicity (duodenal ulcer).
Conclusions: This is the largest prospectively accumulated series of PBT for EBC, and PBT showed favorable outcomes with acceptable toxicity profiles.

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1. Introduction

Biliary tract cancers comprise a heterogeneous cohort of tumors, including intrahepatic, perihilar, extrahepatic, and gallbladder cancers [1]. The global burden of biliary tract cancer is increasing [1]. The prognosis of these diseases is generally very poor. Although the incidence and epidemiology of each disease subsite are variable and complex, due to the relative rarity of biliary tract malignancies, these have been gathered on analysis. However, increasing evidence represents distinctly different characteristics, including different molecular profiles [2]. Therefore, we conducted a detailed analysis of biliary tract cancer focusing on extrahepatic biliary tract cancer (EBC). The surgical intervention is only curative treatment, however, even after complete resection, the 5-year survival rate remains relatively low [3]. The median survival of patients with remaining unresectable biliary tract cancer is approximately within a year [4]. In the advancement of radiotherapy, stereotactic radiotherapy (SBRT) and intensity-modulated radiotherapy (IMRT) were introduced in the clinical situation [5]. SBRT could deliver a higher dose than conventional radiotherapy and provided an improvement in local control and succeeding prolongation of survival in some literature 6–8]. However, increased radiation dose elevated radiotherapy-related severe adverse events, simultaneously, particularly duodenal or gastric ulcers, and are reported to occur 0%-20% of the time [6–9]. IMRT could reduce normal tissue irradiation which may result in the reduction of normal tissue toxicity [5]. Proton beam therapy (PBT), a particle beam therapy, has a superior dose distribution owing to the physical characteristics of the Bragg peak in comparison with photon irradiation, allowing increased dose delivery to the tumor without increasing the dose to healthy tissue except in case of tumor is abutting dose limited organ [10–13]. In Japan, since 2016, all proton beam facilities have tried to build a registration system called Proton-Net to accumulate patient data prospectively. This study aimed to evaluate the outcome of PBT for EBC using the prospective multi-institutional data accumulation database Proton-Net.

2. Materials and methods

From May 2016 to June 2019, Japanese proton beam facilities registered patient data prospectively in a database system called Proton-Net. The inclusion criteria were unresectable or recurrent extrahepatic cholangiocarcinoma that was not suitable for curative surgical treatment (patients who refused surgery were deemed unresectable, and included poor general status or medical comorbidities). Of the 104 patients with Proton-Net registration, 11 patients were excluded for the following reasons: previous surgery or planned surgery (n = 6) (Fig. 1), and 18 recurrence cases were included in this study (nine distal, eight hilar, and one residual disease in hilar lesion after surgery). Ninety-three patients were included in this analysis (Table 1). Of these, unresectable perihilar cholangiocarcinoma was selected for subgroup analysis to compare with other historical data, which is a major target of PBT (n = 55, excluded recurrence case) [10–13].

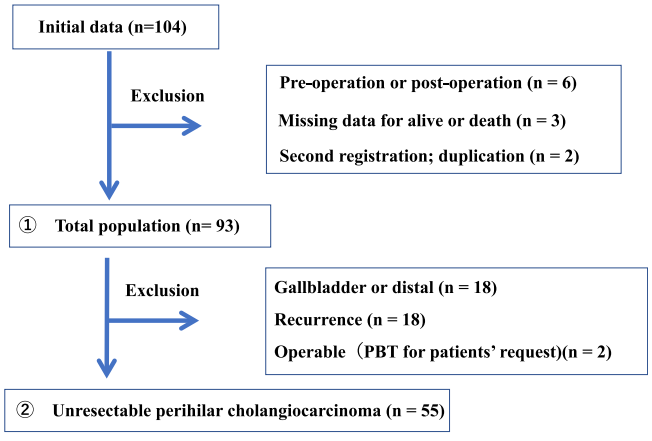

Fig. 1. Scheme of eligibility selection using inclusion or exclusion criteria.

All patients were staged according to the 7th edition of the Tumor-Node-Metastasis Staging System (International Union Against Cancer, 2009). We analyzed the overall survival (OS) as the primary endpoint, and progression-free survival (PFS), local control rate (LC), and toxicity, including consequent secondary cancer, were analyzed as 2nd endpoints. This multicenter prospective data accumulation study was approved by the institutional review board of each participating institution before the data collection started in the registry. The study protocol was performed by the principles of the Declaration of Helsinki. This study was performed by the Biliary tract cancer (excluding intrahepatic cholangiocarcinoma) Cancer Working Group in the Particle Beam Therapy Committee and Subcommittee at the Japanese Society for Radiation Oncology (JASTRO).

Toxicity was evaluated according to the common terminology criteria for adverse events version 4.0.

Adverse events were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. This study was performed by the bile duct carcinoma (excluding intrahepatic cholangiocarcinoma) Cancer Working Group in the Particle Beam Therapy Committee and Subcommittee at JASTRO.

3. Treatment

Details of treatment in each institution was described elsewhere [10–13]. In brief, patients had undergone simulation using CT scanner, and diagnostic CT and/ or MRI images had been fused with planning CT images for target delineation (majorly including 4D-CT images). For PBT planning, a 3-dimensional treatment planning system had been used. Gross tumor volume had been identified from the review of these images (several institutions used additional ERCP/MRCP images) and some institutions utilized the opinions of the liver surgeon, gastroenterologist, and diagnostic radiologists. The clinical target volume had decided according to the institution's criteria (supplemental Table 1), i.e., a 5- to 10-mm radial expansion of the gross tumor volume to target possible microscopic disease extension. Regional lymph nodes had not been intentionally covered unless pathologically enlarged. The planning target volume had been expanded by institutional policies (supplemental Table 1). Several institutions compared the proton plan to photon plan using dose–volume histogram, and chose a proton if it has a superior dose distribution. 91 Patients were treated with passive scatter broad beam and two patients were treated with beam scanning. Daily image guidance/ motion management was performed in several institutions using a gold marker, and pretreatment imaging (MVCT, Orthogonal kVX ray, etc.). Several institutions used respiratory gating system (Anzai Medical, Tokyo, Japan) and treated patients in the exhalation phase (Supplemental Table 1).

The median prescribed dose was 67.5 Gy (RBE) (range, 50–72.6 Gy) in 25 (22–30 fractions) fractions. We used three major treatment schedules majorly according to tumor location and distance between tumor and gastrointestinal tract (Supplemental Table 2; (1) Gastrointestinal proximity type used 50–60 Gy (RBE)/ 25–30 fraction; n = 35, (2) Simultaneous integrated boost (SIB) type used 67.5 Gy (RBE)/ 25 fractions; n = 20, (3) Perihilar type used 70.2–72.6 Gy (RBE)/22–26 fraction; n = 38). The detailed background was depicted in Supplemental Table 2. Schedules used for concurrent therapy with systemic treatment (GEM or TS-1) were 50 Gy (RBE)/25fr in 4 patients, 60 Gy (RBE)/30fr in 7 patients, 67.5/ Gy (RBE)/25fr in 9 patients,70.2 Gy (RBE)/26fr in 13 patients, 1 72.6 Gy (RBE)/22 fr in 1 patient.

Equivalent 2-Gy fractions (EQD2 = n × d([α/β] + d) /([α/β] + 2): n = number of treatment fractions: d = dose per fraction in Gy, α/β = 10) were used for radiation dose estimation.

Based on physician preference, 44 patients received concurrent

Table 1
Patients characteristics in total population and each location of tumor.

Variables	Strata	Total (n = 93)	Perihilar (n = 65)	Distal (n = 20)	Gall bladder (n = 8)	*p*-Value
		No. (%) or Median [range]				
Age		73.00 [44.00, 92.00]	71.00 [44.00, 90.00]	77.50 [51.00, 89.00]	69.50 [57.00, 92.00]	0.599
Gender	Female	32 (34.4)	21 (32.3)	7 (35.0)	4 (50.0)	0.609
	Male	61 (65.6)	44 (67.7)	13 (65.0)	4 (50.0)	
ECOG.PS	0	73 (78.5)	49 (75.4)	17 (85.0)	7 (87.5)	0.092
	1	17 (18.3)	15 (23.1)	1 (5.0)	1 (12.5)	
	2	2 (2.2)	0 (0.0)	2 (10.0)	0 (0.0)	
	3	1 (1.1)	1 (1.5)	0 (0.0)	0 (0.0)	
Liver function (Child Pugh category)	Normal - A	78 (83.9)	53 (81.5)	18 (90.0)	7 (87.5)	0.89
	B	14 (15.1)	11 (16.9)	2 (10.0)	1 (12.5)	
	C	1 (1.1)	1 (1.5)	0 (0.0)	0 (0.0)	
Fresh/recurrence	Primary	75 (80.6)	56 (86.2)	11 (55.0)	8 (100.0)	0.01
	Recurrence/residual	18 (19.4)	9 (13.8)	9 (45.0)	0 (0.0)	
Diagnosis	Pathological	62 (65.9)	41 (63.1)	15 (75.0)	6 (75.0)	0.893
	Imaging + tumor markers	31 (34.1)	24 (36.9)	5 (25.0)	2 (25.0)	
Tumor diameter	mm	32.00 [3.00, 125.00]	32.00 [3.00, 90.00]	30.00 [9.00, 77.00]	44.00 [13.00, 125.00]	0.325
T	1		5 (7.7)	3 (15.0)	0 (0.0)	NA
	2		17 (26.2)	8 (40.0)	1 (12.5)	
	3		12 (18.5)	2 (10.0)	4 (50.0)	
	4		28 (43.0)	2 (10.0)	3 (37.5)	
	NA		3 (4.6)	5 (25.0)	0 (0.0)	
N	0	67 (73.6)	52 (80.0)	9 (45.0)	6 (75.0)	0.597*
	1	24 (26.4)	12 (18.5)	10 (50.0)	2 (25.0)	
	NA	2 (2.2)	1 (1.5)	1 (5.0)	0 (0.0)	
Stage	1		4 (6.2)	5 (25.0)	0 (0.0)	NA
	2		17 (26.1)	7 (35.0)	1 (14.3)	
	3		13 (20.0)	0 (0.0)	4 (57.1)	
	4		30 (46.1)	3 (15.0)	2 (28.6)	
	NA		1 (1.5)	5 (25.0)	0 (0.0)	
Operability	Yes	5 (5.4)	1 (1.5)	1 (5.0)	3 (37.5)	0.0064
	No	88 (94.6)	64 (98.5)	19 (95.0)	5 (62.5)	
Chemotherapy	Yes	44 (47.3)	29 (44.6)	9 (45.0)	6 (75.0)	0.26
	Concurrent	34 (41.0)	21 (32.3)	8 (40.0)	5 (62.5)	
	Neoadjuvant	31 (38.8)	19 (29.2)	7 (35.0)	5 (62.5)	
	Adjuvant	24 (32.9)	15 (23.1)	6 (30.0)	3 (37.5)	
	No	49 (52.7)	36 (55.4)	11 (55.0)	2 (25.0)	
Prescribed dose [EQD2: Gy]	50 Gy (RBE)/ 25 fr [50 Gy]	12	3 (4.6)	6 (30.0)	3 (37.5)	0.004
	52 Gy (RBE)/ 26 fr [52 Gy]	1	0 (0.0)	1 (5.0)	0 (0.0)	
	56 Gy (RBE)/ 28fr [56 Gy]	4	2 (3.1)	1 (5.0)	1 (12.5)	
	60 Gy (RBE)/ 30fr [60 Gy]	18	13 (20.0)	5 (25.0)	0 (0.0)	
	67.5 Gy (RBE)/ 25fr [71 Gy]	20	12 (18.5)	6 (30.0)	2 (25.0)	
	70.2 Gy (RBE)/ 26fr [74 Gy]	25	24 (36.9)	1 (5.0)	0 (0.0)	
	70.3 Gy (RBE)/ 26fr [74 Gy]	1	1 (1.5)	0 (0.0)	0 (0.0)	
	72.6 Gy (RBE)/ 22fr [80.4 Gy]	12	10 (15.4)	0 (0.0)	2 (25.0)	
Distance between tumor and gastrointestinal tract	<1cm	70 (75.3)	43 (66.2)	19 (95.0)	8 (100)	0.042
	1–2 cm	13 (14.0)	12 (18.5)	1 (5.0)	0 (0.0)	
	2 cm≤	10 (10.8)	10 (15.4)	0 (0.0)	0 (0.0)	

chemotherapy with PBT (supplemental Table 1). The major systemic therapy concurrently used was gemcitabine or TS-1. Thirty-one patients received chemotherapy before PBT, and 24 patients received chemotherapy after PBT. The major systemic agent used in a neoadjuvant (adjuvant) setting was a combination of both cisplatin and gemcitabine.

3.1. Statistical analyses

StatView 5.0 and EZR stat package were used for statistical analyses [14] Percentages were analyzed using chi-square tests and Student's *t*-tests were used for normally distributed data. Mann–Whitney U-tests and Kruskal-Wallis test for skewed data were used for comparisons. The Kaplan–Meier method was used to analyze OS, PFS, and LC. Time to event was determined from the start of PBT. Cut-off values were set at the median or mean value if it was not specified. Cox's proportional hazard model was used for uni- and multivariate analyses (variable $p \leq 0.1$ was entered into multivariate analysis). $p < 0.05$ was considered statistically significant.

4. Results

4.1. Patient characteristics

A total of 93 patients underwent PBT for nonmetastatic EBT between 2016 and 2019. Detailed patient, tumor, and treatment characteristics are shown in Table 1. The diagnosis was made with histology (n = 33, 35.5%), cytology (n = 26, 27.9%), cytology and histology (n = 3, 3.2%), imaging, and tumor marker (n = 31, 33.3%). The perihilar group

showed a greater distance between the tumor and the GI tract (15.4 % of patients showed 2 cm ≤) than the distal and gallbladder group (0%, p = 0.042, Table 1) and used a higher prescribed dose. The median age of all the patients was 73 years (range, 44–92). A total of 65.6% of patients were male, and 96.6% had a good PS of 0–1. The median tumor diameter was 32.00 mm (range, 3.00–125.00 mm).

4.2. Local control, progression free survival, failure pattern, and overall survival rate

With a median follow-up of 16.3 months (20.7 months for surviving patients), median survival time (MST) was 20.1 months (95% CI: 15.5–23.5 months), 1- and 2-year OS were 72.1% (95% confidence interval [CI]: 61.5–80.2%) and 37.8% (95% CI: 27.09–48.5%) (Fig. 2a). As shown in Table 2, the predictors of poor OS in the univariate analysis included baseline liver function (Child-Pugh B-C) and tumor diameter (>2 cm). In multivariate Cox regression analysis (Table 2), poor liver function (Child B–C; hazard ratio [HR] = 2.406, 95% CI: 1.257–4.606, p = 0.0081), tumor diameter > 2 cm (HR = 2.038, 95% CI: 1.0890–3.812, p = 0.026), and distance from the GI tract 2 cm ≤ (HR = 0.358, 95% CI: 0.139–0.921, p = 0.032) had significant influences on OS. Patients with normal liver function or Child-Pugh A showed 40.8% at 2-year OS, whereas in Child-Pugh B or C patients, it showed 21.4% (Fig. 2b, p = 0.0366). Patients with a tumor diameter < 2 cm showed a 31.7% 2-year OS, whereas patients with a tumor diameter ≤ 2 cm were 55.4%, respectively (Fig. 2c, p = 0.0223). Patients with a tumor distance from the GI tract ≥ 2 cm showed a 56.2% 2-year OS, whereas < 2 cm showed 35.4% (Fig. 2d, p = 0.0591). In detail, patients with a small tumor diameter ≤ 2 cm and a wider tumor distance from the GI tract > 2 cm showed a superior 2-year overall survival rate of 100%, compared with patients with a tumor diameter ≤ 2 cm and tumor distance from the GI tract ≤ 2 cm with an overall survival rate of 50.3% (25.8–70.6%), patients with diameter > 2 cm and tumor distance from the GI tract > 2 cm with the overall survival rate of 43.8% (10.1–74.2%), patients with diameter > 2 cm and tumor distance from the GI tract ≤ 2 cm with overall survival rate of 30.1% (18.0–43.1%) at 2-year, respectively (Fig. 2e, p = 0.0295). The MST for patients with distal bile duct was 21 months (95% CI: 12.2–31.7 months), which was similar to the 20.5 and 15.0 months for patients with perihilar and gallbladder lesions, respectively (Fig. 2e, p = 0.965). The 2-year OS rates of patients with distal, perihilar, and gallbladder lesions were 31.2%, 40.3%, and 37.5%, respectively (Fig. 2f). No significant difference was found between patients diagnosed with pathological finding (2-year OS: 33.5%) and patients diagnosed with imaging + tumor markers (2-year OS: 42.6%, p = 0.165).

For the type of treatment schedules, gastrointestinal proximity type, simultaneous integrated boost (SIB) type, and perihilar type showed 26.8%, 41.1%, and 47.1%, of 2-year OS (supplemental Fig. 1a, p = 0.403), respectively.

The local control rate was 85.4% (72.7%–92.5%) at 1-year and 66.5% (95% CI: 48.4–79.5%) at 2 years (Fig. 2a). The 2-year local control rate of patients with distal, perihilar, and gallbladder lesions were 55.1%, 68.0%, and 75.0%, respectively (Supplemental Fig. 1b, p = 0.892). No statistically significant prognostic factor was found to be related to local control. For the type of treatment schedules, gastrointestinal proximity type, simultaneous integrated boost (SIB) type, and perihilar type showed 54.3%, 52.5%, and 82.7% of 2-year local control rates (supplemental Fig. 1c, p = 0.297), respectively.

Median PFS was 10.8 months (95% CI:8.6–13.5 months), and 1-year and 2-year PFS were 43.2% (95% CI:32.7–53.2%) and 20.6% (95% CI:12.6–30.0%) (Fig. 2a). The 2-year PFS of patients with distal, perihilar, and gallbladder lesions were 6.25%, 27.1%, and 25.0%, respectively (supplemental Fig. 1d, p = 0.593). No statistically significant prognostic factors were identified in the PFS. The initial site of progression was local (n = 20; 54.1%), lymph node (n = 3; 8.1%), and distant metastases (n = 14; 37.8%). We found nine distant metastases in 67 node-negative patients (13.4%), whereas 5/24 (20.8%) in node-positive patients (p = 0.5918). No statistical difference was found between the presence or absence of lymph node metastases for the development of distant metastases.

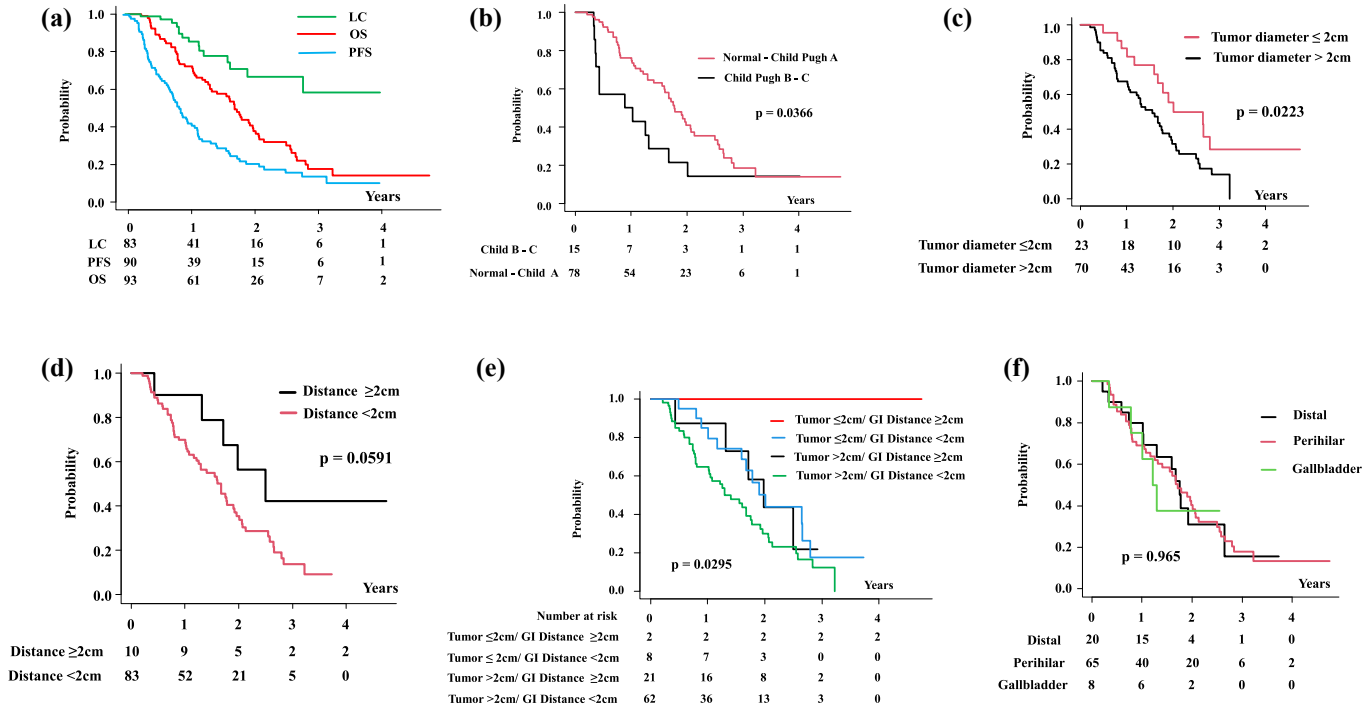

Fig. 2. Survival analysis. Overall survival rate (OS), progression free survival rate (PFS) and local control (LC) in total population. OS according to liver function. OS according to tumor diameter. OS according to distance tumor from gastrointestinal tract (GI distance). OS according to tumor diameter and distance between tumor and gastrointestinal tract (GI distance). OS according to primary site of tumor.

Table 2
Uni- and Multi-variate analysis for overall survival rate using Cox proportional hazards model.

Variables	Strata	Univariate analysis			Multivariate analysis		
		HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age	75≤	1	(referent)	–			
	<75	0.989	0.603–1.624	0.9663			
Gender	Male	1	(referent)	–			
	Female	0.929	0.551–1.567	0.7819			
PS	0–1	1	(referent)	–	1	(referent)	–
	2≤	2.897	0.899–9.335	0.0748	2.848	0.878–9.238	0.0813
Liver function	Normal-A	1	(referent)	–	1	(referent)	–
(Child Pugh category)	B/C	1.935	1.029–3.639	0.0404	2.406	1.257–4.606	0.0081
Recurrence/fresh	Fresh	1	(referent)	–			
	Recurrence/residual	0.877	0.466–1.651	0.6839			
Location	Hilar	1	(referent)				
	Galbladder	1.132	0.4456–2.874	0.7943			
	Distal	0.995	0.5345–1.852	0.9874			
Operability	No	1	(referent)	–			
	Yes	1.596	0.499–5.100	0.4305			
T	1–2	1	(referent)	–			
	3–4	1.402	0.814–2.416	0.2232			
N	0	1	(referent)	–			
	1	1.241	0.682–2.256	0.4793			
Stage	I-II	1	(referent)	–			
	III-IV	1.406	0.822–2.405	0.2134			
Tumor diameter	≤2cm	1	(referent)	–	1	(referent)	–
	2 cm<	2.034	1.092–3.787	0.0252	2.038	1.0890–3.812	0.026
Distance from GI	<2cm	1	(referent)	–	1	(referent)	–
	2 cm ≤	0.424	0.169–1.063	0.0674	0.358	0.139–0.921	0.032
Prescribed dose	Low [EQD2:50–60 Gy]	1	(referent)	–			
	High [EQD2:70–81 Gy]	0.712	0.433–1.172	0.1819			
Chemotherapy	No	1	(referent)	–			
	Yes	0.879	0.534–1.449	0.6142			
	Concurrent	0.74	0.424–1.291	0.2897			
	Neoadjuvant	0.787	0.443–1.399	0.4156			
	Adjuvant	0.753	0.396–1.433	0.3883			

Bold values indicate statistically significance, NA = not available.
Abbreviations; CI = confidence interval; HR = hazard ratio.

4.3. Local control, progression free survival, failure pattern, and overall survival rate excluding gallbladder carcinoma

For the patient with EBC excluding gallbladder cancer. MST was 20.5 months (95% CI: 15.8–23.7 months), 1- and 2-year OS were 71.8% (95% CI: 60.6–80.3%) and 38.2% (95% CI: 26.8–49.4%). As shown in supplemental Table 3, the predictors of poor OS in the univariate analysis included tumor diameter (>2 cm) and distance from the GI tract 2 cm≤. In multivariate Cox regression analysis (Supplemental Table 1), poor liver function (Child B–C; hazard ratio [HR] = 2.328, 95% CI: 1.860–4.569, p = 0.01408), tumor diameter > 2 cm (HR = 2.052, 95% CI: 1.0680–3.945, p = 0.0309), and distance from the GI tract 2 cm ≤ (HR = 0.3903, 95% CI: 0.1534–0.9932, p = 0.04834) had significant influences on OS. Patients with normal liver function or Child-Pugh A showed 41.0% at 2-year OS, whereas in Child-Pugh B or C patients, it showed 23.1% (p = 0.0769). Patients with a tumor diameter < 2 cm showed a 55.9% 2-year OS, whereas patients with a tumor diameter ≤ 2 cm were 32.0%, respectively (p = 0.0264). Patients with a tumor distance from the GI tract ≥ 2 cm showed a 56.2% 2-year OS, whereas <2 cm showed 35.5% (p = 0.0588).

The local control rate was 86.1% (72.7%–93.2%) at 1-year and 65.2% (95% CI: 45.8–79.1%) at 2 years. No statistically significant prognostic factors were found to be related to local control.

Median PFS was 10.8 months (95% CI:8.2–13.9 months), and 1-year and 2-year PFS were 43.8% (95% CI:32.8–54.3%) and 20.6% (95% CI:12.2–30.4%). No statistically significant prognostic factors were identified in the PFS.

4.4. Perihilar cholangiocarcinoma

In 55 patients with unresectable perihilar cholangiocarcinoma, MST was 20.1 months (95% CI = 15.1–24.7 months) and the 2-year OS rate was 38.9% (95% CI = 24.7–52.7%) at 2 years. The local control rate was 68.4% (95% CI: 42.1–84.8%) at 2 years. No statistically significant prognostic factors for OS, PFS, or LC were found.

4.5. Toxicity and subsequent second cancer

Adverse reactions of grade 3 or higher occurred in 14 patients (14/93 = 15%, Table 3). Eight acute toxicities (8.6%) occurred during PBT or within 90 days of completion of PBT. Six late toxicities (6.45%) occurred at 3, 9, 12, 21, 30, and 42 months after PBT. One pyelonephritis that occurred 21 months after PBT was lethal (grade 5 toxicity); however, no apparent relationship was observed between PBT and renal toxicity. Of them, nine toxicities (9.6%), five in the acute phase (5.4%), and four in the late phase (4.3%), were considered PBT-related toxicities (Table 3). Only one duodenal ulcer, grade 3, occurred 9 months after PBT and was considered as PBT-related toxicity [prescribed dose 67.5 Gy (RBE) in 25 fractions, whose tumor was located adjacent to the duodenum (with a distance<1 cm)]. No predisposing factor for PBT-related toxicity grade 3 was found. After treatment, five 2nd cancers (one hematological, one hepatobiliary, one skin/bone, one intestinal, and one breast cancer) were observed.

5. Discussion

The purpose of this study was to evaluate the efficacy and toxicity of PBT in patients with EBC. To our knowledge, this is the largest and first series of outcome reports for PBT-treated EBC prospectively. Our study revealed that tumor diameter and distance between the tumor and gastrointestinal tract are important factors for survival, and PBT with or without chemotherapy is well-tolerated in the treatment of EBC.

Table 3
Toxicity grade 3 or more.

Location	Toxicity	Acute toxicity				Late toxicity			
		PT NO	(%)	PBT related	(%)	PT NO	(%)	PBT related	(%)
Gastrointestinal	Gastric ulcer	1	(1.1%)						
	Duodenal bleeding					1	(1.1%)	1	(1.1%)
Bile duct	Bile duct stenosis	2	(2.2%)	1	(1.1%)	1	(1.1%)	1	(1.1%)
	Cholecystitis	1	(1.1%)	1	(1.1%)				
	Cholangitis: infection	4	(4.3%)	3	(3.2%)				
Liver	γ-GTP elevation					1	(1.1%)	1	(1.1%)
	Liver abscess					1	(1.1%)	1	(1.1%)
	Portal hypertension					1	(1.1%)		
Kidney	Pyelonephritis					1 (Grade 5)	(1.1%)		
Total		8	(7.5%)	5	(5.4%)	6	(6.5%)	4	(4.3%)

Bold values indicate statistically significance, NA = not available.
Abbreviations; CI = confidence interval; HR = hazard ratio.

Systemic chemotherapy is the standard of care for patients with inoperative biliary tract cancers; however, the role of radiotherapy has not been established. The ABC-02 trial showed that gemcitabine plus cisplatin was associated with superior overall survival to gemcitabine alone (11.7 months vs, 8.1 months) in advanced disease including metastasis diseases (76%), and only five (1%) patients were alive with disease-free status at 2 years, implying limitation of chemotherapy alone, which offers the limited chance of long-term survival and disease control. Although radiotherapy could improve the outcome than best supportive care [15,16], it is not established if chemoradiotherapy could add efficacy over chemotherapy or radiotherapy alone, as there is little evidence for this issue [17–19]. For example, Foo et al. demonstrated a 5-year OS of 14% with a trend towards improved OS for patients who received concurrent chemotherapy than radiotherapy alone.[17] Chen et al. also reported that concurrent chemoradiotherapy provides longer OS and PFS for patients with unresectable locally advanced hilar cholangiocarcinoma than RT alone [18]. With the advancement of drug development, a combination with a new drug such as gemcitabine showed 12–14 months of MST [20,21]. Conversely, Phelip et al. reported that a combination of gemcitabine plus oxaliplatin seems to be at least as efficient as chemoradiotherapy (50 Gy plus 5 FU and cisplatin) because OS was 13.5 months in the chemoradiotherapy group and 19.9 months in the chemotherapy group [19]; although, the trial was closed before completion due to slow recruitment. The Japanese multicenter group reported an MST of 13 months in 137 patients treated with radiotherapy alone (82% EBC; 2D-3DCRT ± intraoperative irradiation ± intracavitary irradiation) and 16 months for patients receiving chemotherapy (15 months for concurrent chemotherapy), which seems to be more favorable than the 13 months for patients receiving radiotherapy alone [22].

The large population-based analysis of cholangiocarcinoma suggested several findings of survival benefit of radiotherapy with or without chemotherapy [16,23,24]. Pollom et al. analyzed the Surveillance, Epidemiology, and End Results data using propensity scores and reported that radiation therapy alone was less effective (HR = 1.09, p = 0.34) than non-radiation therapy (e.g., chemotherapy group), but radiotherapy was more effective in patients treated with chemotherapy (HR = 0.82, p = 0.02) [23]. Torgesen et al. reported that a CRT tends to be more useful than RT alone, particularly useful in operable cases [24]. Therefore, the success of neoadjuvant chemoradiotherapy in rectal cancer can be considered, which implies the role of chemotherapy to improve the efficacy of radiotherapy in adenocarcinoma [25]. Although we could not present the efficacy of chemotherapy in our cohort, we could speculate that there is a potential to improve survival. Distant metastasis occurred in 37.8% of patients as an initial failure site in our cohort, which concurred with Avila et al., whose distant metastasis-free survival was 40% in EBC, indicating that systemic control remains a major problem [26]. A phase III trial comparing chemotherapy alone (gemcitabine + cisplatin) and chemotherapy (gemcitabine) + radiotherapy (mainly IMRT) (NCT02773485) is ongoing, including confirmation of the significance of adding radiotherapy to chemotherapy alone (cisplatin/ gemcitabine) (The ABC-07 trial Cancer Research UK trial number CRUK/14/029).

Radiation dose escalation can improve the outcome of several hepatobiliary cancers [26–28]. Crane et al. evaluated the association between EBRT doses of 30 Gy, 36–50.4 Gy, and 54–85 Gy with outcomes for patients with EBC [29]. They identified a prolonged median time to local progression of 9 vs. 11 vs. 15 months with no significant increase in toxicity, suggesting a potential benefit of dose escalation. Several authors have reported similar outcomes [21,28]. These findings have been more strongly demonstrated in cohorts of patients with intrahepatic cholangiocarcinoma for which dose escalation to a dose ≥ 60 Gy or a biologically equivalent dose (BED) > 80.5 Gy10 (proton or photon) has been associated with improved LC and OS [27]. In a prospective multicenter study of intrahepatic cholangiocarcinoma using proton beams, a 2-year survival rate of 46.5% was obtained [30].

In recent years, several advanced radiotherapy techniques, including SBRT, IMRT, and particle beam radiotherapy, have been introduced for the treatment of biliary tract carcinoma (Table 4) [5]. IMRT technique is considered an alternative to 3D conformal RT in upper abdominal malignancies to reduce normal tissue toxicity [32,33]. SBRT has also been explored as a potentially curative RT strategy for patients with biliary cancer with a higher prescribed dose [5–8,34,35]. Lee et al. reported MST of 13 months among those SBRT series with 0%–20% of late toxicity by a systematic review [5–8,34]. Particle beam therapy reported 12–23 months of MST for EBC [10–13,36,12]. Our data concurred with those of previous studies, and MST over 20 months is encouraging for further exploration.

The proximity of the EBC to the bowel limits the ability to completely cover the tumor with a higher dose of radiation above 55 Gy, without potentially life-threatening toxicity [5,26]. Elganainy et al. could not demonstrate any improvement in OS or freedom from local progression using higher dose IMRT using BED > 59.5 Gy10 to segments of tumor away from the small bowel vs. conventional external beam radiotherapy to a BED ≤ 59.5 Gy10 [32]. Our cohort partly concurred with their outcome, that is, a narrower distance between the tumor and digestive tract (2 cm≥) was identified as a poor prognostic factor for OS. Despite the acceptable toxicity of higher RT doses in our study (only one PBT-related grade 3≤ duodenal ulcer), we found that escalated RT doses (70 to 80 Gy (RBE) in EQD2) did not significantly benefit patients with EBC concerning increasing OS or PFS. In SBRT, Brrunner et al. found that OS and LC were significantly improved after higher dose irradiation (maximal biological equivalent dose inside the tumor) but not with a higher prescribed dose [37].

In our study, we used three major treatment schedules ((i) Gastrointestinal proximity type: 50–60 Gy (RBE)/ 25–30 fraction, (ii) Perihilar type: 70.2–72.6 Gy (RBE)/22–26 fraction. and (iii) Simultaneous integrated boost (SIB) type: 67.5 Gy (RBE)/ 25 fraction). However, we could

Table 4
Selected literature of treatment outcome for extrahepatic biliary tract cancer.

Author PY/Country	Study type	Treatment	Schedule	PTNO	OS MST (months)	2 years	LC	PFS (months)	Toxicity Grade 3≤	
Systemic chemotherapy										
[31] Valle et al. 2010/ UK	RCT ABC-02 study	CT	GEM + CDDP vs. GEM	198 vs. 199	11.7 vs. 8.1	17% vs. 4%	NA	8 vs. 5	0.609	
Conventional radiotherapy										Incl. all biliary tract cancer and distant meta (74.6%)
[22] Yoshioka et al.2014/ Japan	Retro-multi	RT ± BT ± IORT vs. CRT	Various	137 vs. 148	13 vs.16	27%	NA	NA	NA	
[24] Torgeson et al. 2017/ USA	Population based (NCDB)	CT vs. CRT	NA	1871 vs. 1070	12.6 vs. 14.5	NA	NA	NA	NA	Incl. 51 intra
Intensity Modulated Radiotherapy (IMRT)										8 %CRT⇒OP
[32] Elganainy et al. 2018/ USA	Retro-single	3D-CRT35 IMRT44 Proton 1	50.4 (30–75) Gy [1.8–4.5 Gy /fr]	80	18.7	30%*	1y80%, 2y50%*		Acute GI 11% ¶Biliary complication 12.5% GI bleeding 13.7%	
[33] Engineer 2018/India	Retro-single	Group 1: IMRT45Gy + BT14Gy Group 2: IMRT57Gy+ GEM		68	Group 1: 17.5Group 2: 16	Group 1:18 % Group 2:22%	NA	NA	Cholangitis 41%, GI bleeding 7.3% liver failure 7.3%, duodenal stricture 1.4%, liver abscess 1.4%	
Stereotactic body radiotherapy (SBRT)										
[7] Sandler et al. 2016/ USA	Retro-single	SBRT	40 Gy/5fr	31	15	33%	2y47%		Duodenal obstruction 9.6%, duodenal hemorrhage 9.6%	
[6] Kopek et al. 2010/ Denmark	Retro-single	SBRT	45 Gy/3fr	27	10.6	15%*	NA		Duodenal/pyloric ulcer 22% duodenal stenosis, liver failure 14.8%	
[35] Frakulli et al. 2018/ Italy	Systemic review	SBRT	Various	231	15	35.5% intra 1y57.1% extra 1y81.5%	1y83.4%	4.2–30	NA	Incl. 1 intra
Particle beam therapy										Incl. intra
[36] Kasuya et al. 2019/ Japan	Retro-single	Carbon	52.8–76 Gy (RBE)/4-26fr	56	12.6	26.3%	2y58.2%		¶¶ Bile duct stenosis 1.7%, liver failure 7.1%	
[13] Makita et al. 2014/ Japan	Retro-single	Proton	68.2(50.6–80) Gy(RBE)/ [2–3.2 Gy (RBE)/fr]	28	12	1y49%	1y67.7%		Acute cholangitis 3.5% Late cholangitis 7.1% bile duct stenosis 3.5%, duodenal ulcer /hemorrhage/ stenosis 3.5–7.1%	
[12] Hung et al. 2020/ Taiwan	Retro-single	Proton	72.6 Gy (RBE)/22fr or 66 Gy(RBE)/ 10fr	30	19.3	8%*	1y88%		Dermatitis 7% Duodenal/gastric ulcer 3.3%	Incl. 6 intra
Current study	Pros-multi	Proton	Various	93	20.5	37.8%	1y85.4% 2y66.5%	10. 8	Acute 7.5% (PBT related 5.4%) Late 6.5% (4.3%)	Incl.18 intra

Study included more than 20 patients. *estimated from figure or Table.
PY = publish years, RCT = randomized controlled study, CT = chemotherapy, incl = including, NA = not available, intra = intrahepatic, extra = extrahepatic, NCDB = National Cancer Database.
Retro = retrospective, Pros = prospective, single = single institution, multi = multi institutional study, LC = local control, OPFS = progression free survival, RT = radiotherapy, BT = brachytherapy, IORT = intraoperative radiotherapy.
CRT = chemoradiotherapy, GEM = gemcitabine, CDDP = cisplatin, GI = gastrointestinal, ¶: hospitalized within 90 days of RT completion (mainly cholangitis), ¶¶incl intra.

not find a statistically significant relationship between tumor control and the prescribed dose in these three types, therefore, we thought that the prescribed dose is not enough indicator for tumor control, and further exploration should be done for appropriate indicator for tumor control, such as the dose received by 90% of the target volume (D90), or maximal biological equivalent dose inside the tumor, etc. [37].

We found that poor liver function, larger tumor diameter, and narrow distance to the GI tract were significant factors for poor survival in

multivariate analysis. It is natural that poor liver function [12] and larger tumors are related to poor outcomes, which have already been cited in several papers [13,22]. In addition, a wider distance than 2 cm to the GI tract is a plausible influential factor, which implies the potential to increase radiation dose, although higher doses did not always translate into improved outcomes in this study; this characteristic implies the future potential of spacer insertion (Space-Making) to widen the space between tumor and gastrointestinal tract [38]. Our data indicated that patients with larger tumor could show equivalent survival to those with small tumor with narrow GI distance if there could be a wider GI distance.

This study has several limitations. First, although we prospectively collected the data, there were several missing data (i.e., gross tumor volume, tumor marker; CEA, and CA 19-9) because these data accumulations did not have a strict protocol like a prospective clinical trial. Then, heterogenous population (unresectable and/or recurrence and/ or chemotherapy refractory cases) was treated with various treatment schedules. In addition, no general rule was applied to the follow-up period, which limits the value of locoregional progression-free period estimation, which was reported based on imaging or clinical reporting of locoregional progression. Third, chemotherapy regimens were not standardized in terms of regimen and timing. Selection bias in choosing proton beam radiotherapy could also be speculated, which is related to potential confounding factors. We admit that it may be challenging to apply these results to patients with distal cholangiocarcinoma, since the majority of patients had perihilar tumors, and it is difficult to prescribe higher dose to tumor located distal part due to their location adjacent to gastrointestinal tract. Despite these limitations, this study was relatively large for this rare tumor type and represents the most comprehensive description of PBT for EBC.

In conclusion, we present the largest reported series of PBT for EBC, and PBT showed favorable outcomes with acceptable toxicity profiles.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2023.100634.

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