Space-making particle therapy for unresectable hilar cholangiocarcinoma

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Research

Keywords: Hilar cholangiocarcinoma, Particle therapy, Dose volume histogram, Space making particle therapy

Posted Date: December 15th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-127933/v1>

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Version of Record: A version of this preprint was published at Digestive Surgery on April 22nd, 2022. See the published version at <https://doi.org/10.1159/000524582>.

Abstract

Background

Although the primary treatment option for hilar cholangiocarcinoma (HC) has been surgical resection, most patients present with unresectable advanced tumors at the time of diagnosis. Particle therapy (PT) holds a great potential for HC, even though the anatomical proximity to the gastrointestinal tract prevents delivering a radical dose to the tumor. Space-making PT (SMPT), consisting of spacer placement surgery and subsequent PT, has been developed to minimize complications and maximize the therapeutic benefit of dose escalation for HC. This study aimed to conduct a dosimetric evaluation and examine the effectiveness of SMPT for the treatment of HC.

Methods

Between 2007 and 2018, 12 patients with unresectable HC treated with SMPT were enrolled. The treatment outcomes and effectiveness of spacer placement surgery were evaluated through analyses of pre- and post- surgical parameters of dose volume histograms.

Results

All patients completed the planned SMPT protocol. The median survival time was 29.6 months, and the 1- and 3-year overall survival rates were 82.5% and 45.8%, respectively. The mean V95% value (volume irradiated with 95% of the planned treatment dose) of the gross tumor volume and clinical target volume after spacer placement surgery improved to 98.5% and 96.6% from preoperative values of 85.6% and 78.1%, respectively ($p = 0.0196$ and $p = 0.0053$ respectively). Grade 3 or higher adverse events after SMPT were seen in 6 patients.

Conclusions

SMPT led to improvements in dosimetric parameters and showed good feasibility and excellent outcomes. SMPT can be a promising novel alternative for unresectable HC.

Background

Hilar cholangiocarcinoma (HC) is one of the most common malignant tumors of the biliary system, accounting for more than 60% of biliary tract cancers [1–3]. Currently, surgical resection is the only potentially curative treatment, but the majority of patients with HC are not indicated for surgical resection due to the local tumor extension or distant metastasis [4, 5]. The standard treatment regimen with gemcitabine-based chemotherapy showed improved survival, but the prognosis of unresectable HC is still extremely poor [6–9].

The role of conventional radiotherapy for unresectable HC is limited because its effectiveness in this setting has not been established [10, 11]. Recent advances in medical radiation technology, including stereotactic body radiation therapy [12–15], intensity modulated radiotherapy [16, 17], and intraluminal radiation therapy [18], can improve dose centralization in the target volume, and may be used as alternative treatment options for unresectable HC. However, it is still difficult to perform radical radiation to the entire tumor using these modalities. Another promising potential option for HC is particle therapy (PT) using proton or carbon ion beams. Unlike X-rays, particle beams reach the Bragg peak at a constant depth, and can deliver high radiation doses to the target with little influence on the skin and the surrounding tissues and organs [19, 20].

A multi-center study from Japan has demonstrated the favorable outcomes of PT for intrahepatic cholangiocarcinoma and at least acceptable outcomes for HC [21]. However, delivering radical doses for HC is far more difficult than for intrahepatic cholangiocarcinoma, since HCs are located anatomically close to the gastrointestinal tract, especially to the stomach and duodenum, which are easily perforated when exposed to high radiation doses. This anatomical feature precludes the widespread use of PT for HC. To overcome this limitation, we have developed a new conceptual approach with space-making PT (SMPT), consisting of spacer placement surgery and subsequent PT since 2006 [22–25]. A spacer is inserted between the tumor and the nearby gastrointestinal tract to reduce the dose to adjacent organs and to increase the total tumor dose. The present study aimed to assess the effectiveness of surgical spacer placement through pre- and post-spacer placement surgery dosimetric evaluation, as well as the safety and long-term outcomes of SMPT during a consecutive case series.

Methods

Patient characteristics

Inclusion criteria were as follows: (1) HC confirmed histologically or clinically by diagnostic imaging, such as computed tomography (CT) and/or magnetic resonance imaging; (2) unresectable HC without lymph node and distant metastases; (3) Eastern Cooperative Oncology Group performance status score 0–2; (4) adequate organ function; (5) no active concomitant malignancy. Resectability was assessed both with preoperative imaging studies and intraoperative findings. Patients whose tumors had bilateral tumor extension to second-order intrahepatic biliary radicles, and/or encasement or occlusion of the major vascular structures, including the main portal vein and/or hepatic artery, were considered unresectable. Patients who fulfilled the inclusion criteria received a thorough explanation of the study, provided written informed consent for participation in the study, and were prospectively enrolled.

A total of 12 patients who underwent SMPT for unresectable HC from January 2007 to March 2018 were enrolled in the present study. Tumor status was staged based on the 8th edition of the American Joint Committee on Cancer staging system. All patients included in the analysis underwent multidisciplinary evaluation by medical, surgical, and radiation oncologists. This study was conducted in accordance with

the ethical standards of the Declaration of Helsinki and approved by the ethics committee of the Kobe University.

Spacer placement surgery

The treatment concept lies in the attempt to exclude the gastrointestinal tract from the irradiation field by placing a surgical spacer (Fig. 1a). All procedures were performed under general anesthesia and conducted via open laparotomy with abdominal midline incision. After confirming that there was no liver metastasis and peritoneal dissemination, surgical spacer placement was designed to secure an adequate margin of more than 10 mm, to the extent possible, between the tumor and gastrointestinal tract in all directions for safe PT irradiation. The Kocher maneuver was performed to mobilize the duodenum to a downward direction in order to increase the distance from the tumor. A 20 cm × 15 cm × 2 mm Gore-Tex sheet (W.L. Gore and Associates, Newark, DE) or omentum was inserted as a spacer in the subhepatic space (Fig. 1b). Surgical spacer placement was performed in a hybrid operating room and the appropriate placement was confirmed intraoperatively before fixing the spacer. We tried to cover the Gore-Tex sheet with omentum, if possible, to prevent direct contact between the Gore-Tex sheet and the gastrointestinal tract. Tumors were never resected because the spacer placement surgery was only a preparatory step for PT.

Particle therapy treatment protocol

The relative biological effectiveness (RBE) values of protons and carbon ions at Hyogo Ion Beam Medical Center were determined to be 1.1 and 2 to 3.7, respectively, using biological experiments. Treatment plans were designed and individualized using computerized radiation dosimetry, based on tumor volume and dosimetric parameters of adjacent normal structures. Considering the calculated dose mapping, patients were treated with proton or carbon ion beams with 76.0 Gy (RBE) in 20 fractions or 70.2 Gy (RBE) in 26 fractions, during the exhalation phase using a respiratory gating system; the setup was performed daily before irradiation using fiducial markers and bony landmarks. Treatment planning was performed using a CT-based three-dimensional system (Xio-M; Mitsubishi Electric Corporation, Tokyo, Japan).

The gross tumor volume (GTV) was defined as the primary tumor through fusion contrast-enhanced CT. The GTV was delineated; the clinical target volume (CTV) comprised the addition of a 5-mm basic margin to the GTV and 10-mm margin along the common and intrahepatic bile ducts. The planning target volume (PTV) was defined as the CTV plus a setup margin (5 mm) and a respiratory gating margin (1–5 mm). The beam settings were planned to be irradiated as much as possible to the GTV, CTV, and PTV, while keeping the maximum dose applied to every 0.5 cm³ of the gastrointestinal tract under 48 Gy (RBE) and the maximum dose to the spinal cord under 45 Gy (RBE). For dosimetric comparison, pre- and post-spacer placement CTs were acquired for each patient. On each pre- and post-spacer placement series, target volumes and organs at risk were re-delineated and treatment planning was re-built.

Figure 2 shows a representative case of HC who underwent SMPT. The preoperative abdominal CT showed bilateral intra-hepatic bile duct dilatation (Fig. 2a), and that the tumor broadly abutted the

duodenum (Fig. 2b). Postoperative abdominal CT shows that the spacer was fixed at the subhepatic space (Fig. 2c). The gastrointestinal tract was successfully excluded from the irradiation field and received minimal irradiation (Fig. 2d).

Study design

The treatment plans were set using CT scans taken pre- and post-spacer placement surgery for the dosimetric comparison study. Each treatment plan was analyzed using a dose-volume histogram (DVH), and V95% (volume irradiated with 95% of the planned treatment dose); D95% (dose intensity covering 95% of the target volume); Dmax (maximum dose of the target volume); Dmean (average dose of the target volume); Dmin (minimum dose of the target volume) of the GTV, CTV, and PTV; and V30Gy and V40Gy (RBE)(cc) (volume irradiated by more than 30 Gy or 40 Gy (RBE), respectively) in the stomach and gastrointestinal tract were compared between plans. V40Gy (RBE)(cc) of the duodenum, and V95% and D95% of the GTV and CTV were considered as the most important parameters to assess the therapeutic effect of SMPT in the present study.

Follow-up and statistical analysis

Patients underwent physical examination, blood tests, and imaging studies (CT or magnetic resonance imaging) every 3 months after SMPT. All patients underwent endoscopic examinations from the esophagus to the horizontal part of the duodenum 3 months after surgery to investigate acute radiation-related gastroduodenal complications.

The statistical significance of differences in each classification for both local control and overall survival rates was estimated by the Kaplan-Meier survival method and compared by the log-rank test. Local progression was defined as radiographic enlargement of the primary tumor. Complications were classified using the National Cancer institute Common Terminology Criteria for Adverse Events version 4.0. Continuous variables were compared by Student's *t*-test if they were normally distributed; otherwise, the Mann-Whitney *U*-test was used. Categorical variables were compared by the chi-squared test. *P*-values < 0.05 were considered statistically significant. All statistical analyses were conducted using the JMP 13 statistical package (SAS Institute, Cary, NC).

Results

Overview

The baseline patient and tumor characteristics are shown in Table 1. There were 8 males and 4 females with a mean age of 65.2 years (standard deviation 10.3). The median tumor size was 31 mm (range 14–76). According to the tumor-node-metastasis classification system, 11 patients (91.7%) were diagnosed as stage IIIB and 1 patient (8.3%) was diagnosed as having postoperative recurrence. The 11 patients' stage IIIB tumors were diagnosed as unresectable due to the bilateral tumor extension to second-order intrahepatic biliary radicles. The median serum level of carcinoembryonic antigen and carbohydrate

antigen 19 – 9 were 2.7 (range 1.2–19) units/mL and 242 (range 2-13508) units/mL, respectively. The median time from spacer placement surgery to the first irradiation was 23.5 days (range 16.0–42.0).

Table 1
Patient Characteristics

	No. of patients (<i>n</i> = 12)
Age (years)*	65.2 (10.3)
Gender, n (%)	
Male	8 (66.7)
Female	4 (33.3)
Child-Pugh classification	
A	10 (83.3)
B	2 (16.7)
Tumor stage**	
IIIB	11 (91.7)
Recurrence tumor	1 (8.3)
Total bilirubin (mg/dL)	
<2.0	11 (91.7)
2.0≤, < 3.0	1 (8.3)
3.0≤	0 (0)
Albumin (g/dL)	
<3.0	1 (8.3)
3.0≤, < 3.5	3 (25.0)
≤3.5	8 (66.7)
Prothrombin time (%)	
<50	0 (0)
50≤, < 80	2 (16.7)
80≤	10 (83.3)
Serum CEA (ng/ml)	

Values in parentheses are percentages unless indicated otherwise; values

are *mean (standard deviation) and †median (range).

Abbreviations: CEA Carcinoembryonic antigen, CA19-9 carbohydrate antigen 19 - 9, AJCC 8th American Joint Committee on Cancer tumor-node-metastasis, 8th edition.

	No. of patients (<i>n</i> = 12)
< 5.0	10 (83.3)
5.0≤	2 (16.7)
Serum CA19-9 (U/ml)	
< 37	2 (16.7)
37≤,<1000	7 (58.3)
1000≤	3 (25)
Preoperative diagnosis	
Maximal tumor size (mm)†	31 (14–76)
Vascular invasion (Yes : No)	8 : 4
Treatment	
Proton	5 (41.7)
Carbon ion	7 (58.3)
Values in parentheses are percentages unless indicated otherwise; values are *mean (standard deviation) and †median (range).	
Abbreviations: CEA Carcinoembryonic antigen, CA19-9 carbohydrate antigen 19 – 9, AJCC 8th American Joint Committee on Cancer tumor-node-metastasis, 8th edition.	

Four patients received chemotherapy during or after the PT period. Two patients were administered gemcitabine alone, one patient was administered gemcitabine and tegafur with gimeracil, and the remaining patient was administered gemcitabine and cisplatin.

The overall survival and local control rates are shown in Fig. 3; the median follow-up period and survival time were 26.6 and 29.6 months, respectively. The 1- and 3-year overall survival rates of all patients were 82.5% and 45.8%, respectively, and the 1- and 3-year local control rates of all patients were both 91.7%.

In the present study, 6 patients (50%) survived for more than 2 years and 4 survived more than 4 years after SMPT. One patient remained alive at the end of the study period without any sign of recurrence, showing the longest survival time (64.9 months).

DVH comparison

Table 2 shows the tumor volume and pre- and post-spacer placement surgery DVH comparison. The GTV, CTV, and PTV V95% values significantly improved from pre- to postoperatively (85.6–98.5%, *p* = 0.0196; 78.1–96.6%, *p* = 0.0053; and 69.5–90.1%, *p* = 0.0014, respectively). A significant improvement was also seen in the GTV, CTV, and PTV D95% (65.3 Gy (RBE) to 73.0 Gy (RBE), *p* = 0.0115; 56.0 Gy (RBE) to

70.8 Gy (RBE), $p = 0.0039$; and 43.9 Gy (RBE) to 65.3 Gy (RBE), $p = 0.0019$, respectively). The Dmin of GTV, CTV, and PTV also significantly improved (42.1 Gy (RBE) to 65.6 Gy (RBE), $p = 0.0067$; 27.6 Gy (RBE) to 55.2 Gy (RBE), $p = 0.0034$; and 16.6 Gy (RBE) to 33.4 Gy (RBE), $p = 0.0304$, respectively). In addition, the Dmax of stomach and small intestine significantly improved (51.2 Gy (RBE) to 34.0 Gy (RBE), $p = 0.0315$; and 44.7 Gy (RBE) to 33.0 Gy (RBE), $p = 0.0025$, respectively). A significant improvement was also seen in V40Gy (RBE) of both stomach and small intestine (5.5 cc to 2.6 cc, $p = 0.0384$; and 2.0 cc to 0.38 cc, $p = 0.0384$, respectively).

Table 2
Parameter Changes Regarding Pre- and Post-spacer Placement Surgery

	Parameter	Preoperative Mean value	Postoperative Mean value	T-test
GTV	Volume (ml)	41.9	52.9	0.0230
	V95% (%)	85.6	98.5	0.0196
	D50% (Gy (RBE))	74.7	75.3	0.1552
	D95% (Gy (RBE))	65.3	73.0	0.0115
	Dmean (Gy (RBE))	73.0	75.1	0.0132
	Dmin (Gy (RBE))	42.1	65.6	0.0067
CTV	V95% (%)	78.1	96.6	0.0053
	D50% (Gy (RBE))	74.0	75.4	0.1114
	D95% (Gy (RBE))	56.0	70.8	0.0039
	Dmean (Gy (RBE))	70.9	75.0	0.0194
	Dmin (Gy (RBE))	27.6	55.2	0.0034
PTV	V95% (%)	69.5	90.1	0.0014
	D50% (Gy (RBE))	72.9	75.2	0.1009
	D95% (Gy (RBE))	43.9	65.3	0.0019
	Dmean (Gy (RBE))	68.5	73.9	0.0036
	Dmin (Gy (RBE))	16.6	33.4	0.0304
Stomach	Dmax (Gy (RBE))	51.2	34.0	0.0315
	V30Gy (RBE) (cc)	10.3	3.7	0.0327
	V40Gy (RBE) (cc)	5.5	2.6	0.0384
Small intestine	Dmax (Gy (RBE))	44.7	33.0	0.0025

Abbreviations: *GTV* gross tumor volume, *CTV* clinical target volume, *PTV* planning target volume, *RBE* relative biological effectiveness, *V95%* volume irradiated with 95% of the planned treatment dose, *D50%* dose intensity covering 50% of the target volume, *D95%* dose intensity covering 95% of the target volume, *Dmean* average dose of the target volume, *Dmin* minimum dose of the target volume, *V5Gy (RBE)* volume irradiated by more than 5 Gy (RBE), *V20Gy (RBE)* volume irradiated by more than 20 Gy (RBE), *V30Gy (RBE)* volume irradiated by more than 30 Gy (RBE), *V40Gy (RBE)* volume irradiated by more than 40 Gy (RBE)

	Parameter	Preoperative Mean value	Postoperative Mean value	T-test
	V30Gy (RBE) (cc)	3.7	0.57	0.0327
	V40Gy (RBE) (cc)	2.0	0.38	0.0384
Large intestine	Dmax (Gy (RBE))	27.5	28.0	0.9768
	V30Gy (RBE) (cc)	2.9	0.014	0.2763
	V40Gy (RBE) (cc)	2.09	0.0	0.3423
Abbreviations: <i>GTV</i> gross tumor volume, <i>CTV</i> clinical target volume, <i>PTV</i> planning target volume, <i>RBE</i> relative biological effectiveness, <i>V95%</i> volume irradiated with 95% of the planned treatment dose, <i>D50%</i> dose intensity covering 50% of the target volume, <i>D95%</i> dose intensity covering 95% of the target volume, <i>Dmean</i> average dose of the target volume, <i>Dmin</i> minimum dose of the target volume, <i>V5Gy (RBE)</i> volume irradiated by more than 5 Gy (RBE), <i>V20Gy (RBE)</i> volume irradiated by more than 20 Gy (RBE), <i>V30Gy (RBE)</i> volume irradiated by more than 30 Gy (RBE), <i>V40Gy (RBE)</i> volume irradiated by more than 40 Gy (RBE)				

Complications

All patients showed complications, which are summarized in Table 3. Six patients had only grade 2 or lower complications, while the remaining 6 patients had grade 3 or higher complications.

Table 3
Complication Details (n = 12)

Complication grade (CTCAE Version 4.0)	
0–2	16 (72.7)
3–4	6 (27.3)
Complication details	
Leukopenia	
Grade 1–2	0
Grade 3–4	2
Thrombocytopenia	
Grade 1–2	4
Grade 3–4	1
Dermatitis	
Grade 1–2	5
Grade 3–4	0
Nausea	
Grade 1–2	2
Grade 3–4	0
Anorexia	1
Grade 1–2	0
Grade 3–4	
Ileus	
Grade 1–2	0
Grade 3–4	1
Cholangitis	
Grade 1–2	1
Grade 3–4	
Ulcer	
Grade 1–2	0
Abbreviations: CTCAE Common Terminology Criteria for Adverse Events.	

Complication grade (CTCAE Version 4.0)	
Grade 3–4	1
Abbreviations: <i>CTCAE</i> Common Terminology Criteria for Adverse Events.	

Among the 6 patients who had grade 3 or higher complications, 2 patients required invasive treatment after SMPT. One patient developed a duodenal ulcer bleeding 5 months after PT and was treated under interventional radiology, while the other was diagnosed with a strangulated ileus due to spacer placement surgery and required re-operation at 20 days postoperatively. The other grade 3 or higher complications corresponded to hematologic disorders, including 2 cases of leukopenia and 1 case of thrombocytopenia.

Another important complication associated with PT is cholangitis. Five patients had cholangitis after initiating PT. One patient with grade 2 cholangitis developed temporary hepatic failure but recovered using conservative treatment, and another patient with grade 4 cholangitis died of hepatic failure due to bleeding from complications arising during the stent placement 29 months after SMPT. The other 3 patients required repeated treatment for recurring grade 2 cholangitis.

Other complications included grade 1–2 dermatitis in 5 patients, grade 2 nausea in 2 patients, and grade 1 anorexia in 1 patient. All these complications were conservatively treated and relieved.

Discussion

DVH histogram of this study showed that the V95% of CTV improved about 20%, while the stomach Dmax decreased more than 15 Gy (RBE) after spacer placement surgery. This indicates that SMPT can deliver a larger radiation dose to the entire tumor and greatly reduce the dose to the nearby gastrointestinal tract. We think that the unprecedented radiation dose of the present study contributed to the better overall survival of 29.6 months, with 4 patients surviving for more than 4 years. A dose-response relationship had already been observed in the treatment of HC by conventional photon radiotherapy [26, 27]. Dose enhancements provided through SMPT surpassed those used in photon radiotherapy and may contribute for longer survival. Although a direct comparison cannot be made, treatment results of the present study are superior to the reported results of any chemotherapy [6, 7, 28] or radiotherapy [14–16] protocol for unresectable HC.

The combined approach of surgical spacer placement and subsequent photon radiotherapy has been attempted for various types of malignancies, especially within the abdominopelvic region [29–31]. However, the low irradiation accuracy and uncertain effectiveness of photon radiotherapy preclude the widespread use of this approach. The following concepts explain why SMPT is an entirely different and superior approach compared with conventional combination treatments: tumors can be controlled with high probability, as long as a sufficient PT dose is delivered to the entire tumor; moreover, only a 10-mm distance between the tumor and adjacent gastrointestinal tract is sufficient for safe irradiation, owing to the precise dose distribution of PT [22, 32].

While SMPT can have significant potential for HC treatment, it is associated with some complications. Regarding surgery-related complications, a patient was diagnosed with a strangulated ileus due to spacer placement surgery and required re-operation 20 days postoperatively. Although the invasiveness of spacer placement surgery is relatively small, significant complications can occur in some cases. Most complications regarding PT were conservatively managed and relieved, but the gastrointestinal ulcers and cholangitis complications are issues to be considered.

In the present study, a patient developed a duodenal ulcer bleeding which required trans-arterial coil embolization. Two possibilities can be considered for the cause of this complication. One is the overexposure to particle beams despite the spacer placement. Intrinsically, the dose centralization of the radiation beams in upper abdominal lesions tends to be disordered compared to lower abdominal lesions due to normal respiratory movements. These movements may evoke dosimetric uncertainties, leading to the unexpected exposure of the gastrointestinal tract. In fact, gastrointestinal ulcers can occur after radiotherapy for intrahepatic or extrahepatic cholangiocarcinoma in 9–22.2% of cases, even with precise radiation treatment planning [15, 33, 34]. Another possibility is the mechanical stimulation caused by the attached spacer. Long-lasting mechanical stimulation caused by the spacer might lead to ulcer formation and occasionally penetration of the gastrointestinal wall. In fact, spacer intraluminal migration after spacer placement surgery has been reported [35]. To increase the safety of SMPT, we developed a novel spacer made from absorbable material. This spacer is already available for clinical use in Japan [36, 37], and may contribute to increase the efficacy and feasibility of SMPT while reducing long-term contact and providing high radiation shielding performance.

The risk of cholangitis is another matter of concern. The reported incidence of cholangitis after photon radiotherapy ranged from 7–50% [11, 38–40]. In the present study, 5 patients (41.7%) developed cholangitis (4 within grades 1–2 and 1 with grade 4). Patients with HC after radiotherapy, including PT, required frequent bile duct stent replacement due to repeated cholangitis. The biliary tract obstruction caused by HC became persistent after PT although cancer cells were not detected. We speculated that the irradiated bile duct lost the normal structure and did not regenerate, which is why patients with HC after radiotherapy need frequent stent replacement. In addition, patients after PT tended to survive longer than those undergoing photon radiotherapy. This explains why patients with HC after PT in this study needed more stent replacement than patients undergoing photon radiotherapy. The damaged bile duct is quite fragile after irradiation, and stent replacement includes significant bleeding and perforation risks. We experienced a case in which the patient died of liver failure 29 months after SMPT due to the perforation of bile duct and bleeding complications during stent replacement. A cautious approach is therefore essential; stent replacement should be performed by an experienced endoscopist after a thorough discussion. Stent replacement complications are preventable and should be the object of future studies.

Based on the favorable outcomes after SMPT, the concomitant use of chemotherapy with PT remains to be solved in future. Among the 4 patients who received chemotherapy during or after the PT period, 1 patient who was administered gemcitabine and cisplatin remains alive after 55 months. However, due to

the limited number of cases, no conclusion can be drawn, and these findings should be confirmed by prospective studies.

The present study has some limitations, especially related to its small sample size and design (single-arm, single-center retrospective study). However, considering the limited indication of SMPT for this condition, the present study can have a substantial impact in HC treatment, based on the favorable treatment results and the long survival seen, which cannot be accomplished by conventional treatment algorithms. Our findings support the survival benefits and provide a treatment option for patients with unresectable HC due to intrahepatic bilateral extension without extrahepatic metastasis. In addition, patients with resectable HC but not indicated for liver resection due to poor health status are also good candidates for SMPT.

Conclusion

SMPT showed significant improvements in dose distribution after spacer placement surgery and excellent outcomes for unresectable HC. SMPT holds the potential to become an alternative treatment option for unresectable HC.

Abbreviations

HC hilar cholangiocarcinoma

PT particle therapy

SMPT space-making particle therapy

CT computed tomography

RBE relative biological effectiveness

GTV gross tumor volume

CTV clinical target volume

PTV planning target volume

DVH dose-volume histogram

V95% volume irradiated with 95% of the planned treatment dose

D95% dose intensity covering 95% of the target volume

Dmax maximum dose of the target volume

Dmean average dose of the target volume

Dmin minimum dose of the target volume

V30Gy (RBE) volume irradiated by more than 30 Gy (RBE)

V40Gy (RBE) volume irradiated by more than 40 Gy (RBE)

Declarations

Ethics approval and consent to participate

This study complied with the standards of the Declaration of Helsinki and the current ethical guidelines, and was approved by the institutional ethics board, with patient consent required.

Consent for publication

Not applicable in this section.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

The authors have indicated that they have no funding regarding the content of this article.

Authors' contributions

SK and KT conceived of the presented idea. TF, TA, YD, ST, RS, TO and HY led the project. YH, SK, KT, DT and MS provided clinical data, treatment planning, analysis of the results, and thoughts and ideas on the study design and method development.

Acknowledgements

Not applicable in this section.

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Figures

Figure 1

A Gore-Tex sheet was placed between the liver and gastrointestinal tract. (a) Space-making particle therapy concept; (b) Operative findings.

Figure 2

A representative case who underwent space-making particle therapy. (a) Preoperative abdominal computed tomography showing bilateral intra-hepatic bile duct dilatation (arrowhead). (b) The tumor broadly abutted the duodenum (white arrow). (c) Postoperative abdominal computed tomography showing that the spacer (Gore-Tex sheets) (arrowhead) maintained a sufficient open space between the tumor and gastrointestinal tract. (d) A treatment plan was designed, and the gastrointestinal tract was successfully excluded from the irradiation field, thus receiving minimal irradiation.

Figure 3

Overall (a) survival rate, and (b) local control rate.