

Recurrent cholangiocarcinoma with long-term survival by multimodal treatment: A case report

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Abstract. Long-term outcomes after surgical resection of bile duct cancer remain unsatisfactory, and survival, particularly after tumor recurrence, is poor. Gemcitabine and cisplatin combination (GC) therapy is the standard first-line treatment; however, second-line approaches are yet to be established. Radiotherapy may prolong the survival of patients with advanced biliary tract cancer, and particle radiotherapy delivers a more concentrated dose than conventional radiotherapy to deeper tumors. The present report describes the long-term survival of a 65-year-old man with distal bile duct cancer of pathological stage IIA (T2N0M0; depth of invasion, 5.5 mm) following multimodal treatment. Following subtotal stomach-preserving pancreatoduodenectomy, multiple hepatic recurrences were identified 9 months later, and GC therapy was initiated. The tumors were no longer evident 18 months later, and GC therapy was discontinued at the patient's request. A computed tomography (CT) scan performed 30 months after surgery identified a new solitary hepatic recurrence and duke pancreatic monoclonal antigen type-2 (DUPAN-2) levels were increased. Further GC therapy was declined. Carbon ion radiotherapy (CIRT) at a dose of 60 Gy [relative

biological effectiveness (RBE)-weighted absorbed dose] was then delivered in four fractions over 4 days [15 Gy (RBE)/day]. Tumor size decreased on CT, and fluorodeoxyglucose-positron emission tomography/CT revealed a decline in the standardized uptake value of the tumor after 2 months, with decreased DUPAN-2 levels. Following regrowth of the hepatic recurrence, CIRT was repeated at a dose of 66 Gy (RBE) in four fractions over 4 days [16.5 Gy (RBE)/day] and stable disease was maintained for 19 months. After 19 months, CT revealed tumor regrowth and another new metastatic lesion was identified in the left kidney. The patient received systematic chemotherapy again and died of the disease 81 months after the initial surgery. In conclusion, CIRT is a potential treatment option to control solitary recurrence of biliary tract cancer.

Introduction

Generally, surgical resection is the only potentially curative treatment for patients with cholangiocarcinoma. However, tumor recurrence occurs in ~70% of patients with biliary tract cancer, even after curative resection, and 5-year postoperative survival is less than 50% (1-3). Long-term survival can rarely be expected once tumor recurrence occurs because the recurrence means 'systematic disease'. Most of the recurrence cases, the curative resection is impossible and the systematic chemotherapy is selected.

Gemcitabine and cisplatin (GC) combination therapy is the first choice of treatment for recurrent or unresectable biliary tract cancer (4), but a strategy for second-line therapies has not yet been established.

Several reports have suggested that conventional or particle radiotherapy might prolong the survival of patients with advanced biliary tract cancer (5,6). It is known that particle therapy has a higher dose concentration compared with conventional radiotherapy and is effective in treating deeply located tumors. Particle therapy is divided into proton beam radiotherapy and heavy particle therapy. Both of them show strong cytotoxicity as a result of high linear energy transfer, unlike the alternative X-ray beam therapy. In heavy particle therapy, carbon ions are usually used. They have potential advantage

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Abbreviations: CIRT, carbon ion radiotherapy; CT, computed tomography; DUPAN-2, duke pancreatic monoclonal antigen type-2; CA19-9, carbohydrate antigen 19-9; FDG-PET/CT, fluorodeoxyglucose-positron emission tomography/computed tomography; GC, gemcitabine and cisplatin; PBT, proton beam therapy; RBE, relative biological effectiveness; GPT, gemcitabine-concurrent proton radiotherapy; NIRS, National Institute of Radiological Science

Key words: cholangiocarcinoma, hepatic recurrence, carbon ion radiotherapy, gemcitabine, cisplatin, chemotherapy

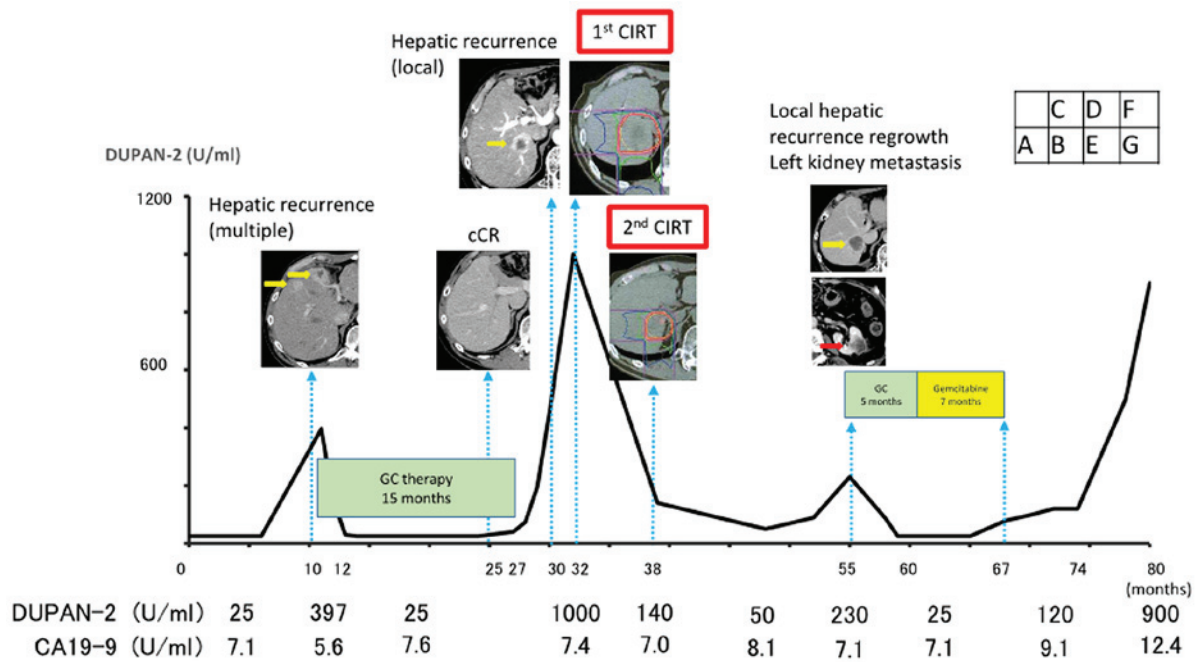


Figure 1. Changes in DUPAN-2 levels following the clinical course and the quantified data of DUPAN-2 and CA19-9. (A) Postoperative CT scan at 10 months revealing multiple solid liver tumors (yellow arrows). The largest tumor was located in segment 4 and had a diameter of 20 mm. (B) CT scan revealing the complete disappearance of the hepatic tumors after GC therapy. (C) A postoperative CT scan at 30 months demonstrated one ring-like enhancement mass measuring 30 mm in diameter in segment 6 (yellow arrow). Planning CT scans demonstrating (D) first and (E) second CIRT imaging. A postoperative CT scan at 55 months demonstrated (F) the same local hepatic recurrence that had increased in size up to 45 mm in diameter (yellow arrow) and (G) identified a new metastatic lesion in the left kidney (red arrow). DUPAN-2, duke pancreatic mono-clonal antigen type-2; CA19-9, carbohydrate antigen 19-9; GC, gemcitabine and cisplatin; CIRT, carbon ion radiotherapy; cCR, clinical complete response; Lt.

compared to protons. For example, they provide a better physical dose distribution because lateral scattering is more lessened. Furthermore, carbon ions exhibit a higher linear energy transfer than protons. This leads to a higher relative biological effectiveness (RBE), where damage caused by carbon ions is clustered in the DNA, overwhelming the cellular repair system (7). Several cohort studies showed the effectiveness of proton beam therapy for biliary tract cancer (8-11), whereas heavy particle therapy for biliary tract cancer has not been evaluated.

We experienced a case of recurrent distal bile duct cancer that achieved long-term survival with a multimodal treatment strategy of systematic chemotherapy and heavy particle therapy. So, we will report this case with additional literature review.

Case report

A 65-year-old male underwent a subtotal stomach-preserving pancreatoduodenectomy for distal bile duct cancer. The pathological depth of tumor invasion was 5.5 mm and there was no lymph node metastasis with a pathological stage of IIA (T2N0M0) according to the eighth Union for International Cancer Control staging (12). The patient was discharged 21 days after surgery without any postoperative complications and did not receive any adjuvant chemotherapy.

Multiple hepatic recurrences were recognized on computed tomography (CT) performed 9 months after the surgery (Fig. 1A), and thus GC therapy was initiated. This therapy consisted of gemcitabine (1,000 mg per square meter of body-surface area) and cisplatin (25 mg per square meter of body-surface area) and was performed 10 cycles with 100% dose. After 18 months, all hepatic tumors had completely

disappeared (Fig. 1B). The GC therapy was discontinued at the patient's request.

Three months later, serum DUPAN-2 levels had elevated, and a CT scan revealed a new hepatic recurrence (Fig. 1C). However, serum carbohydrate antigen 19-9 (CA19-9) levels had not elevated. We proposed that GC therapy should be restarted, but the patient declined because he was suffering from peripheral neuropathy. Because no other recurrences were detected by CT, we consulted with radiologists, and particle therapy was recommended. The patient was treated with heavy particle therapy [carbon ion radiotherapy (CIRT)]. The total dose was 60 Gy (RBE) in four fractions for 4 days [15 Gy (RBE)/day] (Fig. 1D). There were no adverse events during the first CIRT. CT scan revealed shrinkage of the hepatic tumor. In addition, the level of standard uptake value at the center of hepatic recurrence decreased from 8.1 to 0 by fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT). Serum DUPAN-2 levels also decreased.

Six months after the first CIRT, a hepatic tumor was identified at the same site upon CT. The patient received CIRT again, with a total dose of 66 Gy (RBE) in four fractions for 4 days [16.5 Gy (RBE)/day] (Fig. 1E). The only adverse event was slight dermatitis. After the second CIRT, the serum DUPAN-2 level decreased to within the normal range.

Nineteen months after the second CIRT, CT showed a hepatic tumor regrowth with a diameter of 45 mm (Fig. 1F). FDG-PET/CT confirmed an elevated standardized uptake value from 0 to 7.4 in this lesion. Furthermore, a new metastatic lesion was recognized in the left kidney (Fig. 1G). We started GC therapy again because it had been effective against the initial recurrence, and the time interval since the first treatment was approximately

Table I. Previous reports regarding the clinical outcomes of PBT for biliary tract cancer.

Author, year	Number of patients	Tumor type and characteristics	PBT dose, fractionation, technique	Median follow-up, months	Survival outcomes	(Refs.)
Ohkawa <i>et al</i> , 2015	14	Intrahepatic cholangiocarcinoma. Stage II (1/14; 7%); stage IIIA (4/14; 29%); stage IIIC (5/14; 36%); stage IV (4/14; 29%)	Median 72.6 CGE in 26 fractions	12	1 y OS 50%; 1 y PFS 36%, LP in 6/14 (43%); LR in 2/14 (14%); Out-of-field recurrence in 7/14 (50%); DM in 4/14 (28%)	(8)
Makita <i>et al</i> , 2014	28	Cholangiocarcinoma. Intrahepatic (6/28; 21%); hilar (6/28; 21%); distal extrahepatic (3/28; 11%); gallbladder (3/28; 11%); local/nodal recurrence (10/28; 36%)	Median 68.2 CGE in 31 fractions	12	1 y LC 68%, 1 y PFS 30%. 1 y OS 49%. Increased LC with BED>70 Gy (P=0.002)	(9)

PBT, proton beam radiotherapy; CGE, cobalt gray equivalent; OS, overall survival; LP, local progression; DM, distant metastasis; PFS, progression-free-survival.

35 months. We continued GC therapy for 5 months, and then switched to gemcitabine monotherapy because of the peripheral neuropathy and general malaise. Gemcitabine monotherapy (1,000 mg per square meter of body-surface area) was continued administer 3-weeks on/1-week off for 7 months. The patient died 16 months after cessation of the second chemotherapy because of disease progression. The total survival time after the surgery was 81 months.

Discussion

We experienced a case of extrahepatic bile duct cancer in which long-term survival was achieved with multidisciplinary treatment including systemic chemotherapy and CIRT after tumor recurrence. The patient survived more than 70 months after the first hepatic recurrence. Although the appearance of a solitary recurrence is rare after complete remission of multiple recurrences following systematic chemotherapy, our case suggested that multiple sessions of CIRT might be able to control the disease and contribute to prolonging overall survival.

To date, no treatment other than GC therapy has been established for unresectable or recurrent biliary tract cancer. Radiation therapy or chemoradiotherapy is reserved for patients who present locally advanced unresectable disease but there is insufficient evidence for its efficacy as a treatment for patients with distant metastasis (13).

Recently, several case reports demonstrated the outcomes of proton beam therapy (PBT) and CIRT for various malignant primary or recurrent tumor types (14-18).

For example, in the research of performing gemcitabine-concurrent proton radiotherapy (GPT) to pancreatic cancer cases, 50 patients were divided into three groups by every protocol of PBT. The median follow-up period was 12.5 months. The scheduled GPT was feasible for all except 6 patients (12%) due to acute hematologic. Grade 3 or greater late gastric ulcer and hemorrhage were seen in 5 patients (10%). The one-year

freedom from local-progression, progression-free, and overall survival rates were ~74% (14). Like as this research, PBT provide useful local-regional treatment for hepatocellular carcinoma. In this research, 76 patients were treated and followed prospectively for treatment outcomes. Eleven patients had multiple tumors and 46% were within the Milan criteria. Patients received 63 Gy delivered over a 3-week period with PBT. All cases completed the full course of treatment. Finally, median progression-free survival for the entire group was 36 months, with a 60% 3-year progression-free survival rate for patients within the Milan criteria. 18 patients subsequently underwent liver transplantation; 6 (33%) explants showed pathological complete response and 7 (39%) showed only microscopic residual (15). The outcome of performing CIRT for hepatocellular carcinoma is also good. In the 69 cases at National Institute of Radiological Science (NIRS), the five-year local control rate was 81% and survival rate was 33%. Like with the hepatocellular carcinoma, CIRT for pancreatic cancer is effective. In the cases of locally advanced unresectable pancreatic cancer, the combination of gemcitabine and CIRT improved the outcomes. Second-year local control rate was 58% and second-year overall survival was 54% in the 47 cases at NIRS. This result is better than those reported worldwide after surgery alone (7).

CIRT was initiated by the Heavy Ion Medical Accelerator in Chiba, Japan, in 1993. It offers superior dose conformity in the treatment of deeply located malignant tumors compared with conventional X-ray therapy (18). Additionally, its biological effectiveness (a highly localized deposition of energy) can be used for increasing radiation exposure to tumors while minimizing irradiation to adjacent normal tissues. PBT also has this characteristic, but the lateral fall-off around the target is less steep than that of carbon ion beams (19).

Despite this property for cancer treatment, no reports have presented the benefits of CIRT for biliary tract cancer. There have been few studies of PBT in primary, locally recurrent, or nodal metastatic disease (Table I).

Regarding indications for radiation therapy for biliary tract cancer, Kazuki *et al* (20) reported that the best indication for curative beam therapy was locally advanced unresectable hepatic hilar cholangiocarcinoma without distant metastasis. However, long-term outcomes after CIRT have not yet been reported. In our case, CIRT was indicated at the time of second recurrence, and good local control was achieved. Hence, the patient survived for eighty months after surgery.

In conclusion, CIRT may be a treatment option for selected patients with solitary recurrence of biliary tract cancer.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

KK, IF, TT, YT, TI and YM collected the data and assisted with data analysis. KO, YKa, ES, HT, SYas, YI and SYam contributed to interpretation of data and manuscript preparation. YS analyzed the data and wrote the original draft. TE conceived the study, reviewed and revised the manuscript. JY and YKi made substantial contributions to the conception and design. HU made substantial contributions to analysis and interpretation of data. JY, HU and YKi provided supervision of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written informed consent for the publication of their data.

Competing interests

The authors declare that they have no competing interests.

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